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Table SI. Utilized proxy codes ^a

Description	ICD-10-CM codes
<i>Study population</i>	
Prurigo nodularis	ICD-10-CM: L28.1
<i>Outcome: Autoimmune diseases</i>	
Ankylosing spondylitis	ICD-10-CM: M45
Rheumatoid arthritis	ICD-10-CM: M05
Systemic lupus erythematosus	ICD-10-CM: M32
Sjögren syndrome	ICD-10-CM: M35.0
Psoriasis	ICD-10-CM: L40
Crohn disease	ICD-10-CM: K50
Ulcerative colitis	ICD-10-CM: K51
Dermatopolymyositis	ICD-10-CM: M33
<i>Other diseases or covariates</i>	
Neoplasms	ICD-10-CM: C00-D49
Diabetes mellitus	ICD-10-CM: E08-E13
Hypertension	ICD-10-CM: I10
Hyperlipidemia	ICD-10-CM: E78.5
Chronic kidney disease	ICD-10-CM: N18
Cerebrovascular diseases	ICD-10-CM: I60-I69
Vitamin D deficiency	ICD-10-CM: E55
Persons with potential health hazards related to socioeconomic and	ICD-10-CM: Z55-Z65

psychosocial circumstances	
Mental and behavioral disorders due to psychoactive substance use	ICD-10-CM: F10-F19
Hidradenitis Suppurativa	ICD-10-CM: L73.2
Rosacea	ICD-10-CM: L71
Alopecia areata	ICD-10-CM: L63
Encounter for general examination	ICD-10-CM: Z00
<i>Medications</i>	RxNorm/VA codes
Glucocorticoids	VA: HS051
Antidepressants	VA: CN600
Methotrexate	RxNorm: 6851
Dupilumab	RxNorm: 1876376
Corticosteroids for systemic use	ATC code: H02
Pimecrolimus	RxNorm: 321952
Tacrolimus	RxNorm: 42316

^aICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification;

Table SII. Description of all applied sensitivity analysis models

Models	Description	Corresponding table
Applying different definitions of prurigo nodularis (PN)		
Algorithm 1	Only patients with the record of greater than 2 PN diagnosis were included as PN group in this model.	eTable 3
Algorithm 2	Only patients diagnosed PN with more than 2 visit records and was limited to have at least one inpatient visit were included as PN group in this model.	
Algorithm 3	Only patients diagnosed PN with more than 2 visit records and with the record of systemic corticosteroid, pimecrolimus or tacrolimus were included as PN group in this model.	
Applying different follow-up time after index date		
5 years /10 years /15 years after index date	Only the outcome event occurs within the set follow-up time will be counted. In all sub-analyses, the wash-out period was set as 3 months.	eTable 4
Applying different wash-out period after index date		
12 months/24 months/36 months after index date	Outcome event occurs within the set wash-out period will be excluded from further analysis. In all sub-analyses, the follow-up period was set as 15 years.	eTable 5
Applying different matching covariates		
Crude model	Analysis did not undergo propensity score matching.	eTable 6
Matching model 1	Matching covariates include age at index, sex, race, socioeconomic status and substance abuse status.	

Matching model 2	Matching covariates include age at index, sex, race, comorbidity status (including diabetes mellitus, hypertension, hyperlipidemia, cerebrovascular diseases, vitamin D deficiency, chronic kidney disease)	
Excluding atopic dermatitis from both PN and control group		
To avoid potential confounding bias caused by atopic dermatitis, which is common in PN, patients with any records of being diagnosed of atopic dermatitis will be excluded from PN group and control group.		eTable 7
Applying different active comparators		
Comparing with hidradenitis suppurativa patients/ comparing with comparing with alopecia areata patients/ comparing with rosacea patients/	The control cohort in each sub-analysis will consist of the respective inflammatory skin diseases (hidradenitis suppurativa, alopecia areata, rosacea) that has been reported to be associated with autoimmune disorders. In all sub-analyses, the follow-up period was set as 15 years and the wash-out period was set as 3 months.	eTable 8

Table SIII. Sensitivity analysis of applying different definitions in PN patients

Outcomes	Algorithm 1			Algorithm 2			Algorithm 3		
	PN cohort (%) ^a	Control cohort (%)	HR (95% CI) ^a	PN cohort (%) ^a	Control cohort (%)	HR (95% CI) ^a	PN cohort (%) ^a	Control cohort (%)	HR (95% CI) ^a
Ankylosing spondylitis	10 (<0.1)	10 (<0.1)	1.06 (0.38, 2.94)	12 (0.3)	10 (<0.1)	2.97 (0.96, 9.23)	20 (0.2)	15 (<0.1)	1.40 (0.72, 2.74)
Rheumatoid arthritis	10 (<0.1)	10 (<0.1)	1.05 (0.35, 3.14)	10 (<0.1)	10 (<0.1)	1.11 (0.40, 3.07)	22 (0.2)	21 (0.2)	1.07 (0.59, 1.94)
Systemic lupus erythematosus	27 (0.4)	10 (<0.1)	3.89 (1.69, 8.94)	30 (0.7)	11 (0.3)	2.79 (1.40, 5.57)	56 (0.5)	31 (0.3)	1.91 (1.23, 2.97)
Sjögren syndrome	38 (0.6)	23 (0.4)	1.53 (0.91, 2.57)	30 (0.7)	18 (0.4)	1.62 (0.90, 2.91)	77 (0.7)	40 (0.3)	2.00 (1.36, 2.92)
Psoriasis	129 (2.1)	41 (0.7)	3.12 (2.20, 4.44)	110 (2.5)	24 (0.6)	4.73 (3.04, 7.36)	263 (2.3)	74 (0.6)	3.81 (2.94, 4.93)
Crohn disease	10 (<0.1)	11 (0.2)	0.82 (0.34, 1.97)	10 (<0.1)	12 (0.3)	0.52 (0.20, 1.40)	22 (0.2)	29 (0.3)	0.74 (0.42, 1.32)
Ulcerative colitis	21 (0.3)	21 (0.3)	0.99 (0.54, 1.82)	15 (0.3)	12 (0.3)	1.27 (0.59, 2.72)	35 (0.3)	32 (0.3)	1.15 (0.71, 1.86)

PN, prurigo nodularis; 95% CI, 95% confidence interval; HR, hazard ratio. In the TriNetX analytics platform, for deidentification purposes, if the number of incident cases is 10 or fewer, it will be reported as 10. Propensity score matching was performed on age at index, sex, race, body mass index, status of comorbidities (including diabetes mellitus, hypertension, hyperlipidemia, cerebrovascular diseases, vitamin D deficiency, chronic kidney disease), status of comedication use (glucocorticoids, methotrexate, dupliumab, antidepressants), lab data (C-reactive protein), status of smoking, alcoholism and substance use, medical utilization status (ambulatory and acute inpatient visit) and socioeconomic status (problems related to housing and economic circumstances, persons with potential health hazards related to socioeconomic and psychosocial circumstances).

Table SIV. Sensitivity analysis of applying different follow-up time after index date

Outcomes	Followed-up for 5 years			Followed-up for 10 years		
	PN cohort (%) ^a	Control cohort (%)	HR (95% CI) ^a	PN cohort (%) ^a	Control cohort (%)	HR (95% CI) ^a
Ankylosing spondylitis	13 (<0.1)	10 (<0.1)	1.43 (0.63, 3.27)	22 (<0.1)	18 (<0.1)	1.29 (0.69, 2.41)
Rheumatoid arthritis	11 (<0.1)	12 (<0.1)	1.01 (0.44, 2.28)	24 (<0.1)	25 (<0.1)	0.98 (0.56, 1.72)
Systemic lupus erythematosus	47 (0.3)	19 (0.1)	2.72 (1.60, 4.64)	70 (0.4)	34 (0.2)	2.18 (1.45, 3.28)
Sjögren syndrome	54 (0.3)	32 (0.2)	1.86 (1.20, 2.88)	88 (0.5)	50 (0.3)	1.85 (1.31, 2.62)
Psoriasis	224 (1.2)	85 (0.5)	2.92 (2.27, 3.74)	326 (1.8)	129 (0.7)	2.70 (2.20, 3.31)
Crohn disease	17 (<0.1)	12 (<0.1)	1.55 (0.74, 3.25)	32 (0.2)	22 (<0.1)	1.52 (0.88, 2.62)
Ulcerative colitis	27 (<0.1)	27 (<0.1)	1.10 (0.65, 1.88)	48 (0.3)	44 (0.2)	1.16 (0.77, 1.74)

PN, prurigo nodularis; 95% CI, 95% confidence interval; HR, hazard ratio. In the TriNetX analytics platform, for deidentification purposes, if the number of incident cases is 10 or fewer, it will be reported as 10.

^a Propensity score matching was performed on age at index, sex, race, body mass index, status of comorbidities (including diabetes mellitus, hypertension, hyperlipidemia, cerebrovascular diseases, vitamin D deficiency, chronic kidney disease), status of comedication use (glucocorticoids, methotrexate, dupilumab, antidepressants), lab data (C-reactive protein), status of smoking, alcoholism and substance use, medical utilization status (ambulatory and acute inpatient visit) and socioeconomic status (problems related to housing and economic circumstances, persons with potential health hazards related to socioeconomic and psychosocial circumstances).

Table SV. Sensitivity analysis of applying different wash-out period after index date

Outcomes	12 months of wash-out period			24 months of wash-out period			36 months of wash-out period		
	PN cohort (%) ^a	Control cohort (%)	HR (95% CI) ^a	PN cohort (%) ^a	Control cohort (%)	HR (95% CI) ^a	PN cohort (%) ^a	Control cohort (%)	HR (95% CI) ^a
Ankylosing spondylitis	22 (<0.1)	18 (<0.1)	1.29 (0.69, 2.41)	20 (<0.1)	17 (<0.1)	1.23 (0.65, 2.36)	19 (<0.1)	16 (<0.1)	1.24 (0.64, 2.42)
Rheumatoid arthritis	26 (<0.1)	25 (<0.1)	1.03 (0.59, 1.78)	24 (<0.1)	24 (<0.1)	0.98 (0.56, 1.74)	24 (<0.1)	23 (<0.1)	1.03 (0.58, 1.82)
Systemic lupus erythematosus	68 (0.4)	31 (0.2)	2.31 (1.51, 3.53)	57 (0.3)	29 (0.2)	2.05 (1.31, 3.21)	50 (0.3)	25 (<0.1)	2.07 (1.28, 3.34)
Sjögren syndrome	91 (0.5)	50 (0.3)	1.83 (1.30, 2.59)	81 (0.5)	46 (0.3)	1.76 (1.22, 2.52)	77 (0.4)	42 (0.2)	1.82 (1.25, 2.65)
Psoriasis	303 (1.7)	102 (0.6)	3.14 (2.51, 3.93)	265 (1.5)	94 (0.5)	2.95 (2.33, 3.74)	234 (1.3)	82 (0.5)	2.96 (2.30, 3.81)
Crohn disease	29 (0.2)	29 (0.2)	1.05 (0.63, 1.75)	26 (<0.1)	28 (0.2)	0.97 (0.57, 1.66)	25 (<0.1)	25 (<0.1)	1.04 (0.60, 1.81)
Ulcerative colitis	48 (0.3)	45 (0.3)	1.10 (0.73, 1.65)	45 (0.3)	41 (0.2)	1.12 (0.73, 1.71)	42 (0.2)	35 (0.2)	1.21 (0.78, 1.90)

PN, prurigo nodularis; 95% CI, 95% confidence interval; HR, hazard ratio. In the TriNetX analytics platform, for deidentification purposes, if the number of incident cases is 10 or fewer, it will be reported as 10. Wash out period: incident autoimmune disease occurred within the respective wash-out period would be excluded from the analysis. Propensity score matching was performed on age at index, sex, race, body mass index, status of comorbidities (including diabetes mellitus, hypertension, hyperlipidemia, cerebrovascular diseases, vitamin D deficiency, chronic kidney disease), status of comedication use (glucocorticoids, methotrexate, dupilumab, antidepressants), lab data (C-reactive protein), status of smoking, alcoholism and substance use, medical utilization status (ambulatory and acute inpatient visit) and socioeconomic status (problems related to housing and economic circumstances, persons with potential health hazards related to socioeconomic and psychosocial circumstances).

Table SVI. Sensitivity analysis of applying different matching covariates

Outcomes	Crude model			Matching model 1			Matching model 2		
	PN cohort (%) ^a	Control cohort (%)	HR (95% CI) ^a	PN cohort (%) ^a	Control cohort (%)	HR (95% CI) ^a	PN cohort (%) ^a	Control cohort (%)	HR (95% CI) ^a
Ankylosing spondylitis	24 (<0.1)	2,743 (<0.1)	2.38 (1.59, 3.56)	25 (<0.1)	17 (<0.1)	1.50 (0.81, 2.79)	25 (<0.1)	17 (<0.1)	1.52 (0.82, 2.82)
Rheumatoid arthritis	30 (0.2)	5,233 (<0.1)	1.55 (1.09, 2.23)	28 (0.2)	28 (0.2)	0.99 (0.58, 1.67)	28 (0.2)	26 (0.1)	1.08 (0.63, 1.84)
Systemic lupus erythematosus	66 (0.4)	6,021 (<0.1)	3.00 (2.35, 3.82)	74 (0.4)	30 (0.2)	2.56 (1.68, 3.92)	74 (0.4)	30 (0.2)	2.58 (1.69, 3.94)
Sjögren syndrome	100 (0.6)	8,506 (0.2)	3.20 (2.63, 3.90)	103 (0.6)	53 (0.3)	1.97 (1.41, 2.74)	103 (0.6)	47 (0.3)	2.23 (1.58, 3.15)
Psoriasis	339 (1.9)	25,094 (0.5)	3.72 (3.35, 4.15)	344 (1.9)	115 (0.6)	3.13 (2.53, 3.86)	344 (1.9)	108 (0.6)	3.35 (2.70, 4.17)
Crohn disease	31 (0.2)	6,675 (<0.1)	1.27 (0.89, 1.80)	33 (0.2)	25 (<0.1)	1.37 (0.81, 2.30)	33 (0.2)	24 (<0.1)	1.43 (0.85, 2.43)
Ulcerative colitis	54 (0.3)	8,807 (0.2)	1.67 (1.28, 2.18)	56 (0.3)	45 (0.2)	1.27 (0.86, 1.89)	56 (0.3)	42 (0.2)	1.38 (0.92, 2.06)

PN, prurigo nodularis; 95% CI, 95% confidence interval; HR, hazard ratio. In the TriNetX analytics platform, for deidentification purposes, if the number of incident cases is 10 or fewer, it will be reported as 10. Crude model: analysis did not undergo propensity score matching; Matching model 1: matching covariates include age at index, sex, race, socioeconomic status and substance abuse status; Matching model 2: matching covariates include age at index, sex, race, comorbidity status (including diabetes mellitus, hypertension, hyperlipidemia, cerebrovascular diseases, vitamin D deficiency, chronic kidney disease)

Table SVII. Sensitivity analysis of excluding atopic dermatitis patients from PN group and control group

Outcomes	Non-atopic dermatitis		
	PN cohort (%) ^a	Control cohort (%)	HR (95% CI) ^a
Ankylosing spondylitis	21 (<0.1)	14 (<0.1)	1.59 (0.81, 3.13)
Rheumatoid arthritis	25 (<0.1)	26 (0.2)	0.97 (0.56, 1.69)
Systemic lupus erythematosus	64 (0.4)	33 (0.2)	2.03 (1.33, 3.09)
Sjögren syndrome	84 (0.5)	44 (0.3)	1.95 (1.35, 2.81)
Psoriasis	265 (1.7)	95 (0.6)	2.96 (2.34, 3.74)
Crohn disease	27 (0.2)	24 (<0.1)	1.18 (0.68, 2.04)
Ulcerative colitis	44 (0.3)	32 (0.2)	1.43 (0.91, 2.26)

PN, prurigo nodularis; 95% CI, 95% confidence interval; HR, hazard ratio. In the TriNetX analytics platform, for deidentification purposes, if the number of incident cases is 10 or fewer, it will be reported as 10. Propensity score matching was performed on age at index, sex, race, body mass index, status of comorbidities (including diabetes mellitus, hypertension, hyperlipidemia, cerebrovascular diseases, vitamin D deficiency, chronic kidney disease), status of comedication use (glucocorticoids, methotrexate, dupliumab, antidepressants), lab data (C-reactive protein), status of smoking, alcoholism and substance use, medical utilization status (ambulatory and acute inpatient visit) and socioeconomic status (problems related to housing and economic circumstances, persons with potential health hazards related to socioeconomic and psychosocial circumstances).

Table SVIII. Sensitivity analysis of excluding psoriasis patients from PN group and control group

Outcomes	Non-psoriasis		
	PN cohort (%) ^a	Control cohort (%)	HR (95% CI) ^a
Ankylosing spondylitis	25 (<0.1)	11 (<0.1)	2.35 (1.15, 4.77)
Rheumatoid arthritis	42 (0.2)	40 (0.2)	1.05 (0.68, 1.62)
Systemic lupus erythematosus	75 (0.4)	31 (0.1)	2.58 (1.70, 3.92)
Sjögren syndrome	110 (0.5)	65 (0.3)	1.73 (1.27, 2.35)
Crohn disease	38 (0.2)	24 (<0.1)	1.62 (0.97, 2.70)
Ulcerative colitis	68 (0.3)	49 (0.2)	1.38 (0.96, 2.00)

PN, prurigo nodularis; 95% CI, 95% confidence interval; HR, hazard ratio. In the TriNetX analytics platform, for deidentification purposes, if the number of incident cases is 10 or fewer, it will be reported as 10. Propensity score matching was performed on age at index, sex, race, body mass index, status of comorbidities (including diabetes mellitus, hypertension, hyperlipidemia, cerebrovascular diseases, vitamin D deficiency, chronic kidney disease), status of comedication use (glucocorticoids, dupliumab, antidepressants), lab data (C-reactive protein), status of smoking, alcoholism and substance use, medical utilization status (ambulatory and acute inpatient visit) and socioeconomic status (problems related to housing and economic circumstances, persons with potential health hazards related to socioeconomic and psychosocial circumstances).

Table SIX. Sensitivity analysis of excluding type 1 diabetes patients from PN group and control group

Outcomes	Non-atopic dermatitis		
	PN cohort (%) ^a	Control cohort (%)	HR (95% CI) ^a
Ankylosing spondylitis	25 (0.1)	13 (<0.1)	2.00 (1.02, 3.92)
Rheumatoid arthritis	46 (0.2)	34 (0.2)	1.34 (0.86, 2.10)
Systemic lupus erythematosus	77 (0.4)	38 (0.2)	2.13 (1.44, 3.14)
Sjögren syndrome	114 (0.6)	43 (0.2)	2.71 (1.91, 3.85)
Psoriasis	394 (1.9)	132 (0.6)	3.13 (2.57, 3.81)
Crohn disease	39 (0.2)	31 (0.2)	1.30 (0.81, 2.08)
Ulcerative colitis	64 (0.3)	43 (0.2)	1.52 (1.04, 2.24)

PN, prurigo nodularis; 95% CI, 95% confidence interval; HR, hazard ratio. In the TriNetX analytics platform, for deidentification purposes, if the number of incident cases is 10 or fewer, it will be reported as 10. Propensity score matching was performed on age at index, sex, race, body mass index, status of comorbidities (including diabetes mellitus, hypertension, hyperlipidemia, cerebrovascular diseases, vitamin D deficiency, chronic kidney disease), status of comedication use (glucocorticoids, methotrexate, dupliumab, antidepressants), lab data (C-reactive protein), status of smoking, alcoholism and substance use, medical utilization status (ambulatory and acute inpatient visit) and socioeconomic status (problems related to housing and economic circumstances, persons with potential health hazards related to socioeconomic and psychosocial circumstances).

Table SX. Sensitivity analysis of excluding thyroid diseases patients from PN group and control group

Outcomes	Non-atopic dermatitis		
	PN cohort (%) ^a	Control cohort (%)	HR (95% CI) ^a
Ankylosing spondylitis	25 (0.1)	10 (≤0.1)	2.94 (1.37, 6.31)
Rheumatoid arthritis	34 (0.2)	30 (0.2)	1.18 (0.72, 1.93)
Systemic lupus erythematosus	59 (0.3)	28 (0.2)	2.27 (1.45, 3.56)
Sjögren syndrome	84 (0.5)	38 (0.2)	2.30 (1.57, 3.37)
Psoriasis	320 (1.7)	115 (0.6)	2.96 (2.39, 3.67)
Crohn disease	34 (0.2)	21 (0.1)	1.69 (0.98, 2.91)
Ulcerative colitis	51 (0.3)	33 (0.2)	1.61 (1.04, 2.49)

PN, prurigo nodularis; 95% CI, 95% confidence interval; HR, hazard ratio. In the TriNetX analytics platform, for deidentification purposes, if the number of incident cases is 10 or fewer, it will be reported as 10. Propensity score matching was performed on age at index, sex, race, body mass index, status of comorbidities (including diabetes mellitus, hypertension, hyperlipidemia, cerebrovascular diseases, vitamin D deficiency, chronic kidney disease), status of comedication use (glucocorticoids, methotrexate, dupliumab, antidepressants), lab data (C-reactive protein), status of smoking, alcoholism and substance use, medical utilization status (ambulatory and acute inpatient visit) and socioeconomic status (problems related to housing and economic circumstances, persons with potential health hazards related to socioeconomic and psychosocial circumstances).

Table SXI. Sensitivity analysis of applying different active comparators associated with autoimmune diseases

Outcomes	Control group: HS patients			Control group: AA patients			Control group: Rosacea patients		
	PN cohort (%) ^a	Control cohort (%)	HR (95% CI) ^a	PN cohort (%) ^a	Control cohort (%)	HR (95% CI) ^a	PN cohort (%) ^a	Control cohort (%)	HR (95% CI) ^a
Ankylosing spondylitis	20 (<0.1)	19 (<0.1)	1.01 (0.54, 1.89)	18 (<0.1)	14 (<0.1)	1.23 (0.61, 2.48)	21 (<0.1)	13 (<0.1)	1.65 (0.83, 3.30)
Rheumatoid arthritis	21 (<0.1)	29 (0.2)	0.66 (0.38, 1.16)	14 (<0.1)	27 (0.2)	0.49 (0.26, 0.93)	24 (<0.1)	40 (0.2)	0.60 (0.36, 0.99)
Systemic lupus erythematosus	64 (0.4)	40 (0.3)	1.53 (1.03, 2.28)	56 (0.4)	62 (0.5)	0.89 (0.62, 1.28)	70 (0.4)	61 (0.4)	1.21 (0.85, 1.70)
Sjögren syndrome	70 (0.5)	34 (0.2)	1.90 (1.26, 2.87)	70 (0.5)	54 (0.4)	1.24 (0.87, 1.77)	91 (0.5)	118 (0.7)	0.84 (0.64, 1.10)
Psoriasis	262 (1.8)	183 (1.3)	1.40 (1.16, 1.69)	247 (1.9)	109 (0.8)	2.23 (1.78, 2.79)	319 (1.9)	184 (1.1)	1.82 (1.51, 2.18)
Crohn disease	24 (<0.1)	56 (0.4)	0.41 (0.25, 0.66)	23 (<0.1)	26 (0.2)	0.86 (0.49, 1.51)	31 (0.2)	47 (0.3)	0.68 (0.43, 1.08)
Ulcerative colitis	40 (0.3)	50 (0.3)	0.74 (0.49, 1.13)	34 (0.3)	35 (0.3)	0.92 (0.58, 1.48)	47 (0.3)	52 (0.3)	0.93 (0.62, 1.37)

PN, prurigo nodularis; HS, hidradenitis suppurativa; AA, alopecia areata; 95% CI, 95% confidence interval; HR, hazard ratio. In the TriNetX analytics platform, for deidentification purposes, if the number of incident cases is 10 or fewer, it will be reported as 10. Propensity score matching was performed on age at index, sex, race, body mass index, status of comorbidities (including diabetes mellitus, hypertension, hyperlipidemia, cerebrovascular diseases, vitamin D deficiency, chronic kidney disease), status of comedication use (glucocorticoids, methotrexate, dupliumab, antidepressants), lab data (C-reactive protein), status of smoking, alcoholism and substance use, medical utilization status (ambulatory and acute inpatient visit) and socioeconomic status (problems related to housing and economic circumstances, persons with potential health hazards related to socioeconomic and psychosocial circumstances).