Notice of correction 5/23/2019: The name of the second institution listed ("b") in the author affiliations has been corrected.

Risk of Dementia Among Individuals With Psoriasis:
A Nationwide Population-Based Cohort Study in Taiwan

Kuan-Lun Huang, MD[a,b,‡]; Chiung-Chi Yeh, MD[c,‡]; Shu-I Wu, MD, PhD[d,e,f]; Kuo-You Huang, PhD[g]; Yao-Hsu Yang, MD[h,i,j,k]; Ting-Yu Kuo, MS[i]; Hsin-Yi Liang, MD[l,m]; Yi-Chen Lee, PhD[n]; Roger S. McIntyre, MD, PhD[o]; Yena Lee, MS[o]; Jun-Cheng Weng, PhD[n,p]; and Vincent Chin-Hung Chen, MD, PhD[m,n,*]

ABSTRACT

Objective: Psoriasis is a chronic inflammatory disease putatively associated with dementia. However, the epidemiologic evidence of the relationship between psoriasis and dementia has been limited. We used a large national sample to investigate this relationship as well as the association between systemic therapy for psoriasis and incident dementia.

Methods: The cases were identified as a first recorded diagnosis of psoriasis (*ICD-9-CM* codes: 696.0, 696.1, or 696.8) between 1996 and 2013 from Taiwan's National Health Insurance Research Database (NHIRD). Each selected case of psoriasis was compared with 4 sex-, age-, and urbanization-matched comparison subjects. The first diagnosis of dementia (*ICD-9-CM* codes: 290.0–290.4, 294.1–294.2, 331.0–331.2, or 331.82) that covered vascular and nonvascular subtypes until the end of 2013 was tracked in both groups. Cox regression analyses and a competing risk model were applied to evaluate the risk, adjusting for sex, urbanization, age, hypertension, diabetes, heart disease, hyperlipidemia, stroke, and depression. The association between systemic therapy and incidence of dementia in the psoriasis group was examined in further stratified analyses.

Results: Overall, 3,820 patients with psoriasis and 15,280 comparisons were identified. After adjustment, a significantly higher risk of dementia was identified in the psoriasis group than in the comparison group (adjusted hazard ratio [aHR] = 1.23; 95% CI, 1.06–1.42). A significant association between psoriasis and dementia was identified for nonvascular dementia (aHR = 1.25, 95% CI, 1.07–1.45) but not for vascular dementia (aHR = 1.27, 95% CI, 0.83–1.93). Receiving systemic therapy for psoriasis for more than 90 days significantly reduced the risk of developing dementia compared with no systemic therapy (aHR = 0.66; 95% CI, 0.45–0.97). Compared with those who received no systemic therapy, the patients who received disease-modifying antirheumatic drugs and/or biologics had a significantly lower risk of dementia incidence (aHR = 0.69; 95% CI, 0.50–0.97), which was not the case in patients who received only phototherapy.

Conclusions: Individuals with psoriasis have a significantly higher incidence of dementia, particularly the nonvascular type. Systemic therapy might be protective in preventing dementia in patients with psoriasis.

J Clin Psychiatry 2019;80(3):18m12462

To cite: Huang K-L, Yeh C-C, Wu S-I, et al. Risk of dementia among individuals with psoriasis: a nationwide population-based cohort study in Taiwan. *J Clin Psychiatry.* 2019;80(3):18m12462.

To share: https://doi.org/10.4088/JCP.18m12462

[a]Tsaotun Psychiatric Center, Ministry of Health and Welfare, Nantou, Taiwan
[b]National Taichung University of Science and Technology, Taichung, Taiwan
[c]Taichung Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taiwan
[d]Department of Medicine, Mackay Medical College, Taipei, Taiwan
[e]Department of Audiology and Speech Language Pathology, Mackay Medical College, Taipei, Taiwan
[f]Section of Psychiatry, Mackay Memorial Hospital, Taipei, Taiwan
[g]Department of Speech Language Pathology and Audiology, Chung Shan Medical University, Taichung, Taiwan
[h]Department of Traditional Chinese Medicine, Chang Gung Memorial Hospital, Chiayi, Taiwan
[i]Center of Excellence for Chang Gung Research Datalink, Chang Gung Memorial Hospital, Chiayi, Taiwan
[j]Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health, Taipei, Taiwan
[k]School of Traditional Chinese Medicine, College of Medicine, Chang Gung University, Taoyuan, Taiwan
[l]Department of Child Psychiatry, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan
[m]School of Medicine, Chang Gung University, Taoyuan, Taiwan
[n]Department of Psychiatry, Chang Gung Memorial Hospital, Chiayi, Taiwan
[o]Department of Psychiatry and Pharmacology, Mood Disorders Psychopharmacology Unit, University Health Network, University of Toronto, Ontario, Canada
[p]Department of Medical Imaging and Radiological Sciences, Chang Gung University, Taoyuan, Taiwan
‡Doctors Yeh and K-L Huang contributed equally to this article.
**Corresponding author:* Vincent Chin-Hung Chen, MD, PhD, Department of Psychiatry, Chang Gung Memorial Hospital, Chiayi, Taiwan, No 6, Sec. West, Jiapu Rd, Puzih-City, Chiayi County, Taiwan (hjcch@yahoo.com.tw).

Dementia is prevalent[1,2] and is one of the most common causes of disability in individuals over age 65.[3] According to the report[2] of the World Health Organization, the prevalence of dementia for East Asia was 6.99% in 2012. In the analysis from the Taiwan Alzheimer Disease Association in 2011, the prevalence of dementia in individuals older than 65 years old was 7.93%.[4] Several risk factors are related to dementia, including age, cardiovascular disease, stroke, depression, and lifestyle. Activated inflammatory systems have been identified as a risk factor for dementia.[5,6] Research suggests that controlling for vascular and other risk factors during midlife and early old age is beneficial and may attenuate the risk for late-life dementia.[1,7] For example, 1 meta-analysis[7] documented that effective interventions, such as antihypertensive medications, a healthy dietary pattern, cognitive activity, and physical activity, may decrease the incidence of dementia.

Psoriasis is a chronic and recurring inflammatory disease of the skin, and it is both multifactorial and polygenic in origin. Emerging and replicated evidence suggests that individuals with psoriasis have an impairment of cognitive performance,[8,9] and psoriasis poses a genetic overlap with dementia.[10,11] Moreover, 1 retrospective cohort study[12] reported that individuals admitted to the hospital due to

Clinical Points

- In this population-based cohort study in Taiwan, patients with psoriasis had a significantly increased risk of dementia.
- This study showed a positive association between psoriasis and nonvascular dementia.
- Prescriptions of systemic therapy for psoriasis were associated with a reduced risk, particularly in patients who received a longer duration of therapy with disease-modifying antirheumatic drugs and/or biologic treatment.

psoriasis had a higher rate ratio for dementia. However, other studies[13,14] have indicated that patients with psoriasis had a lower risk of developing dementia. Thus, studies investigating the association between psoriasis and dementia remain controversial.

Psoriasis is frequently comorbid with several physical and mental disorders, including psoriatic arthritis, diabetes mellitus, metabolic syndrome, cardiovascular disease, obesity, ulcerative colitis, Crohn's disease, nonalcoholic fatty liver disease, psychiatric illness, malignancy, chronic obstructive pulmonary disease, sleep apnea, and major depressive disorder.[15] Individuals with serious psoriasis have also been noted to have a higher mortality rate due to cardiovascular causes and dementia than individuals without psoriasis.[16] Systemic therapies for psoriasis, such as tumor necrosis factor (TNF) antagonists, are beneficial for psoriasis,[17] psoriatic arthritis, and depression[18] and also reduce cardiovascular risk.[19] Pilot data have suggested potential disease modifying benefits of TNF-α inhibitor in Alzheimer's disease.[20] However, psoriasis remains undertreated given that as many as 40% of patients with moderate to severe psoriasis do not receive treatment, as found in a 2007 study from the National Psoriasis Foundation survey.[21] The foregoing lines of evidence provided the impetus for us to (1) evaluate the incidence of dementia in cases with psoriasis using a large, nationwide database and (2) examine whether systemic therapy for psoriasis attenuates the risk for dementia.

METHODS

Study Design

This research was structured as a nationwide retrospective cohort study. The study was based on the National Health Insurance Research Database (NHIRD), which was extracted from the National Health Insurance (NHI) program in Taiwan. The NHI program is a national mandatory health insurance system initiated in 1995 that is run by the Taiwan government and covers all medical services. The NHI includes over 99.0% of all residents in Taiwan. The NHIRD includes comprehensive information regarding the enrollees, such as demographic data, disease diagnoses, dates of outpatient and emergency visits, hospitalizations, and prescriptions or interventions administered at each clinical visit. The information included in the NHIRD is anonymized to safeguard patient privacy. The National Health Research Institute divided a representative selection of 1,000,000 NHI-insured individuals using a systematic random sampling method and composed the Longitudinal Health Insurance Database (LHID).[22] The age and sex distributions of the LHID, the NHIRD, and the general population in Taiwan are not significantly different from each other ($\chi^2_1 = 0.008$, $P = .931$).[22] Diseases in the NHIRD were diagnosed and recorded using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*). Previous studies[23–25] have demonstrated that the validity and accuracy between NHIRD claim data of major diseases, such as myocardial infarction and ischemic stroke, and actual medical records are moderate to substantial (κ values between 0.55 and 0.95; positive predictive values between 0.5 and 1.0). The substantial concordance between claim records on medication use in the NHIRD and patient self-reports (κ value of 0.64) has also been validated.[26]

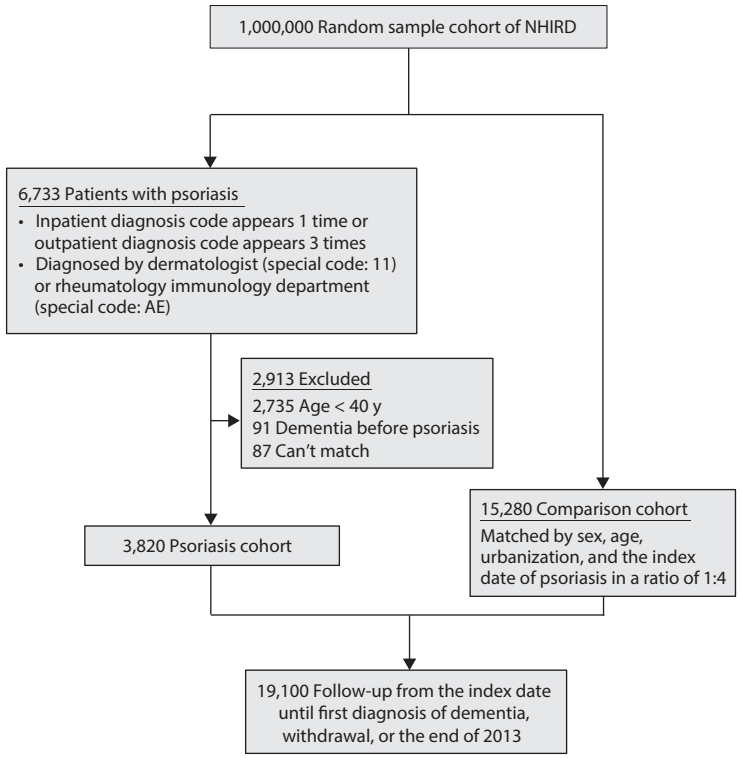
We defined the patients with psoriasis as having at least 1 inpatient or 3 outpatient diagnoses of psoriasis on the basis of recorded *ICD-9-CM* codes (696.0, 696.1, or 696.8) given by a rheumatologist or dermatologist between January 1, 1996, and December 31, 2013. The day of first psoriasis diagnosis was the index date. To examine the relationship between psoriasis and dementia, our study excluded individuals younger than 40 years owing to an insufficient follow-up period for dementia development. Four comparison subjects per study subject, matched for sex, age within a year, level of urbanization, and the index date, were randomly selected from the remaining sample (Figure 1).

Both the psoriasis and control groups were followed for at least 1 inpatient or 3 outpatient recorded diagnoses of dementia (*ICD-9-CM* codes 290.0–290.4, 294.1–294.2, 331.0–331.2, or 331.82) as the main outcome.[27] We subdivided individuals with vascular dementia (290.4) and nonvascular dementia (290.0–290.3, 294.1–294.2, 331.0–331.2, or 331.82). We did not differentiate the patients with Alzheimer's disease because the diagnosis of dementia might not be well coded in the clinical situation, eg, coding Alzheimer's disease as senile dementia (*ICD-9-CM* codes 290.0–290.3) or unspecified dementia (294.1–194.2). We excluded from the analysis individuals who had a dementia diagnosis prior to the index date.

Demographic variables, such as sex, age, and comorbidities, including hypertension (*ICD-9-CM* codes 401.0, 401.1, 401.9, 402–405, or 437.2), heart disease (410–429), diabetes (250), stroke (430–438), hyperlipidemia (272.0–272.4), and depressive disorder (296.2–296.3, 300.4, or 311), were considered as potential confounders.[8,9] All comorbidities were defined as having the previously described medical diagnosis at least once from inpatient care data or on at least 3 occasions from outpatient care data during the entire study period.

The secondary outcome of interest included potential associations between exposure to systemic treatment for psoriasis and the risk of dementia. Information regarding systemic treatment was obtained from the NHIRD by NHI

Figure 1. Flowchart of Data Collection in This Study



Abbreviation: NHIRD = National Health Insurance Research Database.

Table 1. Characteristics of Psoriasis and Comparison Cohorts

Characteristic	Psoriasis Cohort (n = 3,820) n	%	Comparison Cohort (n = 15,280) n	%	*P* Value
Sex					1.0000
Female	1,391	36.4	5,564	36.4	
Male	2,429	63.6	9,716	63.6	
Age at entry, y					1.0000
40–49	1,230	32.2	4,920	32.2	
50–59	1,033	27.0	4,132	27.0	
60–69	761	19.9	3,044	19.9	
≥ 70	796	20.8	3,184	20.8	
Level of urbanization of residence					1.0000
1 (city)	1,243	32.5	4,972	32.5	
2	1,736	45.5	6,944	45.5	
3	597	15.6	2,388	15.6	
4 (village)	244	6.4	976	6.4	
Associated diseases[a]					
Hypertension	2,217	58.0	7,850	51.4	< .0001
Heart disease	1,677	43.9	5,822	38.1	< .0001
Diabetes	1,265	33.1	4,141	27.1	< .0001
Hyperlipidemia	1,702	44.6	5,642	36.9	< .0001
Stroke	849	22.2	2,975	19.5	< .0001
Depression	460	12.0	1,450	9.5	< .0001
Systemic therapy[b]					< .0001
Without systemic therapy	2,518	65.9	…		
With systemic therapy	1,302	34.1	…		
Any dementia[c]	245	6.4	817	5.4	.0101
Vascular dementia	29	0.8	91	0.6	.0347
Nonvascular dementia	216	5.7	726	4.8	
Follow-up period, y, mean (SD)	7.32 (4.52)		7.20 (4.50)		.1288

[a]Whole study period, from the index date to the end of follow-up.
[b]Systemic treatment for psoriasis prescribed on or after the index date.
[c]Dementia diagnosed after the index date.
Symbol: … = not applicable.

drug codes and procedure codes. Systemic therapies for psoriasis, including disease-modifying antirheumatic drugs (DMARDs), phototherapy, and biologic therapy (TNF inhibitors), were considered as exposure variables. The DMARDs included methotrexate, cyclosporine, acitretin, azathioprine, mycophenolate mofetil, leflunomide, and sulfasalazine. The biologics available for the treatment of psoriasis in Taiwan include etanercept, adalimumab, golimumab, and ustekinumab. Exposure to phototherapy included UV-A or UV-B phototherapy. The "prescription of systemic therapy" was included only if the systemic therapy prescribed was no earlier than the index date. We performed a subanalysis with systemic therapy in the psoriasis cohort by 2 models of classification. In model 1, we analyzed the risk of dementia in 3 different subgroups divided by the cumulative exposure period of systemic therapy: (1) the subgroup without systemic therapy, (2) the subgroup that received systemic treatment for fewer than 90 days, and (3) the subgroup that received systemic therapy for 90 days or longer. In model 2, we grouped the patients who received systemic therapy into those receiving DMARDs and/or biologics and those receiving only phototherapy to compare with those without systemic therapy.

To ensure the accuracy of the results, we conducted 2 sensitivity analyses by the different definitions of diagnosis. First, we conducted a sensitivity analysis by defining the first inpatient code or the third outpatient code of psoriasis as the index date. Second, we performed another sensitivity analysis by only including the inpatient codes of both psoriasis and dementia diagnoses.

Statistical Analysis

Distributions for categorical variables between the psoriasis and control groups were described and compared by the χ^2 test. The follow-up period of this study was between January 1, 1996, and December 31, 2013. Survival analysis was applied to compare the risk of dementia from the index date until the endpoints, which included the date of dementia diagnosis, resignation from the registry or the last day of 2013 (ie, the end of the follow-up). Cox regression analysis with a competing risk model was performed to evaluate the relationship between psoriasis and dementia, as well as adjusting for covariates, including sex, age, residence, hypertension, heart disease, diabetes, hyperlipidemia, stroke, and depression. The time variable used for the Cox regression analysis was the interval (years) between the index date and the endpoints. This study was performed in accordance with the STROBE guideline (https://strobe-statement.org). SAS version 9.4 software (SAS Institute Inc, Cary, North Carolina) was used to analyze the data.[28] A *P* value of < .05 and a confidence interval (CI) that did not contain 1 were considered statistically significant.

Table 2. Cox Regression Analysis of Dementia Incidence

		Unadjusted Hazard Ratio			Adjusted Hazard Ratio[a]		
Variable	n	HR	95% CI	*P* Value	aHR	95% CI	*P* Value
Psoriasis							
Comparison cohort	15,280	1.00			1.00		
Psoriasis cohort	3,820	1.21	1.05–1.40	.0085	1.23	1.06–1.42	.0058
Sex							
Female	6,955	1.00			1.00		
Male	12,145	0.93	0.83–1.06	.2827	0.80	0.70–0.90	.0004
Age at entry, y							
40–49	6,150	1.00			1.00		
50–59	5,165	3.99	2.59–6.15	<.0001	3.86	2.50–5.96	<.0001
60–69	3,805	16.76	11.36–24.72	<.0001	15.43	10.35–23.00	<.0001
≥70	3,980	47.14	32.32–68.75	<.0001	41.16	27.76–61.03	<.0001
Level of urbanization of residence							
1 (city)	6,215	0.81	0.63–1.04	.1033	1.10	0.85–1.43	.4811
2	8,680	0.93	0.73–1.20	.5853	1.21	0.94–1.56	.1402
3	2,985	1.11	0.85–1.46	.4395	1.16	0.88–1.53	.2865
4 (village)	1,220	1.00			1.00		
Hypertension[b]							
No	9,033	1.00			1.00		
Yes	10,067	2.63	2.28–3.04	<.0001	1.01	0.85–1.20	.8928
Heart disease[b]							
No	11,601	1.00			1.00		
Yes	7,499	2.33	2.06–2.64	<.0001	0.92	0.80–1.06	.2399
Diabetes[b]							
No	13,694	1.00			1.00		
Yes	5,406	1.52	1.35–1.72	<.0001	1.04	0.91–1.19	.5427
Hyperlipidemia[b]							
No	11,756	1.00			1.00		
Yes	7,344	1.06	0.94–1.20	.3342	0.87	0.76–0.99	.0338
Stroke[b]							
No	15,276	1.00			1.00		
Yes	3,824	3.39	3.00–3.82	<.0001	1.62	1.42–1.85	<.0001
Depression[b]							
No	17,190	1.00			1.00		
Yes	1,910	3.39	3.00–3.82	<.0001	1.62	1.42–1.85	<.0001

[a]Adjusting for sex, age, level of urbanization of residence, hypertension, heart disease, diabetes, hyperlipidemia, stroke, and depression.
[b]Whole study period, from the index date to the end of follow-up.
Abbreviations: aHR = adjusted hazard ratio, CI = confidence interval, HR = hazard ratio.

RESULTS

Subject Characteristics

From 1996 to 2013, we followed 6,733 individuals with psoriasis diagnosed by a dermatologist or a rheumatologist. Subjects aged less than 40 years (n = 2,735) or with a history of dementia (n = 91) were excluded. Of the patients with psoriasis, 87 patients had no matched controls and were excluded. Finally, 3,820 patients with psoriasis and 15,280 control subjects were enrolled in the study via 1-to-4 matching by sex, age, level of urbanization, and the index date of psoriasis (Figure 1). Of the total participants, the mean (SD) age at entry into the study was 57.63 (12.17) years. Men comprised 63.6% of the whole study cohort. The mean (SD) follow-up intervals were 7.32 (4.52) years for the psoriasis group and 7.20 (4.50) years for the comparison group. The proportions of hypertension, heart disease, diabetes, hyperlipidemia, stroke, or depressive disorder before the end of follow-up were greater in the psoriasis group than in the control group. Of the total 19,100 subjects, 1,062 subjects were diagnosed with dementia during the follow-up period: 245 subjects (6.4%) in the psoriasis group and 817 subjects (5.4%) in the comparison group. The baseline sociodemographic and clinical information is shown in Table 1.

Association Between Psoriasis and Dementia

The Cox regression analysis was performed in both groups to assess the risks of having dementia. Table 2 summarizes the results. The psoriasis group had a greater risk of dementia than the control group after 7.32 years of the follow-up period. The psoriasis group continued to have a significantly higher risk of dementia than the control group (unadjusted hazard ratio [HR] = 1.21, 95% CI, 1.05–1.40; adjusted hazard ratio [aHR] = 1.23, 95% CI, 1.06–1.42) after adjusting for several confounders, including sex, level of urbanization, age, hypertension, heart disease, diabetes, hyperlipidemia, stroke, and depression. In addition, female sex, older age, and stroke were found to be related to an increased incidence of dementia. Hyperlipidemia was not significantly related to dementia in the unadjusted model; however, it had a negative association with the incidence of dementia after adjusting for confounders.

We further examined the associations of psoriasis and vascular or nonvascular dementia separately (Table 3). Among the 1,062 cases with dementia, 120 cases had a diagnosis of vascular dementia, and 942 cases had nonvascular dementia. The individuals with psoriasis had a significantly greater risk for nonvascular dementia (aHR = 1.25; 95% CI, 1.07–1.46), but not vascular dementia (aHR = 1.27; 95% CI, 0.83–1.93), than the control group after adjusting for age, sex, and relevant comorbidities.

The result obtained from the sensitivity analysis by defining the date of the first inpatient code or the third outpatient code of psoriasis was similar to the main result. The patients with psoriasis were associated with a higher risk of dementia (aHR = 1.19; 95% CI, 1.02–1.38). Another sensitivity analysis, which identified diagnosis only from hospitalization, indicated a higher dementia risk in the psoriasis group (aHR = 7.52; 95% CI, 1.35–41.87); however, there were very small numbers of events (2/436 in the comparison cohort and 2/109 in the psoriasis cohort).

Association Between Systemic Therapy for Psoriasis and Dementia

Of the 3,820 subjects in the psoriasis group, 1,302 subjects (34.1%) had received systemic therapy during the follow-up period. The secondary analyses involving systemic treatment within the psoriasis group are described in Table 4. In model 1, the individuals with psoriasis who received systemic therapy for 90 days or longer had

Table 3. Cox Regression Analysis of Incidence of Dementia

	Any Dementia				Vascular Dementia				Nonvascular Dementia			
Group	n	aHR[a]	95% CI	*P* Value	n	aHR[a]	95% CI	*P* Value	n	aHR[a]	95% CI	*P* Value
Comparison cohort	817	1.00			91	1.00			726	1.00		
Psoriasis cohort	245	1.23	1.06–1.42	.0058	29	1.27	0.83–1.93	.2749	216	1.25	1.07–1.46	.0058

[a]Adjusted for sex, age, level of urbanization of residence, hypertension, heart disease, diabetes, hyperlipidemia, stroke, and depression.
Abbreviations: aHR = adjusted hazard ratio, CI = confidence interval.

Table 4. Cox Regression Analysis of Dementia Incidence Among Psoriasis Cohort According to Systemic Therapy

			Unadjusted Hazard Ratio			Adjusted Hazard Ratio[a]		
Models	n	Dementia (n)	HR	95% CI	*P* Value	aHR	95% CI	*P* Value
Model 1								
Without systemic therapy	2,518	177	1.00			1.00		
Systemic therapy[b] < 90 d	577	35	0.76	0.53–1.09	.1298	0.82	0.57–1.18	.2795
Systemic therapy[b] ≥ 90 d	725	33	0.47	0.33–0.69	< .0001	0.66	0.45–0.97	.0323
Model 2								
Without systemic therapy	2,518	177	1.00			1.00		
DMARDs and/or biologics[b]	929	41	0.51	0.36–0.71	< .0001	0.69	0.50–0.97	.0321
Phototherapy[b, c]	373	27	0.78	0.52–1.16	.2214	0.80	0.54–1.19	.2755

[a]Adjusted for sex, age, level of urbanization of residence, hypertension, heart disease, diabetes, hyperlipidemia, stroke, and depression.
[b]Systemic therapy for psoriasis prescribed on or after the index date.
[c]Without receiving DMARDs or biologics.
Abbreviations: aHR = adjusted hazard ratio, CI = confidence interval, DMARDs = disease-modifying antirheumatic drugs, HR = hazard ratio.

a significantly lower incidence of dementia (aHR = 0.66; 95% CI, 0.45–0.97) than those without systemic therapy. However, no significant difference was identified in the prevalence of dementia between the patients with psoriasis who received systemic therapy for less than 90 days and those without systemic therapy. In model 2, compared with patients who received no systemic therapy, the patients who received DMARDs and biologics had a significantly lower risk of dementia incidence (aHR = 0.69; 95% CI, 0.50–0.97), but those who received only phototherapy did not.

DISCUSSION

Our study provides empirical support for the association between psoriasis and dementia within a large nationwide sample. After adjusting for sex, age, level of urbanization, and several comorbidities, we found that patients with psoriasis had a greater risk of dementia. Further investigation into dementia subtypes indicated there was a significant association between psoriasis and nonvascular dementia, but not vascular dementia. After adjustment, the elevated risk for dementia was significantly decreased in the subgroup of psoriasis patients who received systemic therapy for 90 days or longer and in the subgroup of patients who received DMARDs and/or biologics.

Psoriasis and Dementia

Our results of increased incident dementia following a diagnosis of psoriasis are consistent with previous studies[8,9,12,16] that reported an association between psoriasis and dementia. In a retrospective cohort study using English National Hospital Episode Statistics, Wotton and colleagues[12] reported a rate ratio of dementia in patients with psoriasis within a similar range as in our study (aHR = 1.29; 95% CI, 1.25–1.34). It is noted that admissions due to vascular dementia were significantly higher relative to Alzheimer's disease in that study, while in our study, the converse was true after adjusting for potential confounders. The contradictory findings are potentially due to inaccuracies in coding in some databases, eg, coding Alzheimer's disease as unspecified dementia.[12] Consequently, we divided dementia into 2 subgroups of vascular dementia and nonvascular dementia, rather than Alzheimer's disease. In addition, the numbers of patients with vascular dementia were small (29 individuals in the psoriasis cohort; 91 individuals in the comparison cohort). It is likely that the association between psoriasis and vascular dementia was underestimated in our study. Further investigations with a larger cohort are required. Second, we included a diagnosis of dementia identified from both hospitalization and outpatient visits, whereas the main outcome of the prior report was subsequent admissions with the diagnosis of dementia and did not include a diagnosis from an outpatient visit.[12] As individuals with vascular dementia are hospitalized more than patients with Alzheimer's disease,[29] differences might occur because of the different sources of patient recruitment. We carried out a sensitivity analysis that included only an inpatient code of diagnosis; however, it resulted in a small number of outcomes. Therefore, we could not perform a further analysis of the different types of dementia.

Dementia has a long preclinical phase. The incidence of dementia approximately doubles with every 5 years in elder age.[2] Given that, in our study, the mean age was approximately 58 years at entry with the mean follow-up

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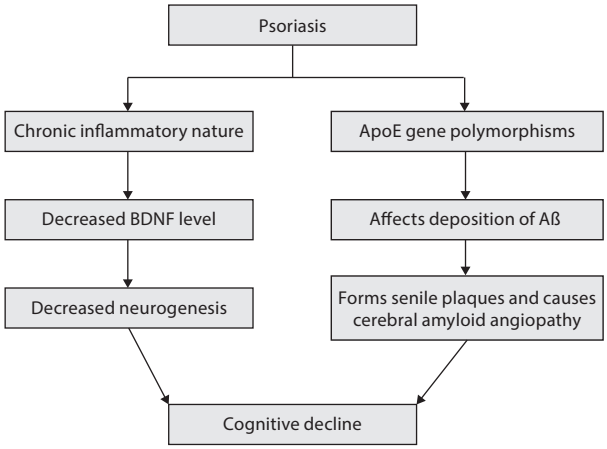
Figure 2. Probable Mechanisms for the Relationship Between Psoriasis and Dementia



Abbreviation: ApoE = apolipoprotein E, BDNF = brain-derived neurotrophic factor.

period approximately 7 years, it is likely that we did not identify some patients who developed dementia after the end of the follow-up. Thus, the true risk of dementia was likely to be underestimated.

The potential mechanisms for the relationship between psoriasis and dementia might be the chronic inflammatory nature of psoriasis that can lead to cognitive decline (Figure 2).[5] Previous studies[5,30] have reported that higher inflammatory cytokines, such as interleukin-6, TNF-α, and C-reactive protein, are related to a higher incidence of dementia. These inflammatory mediators in patients with psoriasis were also reported to be correlated with the activity of psoriasis.[31] The mechanism that underlies the effects of inflammation on neurogenesis may be reductions in the production and function of plasma brain-derived neurotrophic factor (BDNF) via inflammatory cytokines.[32] For example, Brunoni and colleagues[33] have reported decreased BDNF plasma levels in patients with psoriasis. The decrease in BDNF has been associated with age-related decreases in neurogenesis and cognitive decline.[34] Another potential mechanism might be the genetic background that links psoriasis to Alzheimer's disease.[10,11] Increased evidence has shown that apolipoprotein E gene polymorphisms are related to both psoriasis and dementia.[11,35]

Few studies have investigated the impact of systemic therapy on the prevalence of developing dementia among individuals with psoriasis. Our result that approximately 34% of the psoriasis patients received systemic therapy was higher than that in previous studies.[36,37] The explanation might be that we included more comprehensive systemic therapy modalities. In our study, we found a 25.7% decrease in the incidence of dementia after receiving systemic therapy, particularly for patients who received more than 90 days of systemic therapy. When we divided the patients who underwent systemic therapy by treatment modalities, the patients who received DMARDs and/or biologics had a 31% reduction in dementia incidence. However, there was no significant difference between the patients who received systemic therapy with only phototherapy and those who received no systemic therapy (Table 4). The plausible mechanism for the reduced risk of subsequent dementia might be due to decreased chronic systemic inflammations by anti-inflammatory medications.[5,30,31] Further studies evaluating the effect of systemic therapy for psoriasis on neurocognitive outcomes are required.

Strengths and Limitations

The strengths of this study were the nationwide representative sample and the longitudinal dataset of sufficient size for the investigation of the association between psoriasis and dementia. The power for this sample size is within an acceptable range (power = 0.9831), and the results are trustworthy.[38] Furthermore, we were able to explore the impacts of systemic therapy for psoriasis and the incidence of developing dementia.

However, there are several limitations. First, the database may contain coding errors. In the previous studies,[23–25] the validity between the claim data of the *ICD-9-CM* diagnosis in the NHIRD and the actual medical records was only "moderate to substantial" and was not perfect. Furthermore, the validity of the *ICD-9-CM* diagnosis and therapy for psoriasis and dementia in the NHIRD has not previously been examined. To improve the accuracy of our definition of diagnosis, we used a strict algorithm to evaluate claim data, requiring at least 1 inpatient diagnosis or 3 outpatient diagnoses, and we only included patients with psoriasis validated by a rheumatologist or dermatologist. In addition, we measured the 1-year prevalence of dementia and psoriasis in the NHIRD during 2015 by the same definition of diagnosis in this study. The 1-year prevalence of any dementia among individuals aged 65 years and older was 7.73%, and the 1-year prevalence of psoriasis was 0.54%. These rates are comparable to those in previous epidemiologic studies.[2,39,40] Second, no laboratory results were included in the NHIRD; therefore, it was not possible to directly evaluate the severity, involvements, and complications of psoriasis in our study. It is possible that receiving systemic therapy indicates more severe psoriasis. This issue may generate a selection bias, which might underestimate the effect of systemic therapy on reducing the risk of developing dementia. However, the result was still significant in our study. Third, it might be possible that these systemic therapy agents were prescribed for treating other diseases, such as rheumatic arthritis, or for chemotherapy. However, we defined the exposure status for systemic therapy as no earlier than the index date of the first diagnosis of psoriasis among our study subjects with the main diagnosis of psoriasis. Thus, we believe the majority of prescriptions were for psoriasis treatment. Finally, this study lacked data on other potential covariates, such as genetic factors, family history of dementia, body mass index, smoking status, alcohol consumption, or other health habits of each patient. These factors may be important confounders that may contribute to dementia.

CONCLUSION

Our findings support a positive association between psoriasis and dementia based on our analysis of a national health insurance dataset. Psoriasis was found to be independently related to nonvascular dementia but not vascular dementia. However, the association between psoriasis and vascular dementia is likely to be underestimated owing to the small number of events. More importantly, systemic therapy for psoriasis, particularly treatment for more than 90 days and receiving DMARDs and/or biologic therapy, may help reduce the incidence of subsequent dementia following psoriasis. Given the increased incidence of dementia and its negative impacts on quality of life, it is imperative to identify potential factors that could prevent cognitive deterioration. Receiving systemic therapy in the treatment of psoriasis may not only reduce psoriasis severity, but also help prevent future neurocognitive adverse events. Future explorations for the underlying mechanism are warranted.

Submitted: July 14, 2018; accepted December 27, 2018.

Published online: May 14, 2019.

Potential conflicts of interest: All authors declare that they have no conflicts of interest.

Funding/support: The authors are thankful that this research was supported by the Health Information and Epidemiology Laboratory (CLRPG6G0042), Chang Gung Memorial Hospital, Chiayi, Taiwan.

Role of the sponsor: The funder had no role in the study design, data collection, and analysis.

Institutional review board approval: The study was approved by the institutional review board of the Chang Gung Medical Foundation (IRB Number: 104-7528B).

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