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Psoriasis is Associated with An Increased Risk of Osteoporosis: Follow-Up and Nested Case–Control Studies Using A National Sample Cohort

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Abstract

Objectives: The aim of the present study was to evaluate the association between psoriasis and osteoporosis using two different studies.

Methods: Data from the Korean National Health Insurance Service-Health Screening Cohort of participants who were ≥ 40 years old were collected from 2002 to 2013. Psoriasis and osteoporosis were included using ICD-10 codes. In study I (a follow-up study), a total of 25,306 psoriasis participants were matched to 101,224 controls with respect to age group, sex, income group, and region of residence, and the occurrence of osteoporosis was analyzed. Crude (simple) and adjusted hazard ratios (HRs) were analyzed using a stratified Cox proportional hazard model. In study II (a nested case–control study), a total of 79,212 osteoporosis patients were matched to 79,212 controls, and a previous history of psoriasis was analyzed. Crude and adjusted odds ratios (ORs) were analyzed using a conditional logistic regression analysis. Subgroup analyses were conducted according to age group and sex.

Results: The adjusted HR of osteoporosis was 1.11 (95% confidence interval [CI] = 1.07-1.15, P < 0.001) in study I. In the subgroup analysis according to age and sex, the results were consistent except for the ≥ 60-year-old women. The adjusted OR of psoriasis was 1.22 (95% CI = 1.16-1.28, P < 0.001) in study II. All subgroups demonstrated high adjusted ORs of osteoporosis for psoriasis.

Conclusions: Psoriasis increased the risk of osteoporosis in the population of participants aged ≥ 40 years in Korea.

Keywords: psoriasis; osteoporosis; cohort studies; Case-Control Studies; risk factors

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Introduction

Psoriasis is an immune-mediated genetic disease manifesting in the skin, joints or both[1]. It is estimated to affect approximately 2% of the population in Europe and the United States[2]. The prevalence per 10,000 people in Korea increased from 47.4 to 61.5 from 2006 to 2015, with a higher prevalence in men >30 years old[3]. Individuals with psoriasis are at an increased risk of developing other chronic and serious health diseases, including psoriatic arthritis (PsA) (pooled proportion 19.7%; 95% confidence interval [CI] 18.5%-20.9%)[4], type 2 diabetes mellitus (odds ratio [OR] 1.69; 95% CI 1.51-1.89), hypertension (OR 1.43; 95% CI 1.25–1.64)[5], and even depression (OR 2.19; 95% CI 1.97-2.44) [6]. Psoriasis is mainly a dendritic cell- and T-cell-mediated disease, with the production of tumor necrosis factor (TNF)-α and interleukin (IL)-17, 22, 23[1]. The systemic inflammatory state is the probable link between all comorbidities [2].

Although current guidelines on the management of comorbidities of psoriasis do not include bone health, several recent studies have indicated that patients with psoriasis may be at an increased risk of pathologic fractures and osteoporosis [7]. In a longitudinal cohort study among 158,323 psoriasis patients in the UK, patients with severe psoriasis had an elevated risk for incident fracture (adjusted hazard ratio [HR] 1.26; 95% CI 1.15-1.39) [8]. Many studies have indicated possible bone involvement in patients with psoriasis, especially among men[9-11]. Men are usually less affected by osteoporosis, and this factor should be measured carefully during psoriasis patient care[2]. However, osteoporosis occurs more frequently in women than in men, particularly after menopause[12,13].

The hypothesis was that psoriasis increases the risk of osteoporosis. To show this, we conducted two different studies in a nationwide population cohort. First, a follow-up study was designed in psoriasis patients and controls, and the occurrence of osteoporosis was analyzed. As osteoporosis affects mostly older women, the first study method could omit

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female data. Therefore, a nested case–control study was designed in osteoporosis patients. The prevalence of prior psoriasis was evaluated in the osteoporosis patients and controls.

Materials and Methods

Study Population and Data Collection

The ethics committee of Hallym University (2019-01-003) approved the use of these data. The study was exempted from the need for written informed consent by the Institutional Review Board.

This national cohort study relied on data from the Korean National Health Insurance Service-Health Screening Cohort (NHIS-HEALS). The detailed description of these data was described in our previous studies[14].

Participant Selection

Out of 514,866 cases with 497,931,549 medical claim codes, we included participants who were diagnosed with psoriasis (ICD-10: B02) from 2002 through 2013. Among them, we selected participants who were treated for psoriasis by a physician more than 2 times.

Osteoporosis was defined using the ICD-10 codes M80 (osteoporosis with pathological fracture), M81 (osteoporosis without pathological fracture), and M82 (osteoporosis in diseases classified elsewhere) from 2002 through 2013. Among them, we selected participants who were treated ≥ 2 times or participants who were diagnosed with osteoporosis by bone densitometry by dual energy X-ray absorptiometry (DEXA) or DEXA CT scan (ICD-10 codes: E7001-E7004) following protocols from our previous studies[15,16].

Study I (A follow-up study)

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Psoriasis patients were matched 1:4 with participants in this cohort who were not diagnosed with psoriasis (control I) from 2002 through 2013. The control I group was selected from the total population (n = 451,261). Matching was performed for age group, sex, income group, and region of residence. To prevent selection bias when selecting the matched participants, the control I participants were sorted using a random number order and then selected from top to bottom. We set the index date as the date of the diagnosis of psoriasis. It was assumed that the matched control I participants were involved at the same time as each matched psoriasis participant (index date). Therefore, participants in the control I group who died before the index date were substituted by other control participants. Participants who had histories of osteoporosis before the index date were excluded from both the psoriasis and control I groups. In the psoriasis group, 3,717 participants were excluded. None of the psoriasis patients were excluded due to matching. The mean follow-up time from the index date to the last date (December 31, 2013) or death date was similar in both the psoriasis (95.8 months, standard deviation [SD] = 25.1) and control I groups (95.5 months, SD = 25.7). Finally, 1:4 matching resulted in the inclusion of 25,306 psoriasis patients and 101,224 control I participants (Fig. 1a). We analyzed the occurrence of osteoporosis in the psoriasis and control I groups.

Study II (A nested case–control study)

The osteoporosis patients were matched 1:1 with participants in this cohort who were not diagnosed with osteoporosis (control II) from 2002 through 2013. The control II group was selected from the total population (n = 431,482). Matching was performed for age group, sex, income group, and region of residence. To prevent selection bias when selecting the matched participants, the control II participants were sorted using a random number order and then selected from top to bottom. We set the index date as the date of diagnosis of osteoporosis. It

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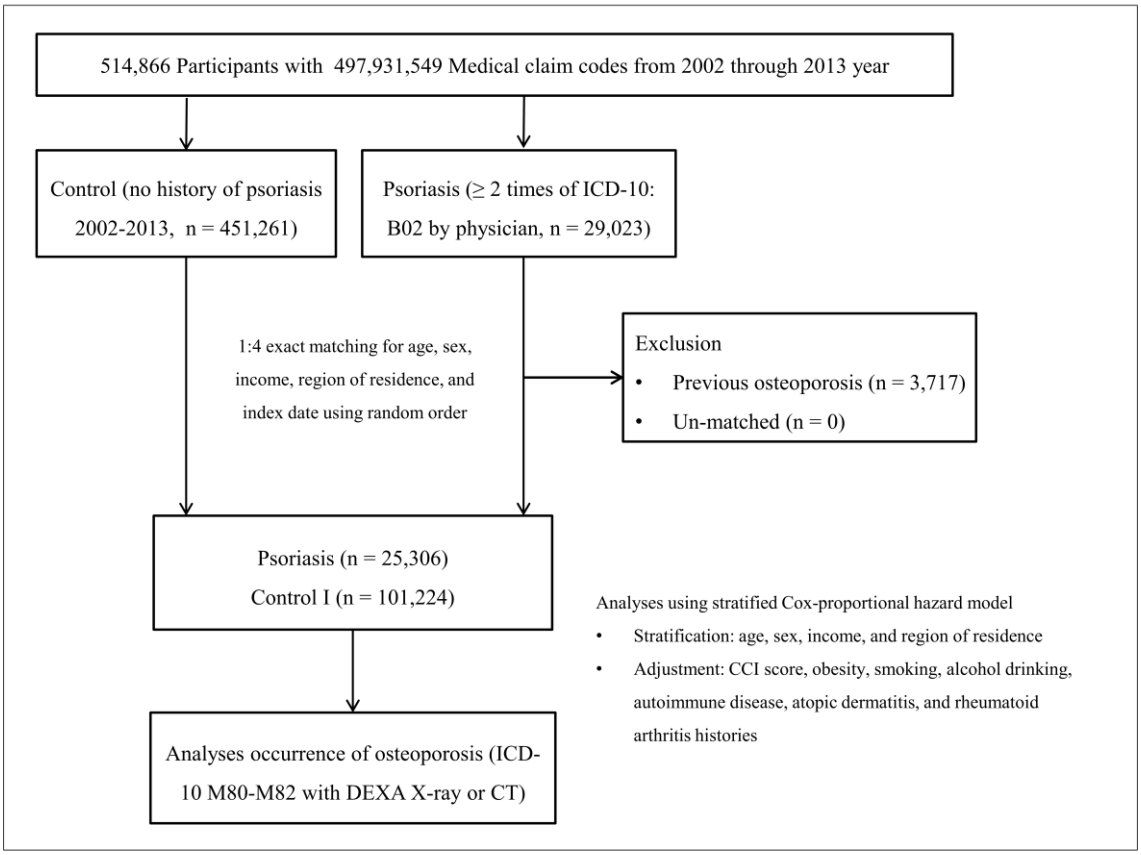
was assumed that the matched control II participants were involved at the same time as each matched osteoporosis participant (index date). In osteoporosis participants, 4,172 participants were excluded due to lack of possible control participants. Finally, 1:1 matching resulted in the inclusion of 79,212 osteoporosis patients and 79,212 control II participants (Fig. 1b). We analyzed the previous history of psoriasis in both the osteoporosis and control II groups.



1a)

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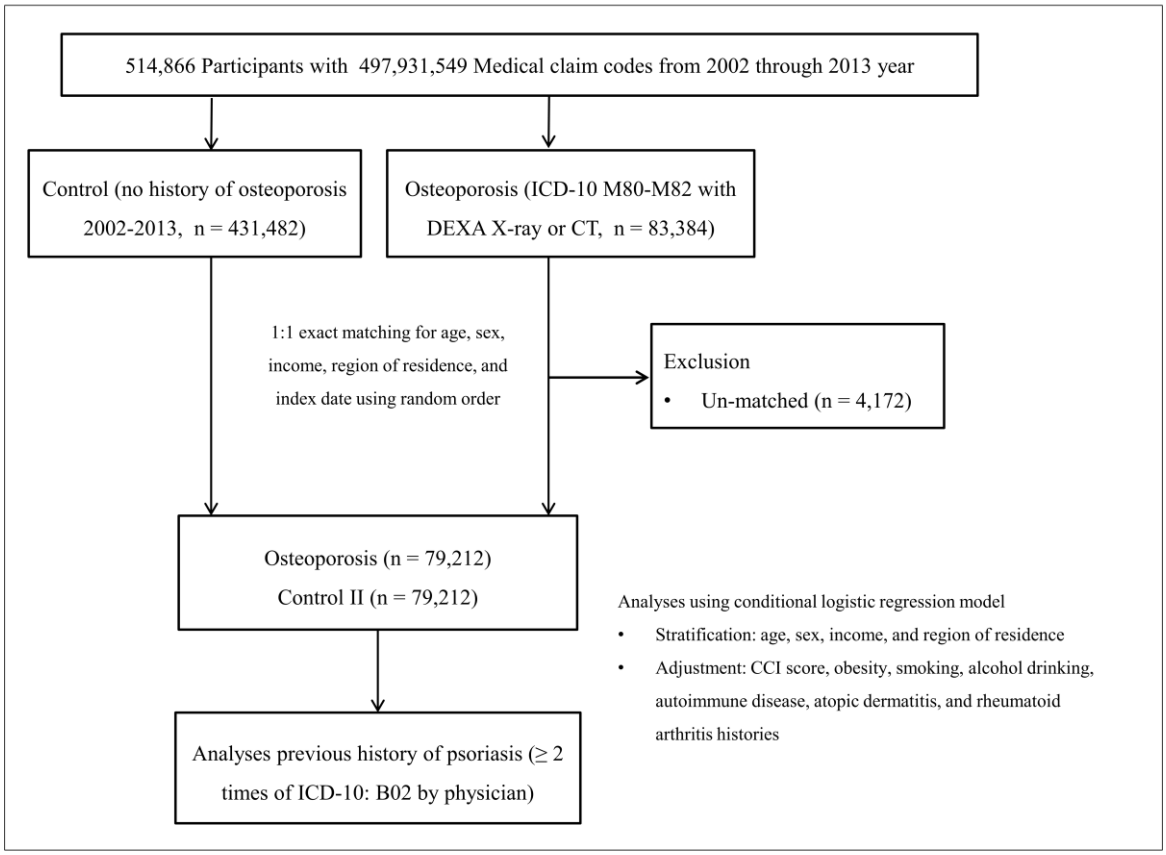

1b)

Figure 1. A schematic illustration of the participant selection process that was used in the present study. **1a)** Out of a total of 514,866 participants, 29,023 psoriasis participants were selected. The psoriasis participants were matched 1:4 with a control group that were not diagnosed with psoriasis. Unmatched and previous osteoporosis patients were excluded (n=3,717). Finally, 25,306 psoriasis patients and 101,224 control participants were included. **2a)** Out of a total of 514,866 participants, 83,384 osteoporosis participants were selected. The osteoporosis participants were matched 1:1 with a control group that were not diagnosed with osteoporosis. Unmatched patients were excluded (n=4,172). Finally, 79,212 osteoporosis patients and 79,212 control participants were included.

Variables

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The age groups were classified using 5-year intervals: 40-44, 45-49, 50-54…, and 85+ years old. A total of 8 age groups were designated. The income groups were initially divided into 41 classes (one health aid class, 20 self-employment health insurance classes, and 20 employment health insurance classes). These groups were re-categorized into 5 classes (class 1 [lowest income]-5 [highest income]). Region of residence was divided into 16 areas according to administrative district. These regions were regrouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

Tabaco smoking was categorized as current smoking state (nonsmoker or former/current smoker). Below, we used 'smoking' as the current smoker compared to nonsmoker or former smoker. Alcohol consumption was categorized as frequency (< 1 time a week or ≥ 1 time a week). Below, we used 'alcohol consumption' as drinking alcohol ≥ 1 time a week compared to drinking < 1 time a week. Obesity was measured using body mass index (BMI, kg/m^2). It was categorized as < 18.5 (underweight), ≥ 18.5 to < 23 (normal), ≥ 23 to < 25 (overweight), ≥ 25 to < 30 (obese I), and ≥ 30 (obese II), following Western Pacific Region of the World Health Organization (WPRO) 2000 guidelines[17].

Atopic dermatitis was defined as the ICD-10 code of L20. Rheumatoid arthritis was selected using ICD-10 codes M05 or M06 and a prescription for a biologic agent or any disease-modifying antirheumatic drugs (DMARD)[18,19]. Autoimmune disease was defined as systemic lupus erythematosus (ICD-10 code: M32), systemic sclerosis (ICD-10 code: M34), Sjogren syndrome (ICD-10 code: M350), dermatopolymyositis (ICD-10 code: M33), and polyarteritis nodosa and related conditions (ICD-10 code: M30). The Charlson comorbidity index (CCI) was used as the continuous variable (0 [no comorbidity] through 28 [multiple comorbidities]) for 16 comorbidities except for connective tissue diseases[20].

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Statistical Analyses

The chi-square test was used to compare the rate of general characteristics between the psoriasis and control I groups (study I) and between the osteoporosis and control II groups (study II).

To analyze the HRs of psoriasis (independent variable) on osteoporosis (dependent variable), a stratified Cox proportional hazard model was used (study I). In this analysis, crude (simple) and adjusted (CCI score, obesity, smoking, alcohol drinking, and history of autoimmune disease, atopic dermatitis, and rheumatoid arthritis) models were used. In these analyses, age, sex, income, and region of residence were stratified, and the 95% CI was calculated. The Kaplan-Meier analysis and log-rank test were used.

To analyze the ORs of psoriasis (dependent variable) in osteoporosis (independent variable), a conditional logistic regression analysis was used (study II). In this analysis, crude (simple) and adjusted (CCI score, obesity, smoking, alcohol drinking, and history of autoimmune disease, atopic dermatitis, and rheumatoid arthritis) models were used.

For the subgroup analysis, we divided the participants by age and sex (<60 years old and 60+ years old; men and women). The division point of age was determined around median values. Two-tailed analyses were conducted, and P values less than 0.05 were considered significant. The results were statistically analyzed using SPSS v. 22.0 (IBM, Armonk, NY, USA).

Results

Study I

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The rate of osteoporosis was higher in psoriasis patients (14.7%, 3,712/25,306) than in control participants (13.0%, 13,187/101,224). The distribution of age, sex, income and region of residence were comparably matched between the psoriasis and control I groups (each P = 1.000, Table 1). The rates of autoimmune disease, atopic dermatitis and rheumatoid arthritis were higher in the psoriasis group than in the control I group ($P < 0.001$ for each comparison).

Table 1 General Characteristics of Participants

Characteristics	Study I			Study II		
	Psoriasis (n, %)	Control I (n, %)	P-value	Osteoporosis (n, %)	Control II (n, %)	P-value
Age (years old)			1.000			1.000
40-44	1,234 (4.9)	4,936 (4.9)		1,329 (1.7)	1,329 (1.7)	
45-49	4,214 (16.7)	16,856 (16.7)		5,450 (6.9)	5,450 (6.9)	
50-54	4,648 (18.4)	18,592 (18.4)		10,945 (13.8)	10,945 (13.8)	
55-59	4,267 (16.9)	17,068 (16.9)		12,496 (15.8)	12,496 (15.8)	
60-64	3,901 (15.4)	15,604 (15.4)		14,743 (18.6)	14,743 (18.6)	
65-69	3,492 (13.8)	13,968 (13.8)		17,165 (21.7)	17,165 (21.7)	
70-74	2,216 (8.8)	8,864 (8.8)		9,920 (12.5)	9,920 (12.5)	
75-79	1,013 (4.0)	4,052 (4.0)		5,082 (6.4)	5,082 (6.4)	
80+	321 (1.3)	1,284 (1.3)		2,083 (2.6)	2,083 (2.6)	
Sex			1.000			1.000

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Male	12,448 (49.2)	49,792 (49.2)		8,140 (10.3)	8,140 (10.3)	
Female	12,858 (50.8)	51,432 (50.8)		71,072 (89.7)	71,072 (89.7)	
Income			1.000			1.000
1 (lowest)	7,315 (28.9)	29,260 (28.9)		26,445 (33.4)	26,445 (33.4)	
2	9,122 (36.0)	36,488 (36.0)		28,520 (36.0)	28,520 (36.0)	
3 (highest)	8,869 (35.0)	35,476 (35.0)		24,247 (30.6)	24,247 (30.6)	
Region of residence			1.000			1.000
Urban	11,662 (46.1)	46,648 (46.1)		31,923 (40.3)	31,923 (40.3)	
Rural	13,644 (53.9)	54,576 (53.9)		47,289 (59.7)	47,289 (59.7)	
CCI (score)†			<0.001*			<0.001*
0	24,785 (97.9)	98,506 (97.3)		77,727 (98.1)	77,053 (97.3)	
1	51 (0.2)	427 (0.4)		122 (0.2)	288 (0.4)	
2	74 (0.3)	387 (0.4)		192 (0.2)	275 (0.3)	
≥ 3	396 (1.6)	1,904 (1.9)		1,171 (1.5)	1,596 (2.0)	
BMI			<0.001*			<0.001*
< 18.5 (underweight)	546 (2.2)	2,572 (2.5)		2,492 (3.1)	1,908 (2.4)	
≥ 18.5 to < 23 (normal)	8,787 (34.7)	35,596 (35.2)		29,264 (36.9)	26,363 (33.3)	
≥ 23 to < 25 (overweight)	7,060 (27.9)	27,603 (27.3)		20,831 (26.3)	20,724 (26.2)	

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≥ 25 to < 30 (obese I)	8,217 (32.5)	32,428 (32.0)		24,189 (30.5)	26,742 (33.8)	
≥ 30 (obese II)	696 (2.8)	3,025 (3.0)		2,436 (3.1)	3,475 (4.4)	
Smoking			<0.001*			<0.001*
Nonsmoker or past smoker	21,788 (86.1)	82,921 (81.9)		75,500 (95.3)	74,950 (94.6)	
Current smoker	3,518 (13.9)	18,303 (18.1)		3,712 (4.7)	4,262 (5.4)	
Drinking alcohol			<0.001*			<0.001*
< 1 time a week	19,766 (78.1)	76,799 (75.9)		73,081 (92.3)	72,516 (91.5)	
≥ 1 time a week	5,540 (21.9)	24,425 (24.1)		6,131 (7.7)	6,696 (8.5)	
Autoimmune disease	398 (1.6)	1,241 (1.2)	<0.001*	1,662 (2.1)	1,171 (1.5)	<0.001*
Atopic dermatitis	3,071 (12.1)	9,080 (9.0)	<0.001*	8,968 (11.3)	7,247 (9.1)	<0.001*
Rheumatoid arthritis	827 (3.3)	2,349 (2.2)	<0.001*	4,841 (6.1)	2,130 (2.7)	<0.001*
Psoriasis	25,306 (100.0)	0 (0.0)	<0.001*	4,007 (5.1)	3,254 (4.1)	<0.001*
Osteoporosis	3,712 (14.7)	13,187 (13.0)	<0.001*	79,212 (100.0)	0 (0.0)	<0.001*

* Chi-square test, Significance at P < 0.05

† Charlson Comorbidity Index was calculated without rheumatic diseases.

The psoriasis group included a higher proportion of individuals with osteoporosis than the control I group (Fig. 2). The adjusted HR of psoriasis for osteoporosis was 1.11 (95% CI = 1.07-1.15, *P* < 0.001, Table 2).

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Figure 2 Kaplan–Meier plot of overall osteoporosis-free survival in the psoriasis and control groups. The psoriasis group included a higher proportion of individuals with osteoporosis than the control I group.

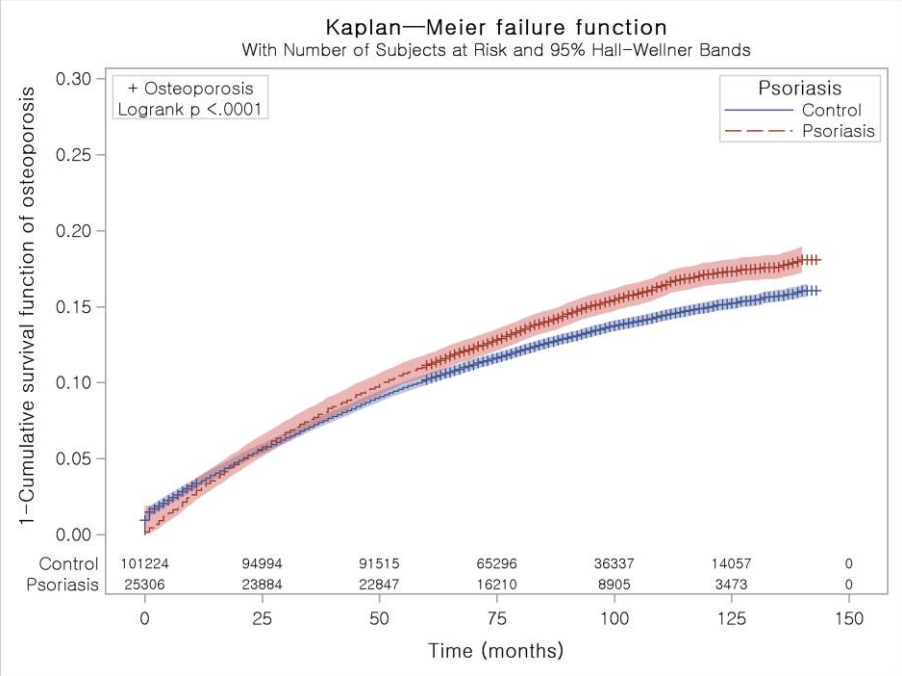

Table 2 Crude and adjusted hazard ratios (95% confidence interval) of psoriasis for osteoporosis according to age and sex (study I)

Characteristics	Hazard ratios for osteoporosis			
	Crude†	P-value	Adjusted†‡	P-value
Total participants (n = 126,530)				
Psoriasis	1.12 (1.08-1.16)	<0.001*	1.11 (1.07-1.15)	<0.001*
Control I	1.00		1.00	
Age < 60 years old, men (n = 33,735)				
Psoriasis	1.63 (1.27-2.09)	<0.001*	1.58 (1.23-2.03)	<0.001*
Control I	1.00		1.00	
Age < 60 years old, women (n = 38,080)				

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Psoriasis	1.17 (1.10-1.25)	<0.001*	1.16 (1.09-1.23)	<0.001*
Control I	1.00		1.00	
Age ≥ 60 years old, men (n = 28,505)				
Psoriasis	1.23 (1.10-1.37)	<0.001*	1.21 (1.08-1.35)	0.001*
Control I	1.00		1.00	
Age ≥ 60 years old, women (n = 26,210)				
Psoriasis	1.06 (1.01-1.11)	0.028*	1.05 (1.00-1.10)	0.077
Control I	1.00		1.00	

* Cox-proportional hazard regression model, Significance at P < 0.05

† Stratified model for age, sex, income, and region of residence.

‡ Adjusted model for autoimmune disease, atopic dermatitis, rheumatic arthritis, Charlson Comorbidity Index (except rheumatoid diseases), obesity (BMI), smoking, and alcohol intake histories

Through the stratification analysis by age and sex, all participants in the male and younger-aged female groups were found to have an association between psoriasis and an increased risk of osteoporosis based on the adjusted HRs ($P < 0.001$ for each comparison). In older-aged female participants, the crude HR was 1.06 (95% CI 1.01-1.11, $P = 0.028$) but did not reach statistical significance in the adjusted model.

Study II

The rate of psoriasis was higher in osteoporosis patients (5.1%, 4,007/79,212) than in control II participants (4.1%, 3,254/79,212). The distribution of age, sex, income and region of residence were comparably matched between the osteoporosis and control II groups (each *P*

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= 1.000, Table 1). The rates of autoimmune disease, atopic dermatitis and rheumatoid arthritis were higher in the osteoporosis group than in the control II group ($P < 0.001$ for each comparison).

The adjusted OR of osteoporosis for psoriasis was 1.22 (95% CI = 1.16-1.28, $P < 0.001$, Table 3). In the subgroup analyses, all the adjusted ORs for psoriasis reached statistical significance. The adjusted ORs were higher in males than in females, with the highest OR in younger-aged men (2.36, 95% CI = 1.46-3.82).

Table 3 Crude and adjusted odd ratios (95% confidence interval) of osteoporosis for psoriasis according to age and sex (study II)

Characteristics	Odd ratios for psoriasis			
	Crude†	P-value	Adjusted†‡	P-value
Total participants (n = 158,424)				
Osteoporosis	1.25 (1.19 – 1.31)	<0.001*	1.22 (1.16-1.28)	<0.001*
Control II	1.00		1.00	
Age < 60 years old, men (n = 2,628)				
Osteoporosis	2.42 (1.51-3.89)	<0.001*	2.36 (1.46-3.82)	<0.001*
Control II	1.00		1.00	
Age < 60 years old, women (n = 57,812)				
Osteoporosis	1.31 (1.19-1.43)	<0.001*	1.27 (1.16-1.39)	<0.001*
Control II	1.00		1.00	
Age ≥ 60 years old, men (n = 13,652)				
Osteoporosis	1.34 (1.19-1.52)	<0.001*	1.34 (1.18-1.52)	<0.001*
Control II	1.00		1.00	
Age ≥ 60 years old, women (n = 84,332)				

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Osteoporosis	1.18 (1.11-1.26)	<0.001*	1.16 (1.09-1.23)	<0.001*
Control II	1.00		1.00	

* Conditional logistic regression model, Significance at $P < 0.05$

† Stratified model for age, sex, income, and region of residence.

‡ Adjusted model for autoimmune disease, atopic dermatitis, rheumatic arthritis, Charlson Comorbidity Index (except rheumatoid diseases), obesity (BMI), smoking, and alcohol intake histories

Discussion

We designed 2 studies to clearly analyze the effect between psoriasis and osteoporosis. In study I, we analyzed the occurrence of osteoporosis after psoriasis in the psoriasis and control I groups; in study II, we analyzed the previous history of psoriasis in both the osteoporosis and control II groups. The present study demonstrated that psoriasis increased the risk of osteoporosis (adjusted HR = 1.11, 95% CI = 1.07-1.15). In the subgroup analyses by age and sex, this association was consistently observed in all men and in younger women. Additionally, a previous history of psoriasis was more prevalent in the osteoporosis group (adjusted OR 1.22, 95% CI = 1.16-1.28). This result was consistent in all subgroups according to age and sex. To the best of our knowledge, this study is the first to investigate the relationship between psoriasis and osteoporosis using 2 different study designs.

Several studies with small numbers of patients have investigated the risk of osteoporosis in psoriasis patients, and the results are conflicting. Few studies found an association[21,22], others found no association[23-27], and one study found a higher bone mineral density (BMD) in psoriasis patients than in controls[28]. Few large population-based studies have been reported. In a study with a commercial claims database, the prevalence and

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incidence of osteoporosis in psoriasis were 5.9% and 4.4%, respectively, without a risk analysis[29]. In a case–control study with 7,936 psoriasis patients in Israel, psoriasis was significantly associated with osteoporosis in males (adjusted OR = 1.70, 95% CI = 1.31-2.19) but not in females[9]. Their study did not clearly indicate the subject's inclusion period and the data lacked the date of diagnosis. A cross-sectional study in a US emergency care visit sample demonstrated that patients with psoriasis had significantly higher odds of osteoporosis (2.97, 95% CI = 2.89-3.06)[30]. In a Norwegian study with 2,804 questionnaire-based diagnosed psoriasis patients, no association between psoriasis and osteoporosis was found[31]. However, studies with emergency care visits or questionnaire-based diagnoses may have selection bias. Moreover, only retrospective cohort studies investigated the risk of osteoporosis in psoriasis patients, and previous studies did not match participants for age group, sex, income group, and region of residence.

One study in Taiwan investigated the risk of psoriasis in 17,507 osteoporosis patients[32]. Subjects with osteoporosis had a significantly higher prevalence of previously diagnosed psoriasis (1.50% vs. 0.87%) than that in controls in their study; that prevalence was lower than that of our study (5.1% vs 4.1%). The adjusted OR 1.65 (95% CI = 1.42-1.94) of osteoporosis for psoriasis was similar to that of our study. However, the adjusted OR was higher in female patients (male 1.52, female 1.73) in that study than in our study. The prevalence gap between the two studies might be suggested by environmental factors. Additionally, the previous study did not match participants for CCI score, although the researchers adjusted for various medical histories. The consideration of general condition might be crucial because multimorbidity is very common in adults with osteoporosis[33]. In addition, the previous study lacked classification by BMI. A positive correlation between BMD and BMI was observed in several studies[11,24,34].

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In addition to osteoporosis, a cross-sectional study reported an increased prevalence of osteopenia (pooled OR 2.86; 95% CI 2.70-3.02) and osteomalacia (pooled OR 4.40; 95% CI 2.50-7.74) in patients with psoriasis[30]. BMD levels in psoriatic patients were reported to be located halfway between healthy controls and osteoporosis patients[10,11]. Several mechanisms, such as elevation of inflammatory cytokines, drug use in the treatment of psoriasis and joint immobilization due to dysfunction and joint pain secondary to PsA, are involved in the association of psoriasis with osteoporosis[2]. Another study reported a decrease in BMD only in patients with PsA and not in those with psoriasis[35]. Additionally, a possible association of psoriasis and reduced BMD due to increased TNF-α and IL-6 concentrations was suggested[36]. One study observed that the probability of a patient with psoriasis developing osteopenia/osteoporosis correlates directly with the number of years with the disease[23]. Potentially, psoriasis patients have higher bone resorption markers and bone loss related to inflammatory processes and disability than those in controls[37].

A recent meta-analysis showed that serum 25-OH vitamin D levels were decreased in psoriasis patients compared with healthy controls (standardized mean differences -0.64; 95% CI -1.22 to -0.05) and were negatively associated with disease severity[38]. However, it is argued that a lack of vitamin D might explain the increased risk of osteoporosis in patients with psoriasis[7]. One study found significantly lower serum levels of vitamin D in female psoriasis patients ($P = 0.012$), although it showed no correlation with BMD measurements[22]. A cross-sectional study found that 63% of patients had inadequate vitamin D levels and an inverse correlation between 25-OH vitamin D and the severity of skin involvement[27]. However, there was no statistically significant correlation between 25-OH vitamin D levels and BMD scores. Large-scale clinical studies are needed to evaluate the potential role of vitamin D in psoriasis.

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Few studies have demonstrated a significant correlation between BMI and BMD. In a 2011 study, femur BMD presented a positive correlation with BMI ($r = 0.43$, $P < 0.001$) in psoriasis patients[24]. In a recent study, BMI was higher in psoriasis patients (30.34±6.50 vs 26.10±3.25) and positively correlated with hip T-score ($r = 0.272$, $P = 0.035$)[11]. The high BMI may protect psoriasis patients against osteoporosis[11] or possibly conceal a higher risk of bone mineral loss[34], and further research will be needed to prove this association.

In the stratification analysis, osteoporosis in men with psoriasis was higher than in women with psoriasis, similar to previous studies[9-11]. In study II, the subgroup analysis revealed that a previous history of psoriasis was more prevalent in younger-aged (<60 years) male osteoporosis patients than in elderly (≥60 years) male osteoporosis patients. Additionally, there were higher odds for having a previous history of psoriasis in all subgroups of male osteoporosis patients than any subgroup of female osteoporosis patients. Osteoporosis in women is usually the result of estrogen deficiency, and menopause is a stronger risk factor for osteoporosis than for psoriasis[9]. On the other hand, osteoporosis in men is more commonly the result of a systemic disease, such as psoriasis. Alternatively, as women are more likely to be routinely referred for BMD scans, men diagnosed with osteoporosis are more likely to represent a chronically ill population. Because of the different sex ratios in osteoporosis, studying osteoporosis in psoriasis may have selection bias. However, female sex was associated with lower BMD in psoriasis[22] and in PsA[39]. Further prospective studies are needed to evaluate the association with sex in another database.

Several strengths of the present study include the large sample size, representative national study population, unbiased matching strategy, unbiased confounder adjustment, objective inclusion criteria for both psoriasis and osteoporosis patients, and use of 2 different study designs. This study is the first large prospective study to explore the risk of osteoporosis in patients with psoriasis and a previous history of psoriasis in osteoporosis

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patients. In addition to age and sex, the socioeconomic factors of income and region of residence, a past medical history of autoimmune disease, atopic dermatitis, rheumatic arthritis and CCI score were matched between psoriasis patients and control I groups in study I and between osteoporosis and control II groups in study II. Therefore, loss of information in study I with women with osteoporosis was prevented by study II.

There were several limitations to our study. First, diseases were identified by ICD-10 codes in the claims database. Therefore, coding/mismatching/misclassification errors are possible. Second, although both psoriasis and osteoporosis were defined with multiple objective standards, the severity of these diseases was heterogeneous in this study. Psoriasis and PsA could not be differentiated, and we lacked data on the types, onset, severity index score and medication use. A future study with profound data could delineate the potential predictive factors for osteoporosis in psoriasis patients. Third, although the study outcomes were significant, the differences were minimal, and the risk of osteoporosis was 11% higher in psoriasis patients than in control I participants in the adjusted model in study I; the prevalence of psoriasis was 22% higher in osteoporosis patients than in control II participants in the adjusted model in study II. We did not consider other possible confounding factors, and the results should be carefully interpreted. Finally, the ability to determine definite causality was limited because our study had an observational design. Our study could not confirm the pathophysiological mechanism between psoriasis and osteoporosis, as only ORs and HRs were calculated.

Conclusion

We suggest that psoriasis and osteoporosis might have a bidirectional association. Psoriasis increased the risk of osteoporosis in psoriasis patients compared to control I participants, and a higher previous history of psoriasis was detected in osteoporosis patients than in control II

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participants. Specifically, all males and younger females with psoriasis might have an increased risk of osteoporosis, and the odds of psoriasis were higher in male participants than in female participants. Evaluation and risk management for osteoporosis might be required in psoriasis patients, and future studies should evaluate the underlying mechanisms between these two conditions.

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