

Late-onset development of psoriasis in Japan: a population-based cohort study



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Background: Evidence of factors associated with psoriasis from large population-based cohort studies is scarce.

Objective: We aimed to explore the risk factors of late-onset psoriasis.

Methods: This study included 487,835 Japanese participants aged 40-107 years, who were followed prospectively from 2012 to 2018 using individually linked databases between annual health checkups and medical claims.

Results: During the study period, 2793 patients (0.57%) newly developed psoriasis; 13.8% had moderate-to-severe psoriasis. In the multivariate analysis, factors associated with psoriasis onset were age (hazard ratio [HR] 1.11 [95% confidence interval [CI]: 1.06-1.16]), male sex (HR: 1.11 [95% CI: 1.02-1.21]), body mass index (HR: 1.09 [95% CI: 1.05-1.14]), smoking (HR: 1.46 [95% CI: 1.31-1.63]), not exercising ≥ 1 hour per week (HR: 1.13 [95% CI: 1.05-1.22]), and gamma-glutamyl transpeptidase (HR: 1.04 [95% CI: 1.01-1.06]). When we used weight increment of ≥ 10 kg since the age of 20 years instead of body mass index in the multivariate model, this was also a risk factor (HR: 1.12 [95% CI: 1.04-1.21]).

Limitations: This study targeted people aged >40 years, thereby narrowing the search to the risk factors of late-onset psoriasis.

Conclusion: We showed that increasing age, male sex, body mass index, smoking, low physical activity, weight gain, and gamma-glutamyl transpeptidase are associated with late-onset development of psoriasis and revealed a relationship between liver dysfunction and psoriasis development. (JAAD Int 2021;2:51-61.)

Key words: incidence; onset; predictive factor; psoriasis; risk.

INTRODUCTION

Psoriasis is a chronic inflammatory skin disease, which has been estimated to affect 0.51%-11.43% of the global population.¹ The prevalence of psoriasis in the United States and Europe is 2.3%-3.2%^{2,3}; this prevalence is lower in Asian countries, from 0.23% to 0.47%.^{4,5} About 13%-30% of patients with psoriasis also have psoriatic arthritis.^{6,7} Psoriasis causes skin

and joint disorders, which lead to decreased quality of life.⁸ Recent studies show that psoriasis is related to various comorbidities such as diabetes, hypertension, and cardiovascular disease.⁹⁻¹¹

Population-based studies indicate a relationship between psoriasis and metabolic syndrome.¹² Owing to an increased risk of comorbidities, the risk of death in patients with psoriasis is also

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Drs Goto and Nakatani contributed equally to this article.

Funding sources: None.

Conflict of interest: None disclosed.

IRB approval status: The study protocol was approved by the ethics committee of Shizuoka General Hospital (SGHIRB#2019009, 2019).

Accepted for publication October 30, 2020.

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2666-3287

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<https://doi.org/10.1016/j.jdin.2020.10.011>

increased and life expectancy is shortened in patients with severe psoriasis.¹³ Thus, it is considered that early intervention for people with a high risk of developing psoriasis can prevent psoriasis onset and avoid greater severity of psoriasis, leading to improved social productivity and increased life expectancy.

Several studies have identified age, family history of psoriasis, smoking, alcohol consumption, obesity, and physical inactivity as factors associated with psoriasis.¹⁴⁻¹⁸ However, the published studies have limitations of research design and provide data on specific aspects of factors associated with psoriasis from cross-sectional surveys or case-control studies; little has been reported on the risk factors of psoriasis in the general population.

In recent years, several studies have been conducted using databases to research the epidemiology of psoriasis.^{5,19} The Kokuho database system of the Federation of National Health Insurance Association in Japan includes the Japanese national database of health insurance claims and health checkup data. This database includes the information of Japanese citizens insured through the National Health Insurance and Late Elderly Care Insurance; thus, these data are useful for analyzing the acquired risk factors of psoriasis onset in Japanese population. Using these data, we conducted a population-based cohort study to identify the risk factors associated with the occurrence of psoriasis.

METHODS

Data resource

The Shizuoka Kokuho database is derived from a database that provides the linked data of Federation of National Health Insurance Association subscribers, including demographic and registration data, medical claims data, and health checkup data of enrollees in Shizuoka Prefecture. Shizuoka Prefecture has a population of about 3.6 million people and is located nearly in the center of Japan, with representative climatic conditions and population distribution of Japan. The database represented 25% of the population aged below 65 years and 75% of the population aged above 65 years in Shizuoka Prefecture as it included beneficiaries of the Japanese National Health Insurance and Late Elderly Care Insurance.

Japanese medical insurance and health checkups

Japan's medical system is based on an exhaustive insurance system. In Japan, there are 2 types of health insurance for people aged <75 years. One is Employees Health Insurance for the employees of companies; the other is the National Health Insurance for small business owners and their employees. Health insurance for people aged ≥ 75 years is the Latter-Stage Elderly Medical Care System. The Ministry of Health, Labour, and Welfare in Japan recommends registrants to have a health checkup once a year. The annual health checkups are specifically focused on visceral fat obesity starting at the age of 40 years.

CAPSULE SUMMARY

- Mild liver dysfunction, monitored using gamma-glutamyl transpeptidase, was associated with the involvement of metabolic syndrome in late-onset psoriasis.
- Physicians may wish to consider lifestyle-related risk factors such as weight gain and smoking that may be associated with the development of psoriasis.

Population and observational period

We used a dataset that comprised 6.5 years of longitudinal data from April 2012 to September 2018. All enrollees were investigated by using individually linked databases between their annual health checkups and medical claims. We excluded patients who received a diagnosis of psoriasis before the start date of health checkups, those who did not undergo a health checkup, and individuals aged <40 years.

Data pick-up points are shown in Fig 1. Each enrollees' observation period was defined as the time from the date of insurance registration or April 2012, whichever came earlier to the date of insurance withdrawal or September 2018, whichever came later.

Potential factors associated with psoriasis onset

Patients with psoriasis were defined as those who had a medical claim with an International Classification of Diseases, 10th Revision code for psoriasis (L40). Japanese disease codes and the corresponding types of psoriasis with L40.x are shown in Table I.

Psoriasis severity

We categorized the severity of psoriasis as mild or moderate-to-severe, according to the treatment. We defined patients with moderate-to-severe psoriasis as those who received phototherapy or systemic therapy, including oral retinoids (etretinate), apremilast, methotrexate, cyclosporine, azathioprine, granulocyte and monocyte adsorption apheresis, or biologics (adalimumab, infliximab, ustekinumab,

Abbreviations used:

BMI:	body mass index
CI:	confidence interval
GGT:	gamma-glutamyl transpeptidase
HR:	hazard ratio

secukinumab, ixekizumab, brodalumab, or guselkumab). Patients were classified as having mild psoriasis if they had never received any of these therapies. Several studies have used this approach to approximate the severity of psoriasis.^{20,21} We referred to treatment for 6 months after a diagnosis of psoriasis was given.

Statistical analysis

The missing covariates used in the multivariate analysis did not occur completely at random among all participants; therefore, we did not impute the missing data. Because the characteristics of the multivariate model with risk factor analysis differed from those of all cases (Table II), the participants included in the multivariate model were analyzed as a full analysis set.

We summarized the data as mean and standard deviation for continuous variables and frequency and percentage for categorical variables. Univariate and multivariate Cox proportional hazards regression were performed to explore the factors associated with psoriasis onset. We calculated the hazard ratio (HR), 95% confidence interval (CI), and *P* value and conducted the Wald test. The reported risk factors such as age,¹⁴ smoking,²² body mass index (BMI),²³ weight increment of ≥ 10 kg since the age of 20 years,²³ and potential risk factors such as key etiologic and epidemiologic factors were used in the regression analysis.²⁴ Variables with a relatively large number of missing values ($>55,000$) in the health checkup data were excluded from the multivariate model. One of 2 variables with high correlation was not used in the multivariate model owing to multicollinearity, based on the criterion of an absolute Spearman correlation coefficient >0.4 (Table III). For internal validation, we also performed multivariate analyses stratified by areas with 42 municipalities in Shizuoka Prefecture. A *P* value of .05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Ethics

The data of all enrollees were anonymized in the Federation of National Health Insurance Association to protect participant confidentiality. The study

protocol was approved by the ethics committee of Shizuoka General Hospital (SGHIRB#2019009, 2019).

RESULTS**Participant characteristics**

Among the 2,188,609 individuals in the Shizuoka Kokuho database, 718,140 underwent health checkups. Among them, 148,964 patients had an observation period of <1 year, 3151 had already developed psoriasis, and 4056 patients aged <40 years were excluded. A total of 561,969 individuals without psoriasis were included in our study. We analyzed the data of 487,835 individuals (203,927 men [41.8%], mean [standard deviation] age 67.9 [10.8] years) in the analysis; this full analysis set did not include individuals with missing values for explanatory variables in the multivariate models.

Psoriasis onset and severity

During the observation period (median 5.50 years), 2793 patients (0.57%) were newly diagnosed with psoriasis. Among these 2793 patients, 86.2% and 13.8% had mild and moderate-to-severe psoriasis, respectively. The baseline characteristics for new-onset psoriasis patients and others are shown in Table IV. We assumed that the severity of psoriasis could be defined according to the treatment within 6 months after the onset of psoriasis. Systemic therapies used at least once within 6 months after onset in patients with moderate-to-severe psoriasis are shown in Table V.

Identification of factors associated with psoriasis onset

We evaluated the potential risk factors and significant variables using univariate Cox regression analysis (Table VI, univariate model). In the multivariate analysis, we identified the following as risk factors for the onset of psoriasis: age per 10 years: (HR: 1.11 [95% CI: 1.06-1.16]), male sex (versus female sex; HR: 1.11 [95% CI: 1.02-1.21]), BMI per 1 unit (HR: 1.09 [95% CI: 1.05-1.14]), current smoker (versus non-smoker; HR: 1.46 [95% CI: 1.31-1.63]), not walking or exercising ≥ 1 hour per week (HR: 1.13 [95% CI: 1.05-1.22]), and gamma-glutamyl transpeptidase (GGT) 100 IU/L (HR: 1.04 [1.01-1.06]) (Table VI, multivariate model 1). When weight increment of ≥ 10 kg since the age of 20 years was used instead of BMI in the multivariate model, although the Spearman's correlation coefficient for these factors was -0.581 , it was also a risk factor (HR: 1.12 [95% CI: 1.04-1.21]) (Table VI, multivariate model 2). Further, similar results were obtained in the sensitivity analysis (Table VII).

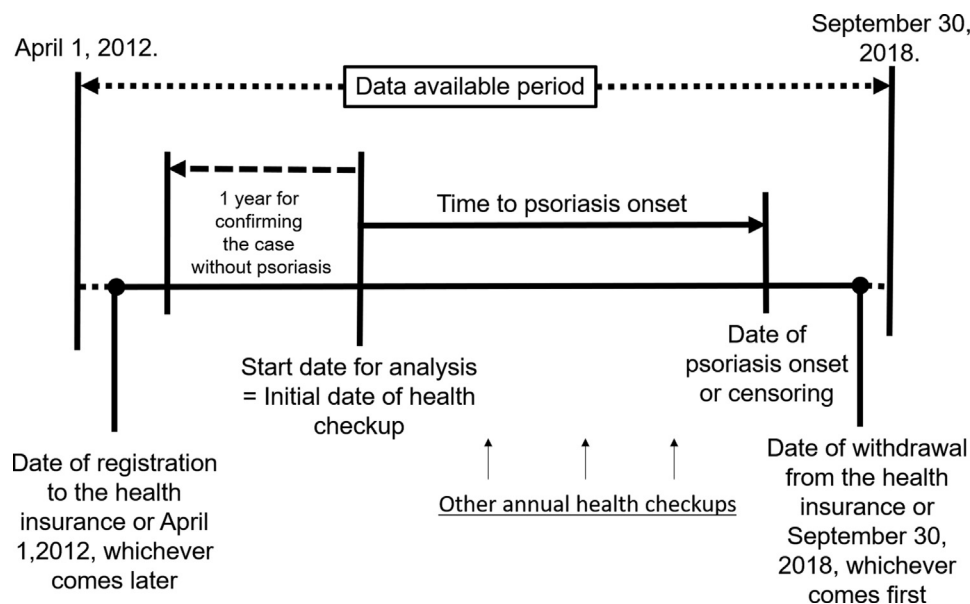


Fig 1. Data pick-up points in the dataset.

Table I. Japanese disease codes and names for the definition of psoriasis

ICD-10	Japanese disease code	Disease name
L400	6961004	Psoriasis vulgaris
L400	6961013	Diffuse psoriasis
L400	6961014	Nummular psoriasis
L400	6961015	Follicular psoriasis
L400	6961017	Seborrheic psoriasis
L400	8832096	Facial psoriasis vulgaris
L400	8832675	Plaque psoriasis
L400	8834312	Psoriasis vulgaris of extremities
L400	8836536	Psoriasis vulgaris of entire body
L400	8838120	Psoriasis vulgaris of head
L400	8840843	Psoriasis vulgaris of lower back
L401	6961007	Pustular psoriasis
L401	8846041	Generalized pustular psoriasis
L401	8846111	Acute generalized pustular psoriasis
L401	8846144	Pediatric generalized pustular psoriasis
L404	6961006	Guttate psoriasis
L404	6961012	Psoriasis punctata
L405	7133001	Psoriatic arthritis
L405	8831630	Psoriatic spondylitis
L405	8846362	Psoriatic arthritis/shoulder joint
L405	8846363	Psoriatic arthritis/hip joint
L405	8846364	Psoriatic arthritis/finger joints
L405	8846365	Psoriatic arthritis/knee joint
L405	8846366	Psoriatic arthritis/wrist joint
L405	8846367	Psoriatic arthritis/sacroiliac joint
L405	8846368	Psoriatic arthritis/ankle joint
L405	8846369	Psoriatic arthritis/elbow joint
L405	8846418	Multiple psoriatic arthritis
L408	6961002	Psoriatic erythroderma
L408	8832799	Flexural psoriasis
L409	6961009	Psoriasis
L409	8834298	Psoriasis of extremities

ICD-10, International Classification of Diseases, 10th Revision.

DISCUSSION

Our objective was to evaluate the risk factors associated with the onset of psoriasis. We analyzed 487,835 individuals who received health checkups and identified age, sex, smoking, BMI, weight gain since the age of 20 years, low physical activity level, and GGT as factors associated with psoriasis development in the Japanese population.

From the data presented, the prevalence of psoriasis in the population who had undergone health checkups would appear to be 0.44% (3151 out of 718,140). Kubota et al reported that the national prevalence of psoriasis was 0.34% in a Japanese national claims database.¹⁹ The higher figure would be expected as our cohort included patients with psoriasis over the age of 40 years. During this study period, 13.8% of newly diagnosed patients with psoriasis progressed to moderate or severe psoriasis. Subgroup analysis of older-onset psoriasis is shown in [Table VIII](#). Liver dysfunction may be higher in young patients with psoriasis. In addition, smoking and weight gain since the age of 20 years were also higher in young patients with psoriasis.

In recent years, the concept of “psoriatic march” has been used to explain psoriatic inflammation leading to insulin resistance and atherosclerosis and contributing to cardiovascular comorbidity.²⁵ According to this concept, as a chronic systemic inflammatory disease, the control of psoriasis is essential in terms of its impact on comorbidities.

Several studies have reported the relationship between psoriasis and obesity.²⁶ BMI, weight change since the age of 18 years, waist circumference, and hip circumference are associated with an increased risk of psoriasis.²³ Our research also indicated that

Table II. Comparison between datasets of all cases and full analysis set*

Variable	Full analysis set N = 487,835	Cases with missing covariates N = 74,134
Age (y)	67.9 ± 10.8	72.1 ± 11.2
Sex (male)	203,927 (41.8)	30,506 (41.1)
BMI	22.7 ± 3.4	22.4 ± 3.4
Current smoker (Yes)	57,630 (11.8)	Missing: 478 6843 (9.2)
Walking or physical exercise ≥1 h/wk (No)	240,255 (49.2)	10,084 (48.2) Missing: 53,203
Increment in weight ≥10 kg since the age of 20 y (Yes)	142,332 (29.2)	5340 (24.7) Missing: 52,545
Eats dinner within 2 h before bedtime, ≥3 times/wk	61,906 (12.7)	2467 (11.5) Missing: 52,669
Use of hypotensive agents	204,934 (42.0)	37,103 (50.0)
Use of lipid-lowering agents	129,618 (26.6)	21,441 (28.9)
Triglyceride (mg/dL)	115.4 ± 76.4	109.5 ± 67.7
LDL cholesterol (mg/dL)	124.7 ± 31.4	Missing: 291 119.3 ± 30.2 Missing: 352
HDL cholesterol (mg/dL)	62.5 ± 16.7	61.3 ± 16.4 Missing: 342
Use of antidiabetic agents	43,174 (8.9)	7212 (9.7)
HbA1c (%)	5.7 ± 0.7	5.8 ± 0.7
AST (IU/L)	Missing: 2948 24.2 ± 12.4	Missing: 7175 24.7 ± 10.8
ALT (IU/L)	Missing: 2 20.3 ± 14.3	Missing: 146 19.3 ± 12.6
GGT (IU/L)	Missing: 5 32.9 ± 47.1	Missing: 146 31.0 ± 40.3
Estimated GFR (mL/min/ 1.73 m ²)	69.6 ± 15.7	Missing: 352 66.0 ± 16.5 Missing: 26,671

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GFR, glomerular filtration rate; GGT, gamma-glutamyl transpeptidase; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*The full analysis set did not include missing values for explanatory variables in the multivariate models (see Table VI).

BMI, weight gain since the age of 20 years, and low levels of physical activity were the factors associated with psoriasis. Thus, weight loss may be useful for the prevention and control of psoriasis. Dietary intervention together with physical exercise significantly reduced the Psoriasis Area and Severity Index.²⁷ Further, it was proven that reduced physical activity is associated with an increased risk of developing psoriasis.^{18,28} Physical activity can have anti-inflammatory effects because increasing the physical activity can decrease some inflammatory molecules such as tumor necrosis factor- α , interferon γ , interleukin 6, and C-reactive protein.^{29,30} Therefore, physical activity may improve psoriasis symptoms and reduce the risks related to systemic inflammation and psoriasis-linked comorbidities.

Smoking has been found to be an independent risk factor for psoriasis, and the increase in the number of cigarettes is proportional to the risk of psoriasis.^{17,22} In the present study, multivariate analysis demonstrated

that smoking was a risk factor (HR: 1.46 [95% CI: 1.31-1.63], $P < .001$ in model 1 of Table VI). A meta-analysis of smoking in psoriasis indicated a strong association with current and ex-smokers.³¹ Smoking cessation is essential to prevent the onset of psoriasis and control psoriatic comorbidities.

A previous study indicated that moderate-to-severe psoriasis is associated with an increased risk of chronic kidney disease.³² However, our study did not identify a relationship between psoriasis onset and renal function (estimated glomerular filtration rate). Impaired renal function was not a risk factor for developing psoriasis but might be a prognostic factor for the severity of psoriasis.

Compared with other well-known comorbidities such as obesity and myocardial infarction, the relationship between psoriasis and liver disease is not well understood. Recently, several studies have revealed an increased frequency of nonalcoholic fatty liver disease in patients with psoriasis.^{33,34}

Table III. Matrix of Spearman's correlation coefficient*

Matrix of Spearman's correlation coefficient	Age	Sex	BMI	Current smoker	Increment in weight ≥ 10 kg since the age of 20 y	Exercise to sweat lightly for ≥ 30 min, 2 times/wk, for ≥ 1 y	Walking or physical exercise ≥ 1 h/wk	Eats dinner within 2 h before bedtime, ≥ 3 times/wk	Frequency and volume per day of drink	Systolic blood pressure	Use of hypotensive agents	Triglyceride	LDL cholesterol	HDL cholesterol	Use of lipid-lowering agents	HbA1c	Use of antidiabetic agents	AST	ALT	GGT	Uric acid	Serum creatinine	Estimated GFR
Age	1																						
Sex	0.023	1																					
BMI	-0.044	-0.169	1																				
Current smoker	-0.186	-0.244	0.014	1																			
Increment in weight ≥ 10 kg since the age of 20 y	0.100	0.130	-0.581	-0.045	1																		
Exercise to sweat lightly for ≥ 30 min, 2 times/wk, for ≥ 1 y	-0.110	0.068	0.001	0.056	-0.037	1																	
Walking or physical exercise ≥ 1 h/wk	-0.064	0.027	0.044	0.034	-0.066	0.417	1																
Eats dinner within 2 h before bedtime, ≥ 3 times/wk	0.057	0.117	-0.057	-0.125	0.071	-0.031	-0.014	1															
Frequency and volume per day of drink	0.157	0.423	-0.068	-0.197	0.058	0.047	0.031	0.154	1														
Systolic blood pressure (mm Hg)	0.242	-0.050	0.186	-0.034	-0.093	-0.027	-0.016	-0.009	-0.045	1													
Use of hypotensive agents	0.333	-0.047	0.202	-0.062	-0.120	-0.018	0.005	-0.012	-0.004	0.249	1												
Triglyceride (mg/dL)	0.009	-0.132	0.333	0.110	-0.246	0.020	0.057	-0.029	-0.036	0.130	0.106	1											
LDL cholesterol (mg/dL)	-0.126	0.122	0.066	-0.038	-0.044	0.012	0.011	0.041	0.100	0.018	-0.186	0.185	1										
HDL cholesterol (mg/dL)	-0.099	0.300	-0.351	-0.128	0.248	-0.025	-0.060	0.033	-0.050	-0.070	-0.141	-0.501	-0.001	1									
Use of lipid-lowering agents	0.171	0.111	0.119	-0.089	-0.073	-0.038	-0.009	0.046	0.126	0.055	0.253	0.100	-0.188	-0.049	1								
HbA1c (%)	0.135	-0.031	0.203	-0.030	-0.154	-0.035	-0.003	0.021	0.090	0.086	0.141	0.165	0.037	-0.162	0.198	1							
Use of antidiabetic agents	0.090	-0.089	0.118	0.009	-0.090	-0.032	0.002	-0.013	0.015	0.055	0.158	0.058	-0.115	-0.119	0.160	0.415	1						
AST (IU/L)	0.112	-0.089	0.052	-0.033	-0.048	-0.047	-0.042	-0.035	-0.112	0.105	0.074	0.054	-0.047	0.030	0.074	0.041	0.009	1					
ALT (IU/L)	-0.158	-0.219	0.287	0.047	-0.239	-0.023	-0.009	-0.052	-0.131	0.065	0.036	0.206	0.024	-0.121	0.085	0.143	0.073	0.664	1				
GGT (IU/L)	-0.121	-0.385	0.260	0.173	-0.229	-0.006	0.020	-0.100	-0.370	0.108	0.086	0.277	-0.002	-0.131	0.014	0.107	0.057	0.352	0.516	1			
Uric acid (mg/dL)	0.025	-0.453	0.277	0.116	-0.202	-0.029	0.006	-0.074	-0.256	0.098	0.146	0.247	-0.010	-0.259	-0.010	0.079	0.032	0.134	0.208	0.333	1		
Serum creatinine (mg/dL)	0.152	-0.629	0.173	0.086	-0.112	-0.072	-0.016	-0.047	-0.198	0.053	0.159	0.160	-0.081	-0.272	0.004	0.029	0.076	0.077	0.091	0.209	0.534	1	
Estimated GFR (mL/min/1.73 m ²)	-0.401	0.027	-0.075	0.123	0.017	0.072	0.019	-0.054	-0.100	-0.086	-0.226	-0.099	0.023	0.122	-0.128	-0.052	-0.046	-0.058	0.074	0.048	-0.303	-0.749	1

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GFR, glomerular filtration rate; GGT, gamma-glutamyl transpeptidase; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Categorical variables were treated as ordered-category variables, then Spearman's correlation coefficient was calculated. The category for frequency and volume per day of alcohol included "rarely (cannot) drink," "sometimes," "<180 mL/d," "180 to <360 mL/d," "360 to <540 mL/d," and " ≥ 540 mL/d." Bold type without and with underlining indicates that the absolute coefficient was >0.3 and >0.4 , respectively.

Table IV. Participant characteristics at baseline health checkup*

Variable	Psoriasis onset in cohort period (median 5.5 y) N = 2793	Controls N = 485,042
Age (y)	69.0 ± 10.0	67.9 ± 10.8
Sex (male)	1331 (47.7)	202,596 (41.8)
BMI	23.0 ± 3.5	22.7 ± 3.4
Current smoker (Yes)	450 (16.1)	57,180 (11.8)
Walking or physical exercise ≥1 h/wk (No)	1462 (52.3)	238,793 (49.2)
Increment in weight ≥10 kg since the age of 20 y (Yes)	958 (34.3)	141,374 (29.1)
Eats dinner within 2 h before bedtime, ≥3 times/wk (Yes)	369 (13.2)	61,537 (12.7)
Use of hypotensive agents	1303 (46.7)	203,631 (42.0)
Use of lipid-lowering agents	784 (28.1)	128,834 (26.6)
Triglyceride (mg/dL)	120.0 ± 73.3	115.3 ± 76.5
LDL cholesterol (mg/ dL)	123.3 ± 31.7	124.7 ± 31.4
HDL cholesterol (mg/ dL)	61.2 ± 16.8	62.5 ± 16.7
Use of antidiabetic agents	258 (9.2)	42,916 (8.8)
HbA1c (%)	5.7 ± 0.6	5.7 ± 0.7
AST (IU/L)	25.0 ± 13.1	24.2 ± 12.4
ALT (IU/L)	20.9 ± 13.3	20.3 ± 14.3
GGT (IU/L)	36.8 ± 52.1	32.9 ± 47.0
Estimated GFR (mL/ min/1.73 m ²)	68.7 ± 15.7	69.6 ± 15.7

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GFR, glomerular filtration rate; GGT, gamma-glutamyl transpeptidase; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Continuous and categorical variables are summarized using mean ± standard deviation and frequency (percentage), respectively.

Patients with psoriasis and psoriatic arthritis have higher scores on enhanced liver fibrosis tests, indicative of liver fibrosis.³⁵ However, there are no prospective data on the relationship between liver disease and the onset of psoriasis. In liver function tests, alanine transaminase and aspartate transaminase are increased when hepatocytes are damaged, but GGT is increased in alcoholic liver injury and fatty liver. Alcohol consumption is reported to be a risk factor for developing psoriasis.¹⁶ Furthermore, GGT is a marker of nonalcoholic fatty liver disease and is frequently elevated in patients with nonalcoholic fatty liver disease.^{36,37} Fatty liver disease occurs with obesity at a high rate, but inflammatory cytokines such as tumor necrosis factor- α are secreted from adipose cells, which causes low levels of persistent general inflammation in the body as well as insulin resistance.³⁸⁻⁴¹ Such

inflammation has recently attracted attention as a risk factor in the development of various diseases, and its involvement in psoriasis has been suggested.²⁵ Therefore, our results may be related to alcohol consumption or fatty liver and the related inflammation. Liver dysfunction is a prominent indicator of the involvement of metabolic syndrome at psoriasis onset. It is possible that alcohol consumption may confound the relationship between psoriasis and liver disease, and further study is warranted.

The onset of psoriasis before the age of 40 years is strongly associated with genetic factors. The onset after this age may be related to acquired factors, such as lifestyle and chronic diseases.⁴² This study targeted people over the age of 40 years, thereby narrowing the search to primarily acquired risk factors of psoriasis onset.

Table V. Systemic therapies used at least once within 6 months after onset in patients with moderate-to-severe psoriasis*

Systemic therapy used at least once within 6 mo after onset	Moderate-to-severe psoriasis	
	N = 385	
	Frequency	%
Phototherapy	239	62.1
Cyclosporine	55	14.3
Oral retinoids (etretinate)	45	11.7
Methotrexate	28	7.3
Apremilast	6	1.6
Adalimumab	3	0.8
Azathioprine	3	0.8
Infliximab	2	0.5
Secukinumab	2	0.5
Ustekinumab	1	0.3
Granulocyte and monocyte adsorption apheresis	1	0.3

*Systemic therapies for patients with moderate-to-severe psoriasis (385 of 2793 patients, 13.8%) used at least once in the first 6 months after onset. In patients with mild severity (2408 of 2793 patients, 86.2%), treatments other than the above systemic therapies or observation were used.

There are several limitations in the current study. First, it is difficult to determine the exact severity of psoriasis because our claims data did not include the index of severity and extent of psoriasis, such as the Psoriasis Area and Severity Index score. Second, we defined the development of psoriasis based on the International Classification of Diseases, 10th Revision code, but this was not validated using medical chart data. Third, the exact incidence of psoriasis is unknown in Shizuoka Prefecture because we did not have data for all individuals in the prefecture; however, this would not influence the results of risk factor analysis. In this study, we were unable to truly determine the age of onset, and we used the age at diagnosis as a surrogate. Finally, in this study, we ensured that enrollees who were newly diagnosed with psoriasis had not received any psoriatic treatment using the insurance during the 1-year baseline period. Therefore, patients with psoriasis who did not use the insurance for the treatment of psoriasis during this period were considered as new onset. However, owing to the universal insurance system in Japan, such patients

Table VI. Results of univariate and multivariate Cox regression analysis for developing psoriasis*

Variable (reference) N = 487,835	Category or unit	Univariate model		Multivariate model 1		Multivariate model 2	
		HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age (y)	10.8	1.08 (1.04-1.12)	<.001	1.11 (1.06-1.16)	<.001	1.11 (1.06-1.16)	<.001
Sex (women)	Men	1.21 (1.12-1.30)	<.001	1.11 (1.02-1.21)	.012	1.11 (1.02-1.20)	.016
BMI	3.4	1.10 (1.06-1.14)	<.001	1.09 (1.05-1.14)	<.001		
Current smoker (No)	Yes	1.43 (1.29-1.58)	<.001	1.46 (1.31-1.63)	<.001	1.45 (1.30-1.62)	<.001
Walking or exercise ≥ 1 h/wk (Yes)	No	1.14 (1.05-1.22)	.001	1.13 (1.05-1.22)	.002	1.25 (1.15-1.36)	<.001
Weight increment ≥ 10 kg since age 20 y (No)	Yes	1.27 (1.18-1.37)	<.001			1.12 (1.04-1.21)	.002
Eats dinner within 2 h before bedtime ≥ 3 times/wk (No)	Yes	1.04 (0.93-1.16)	.458	0.97 (0.87-1.09)	.604	0.97 (0.86-1.08)	.548
Use of hypotensive agents (No)	Yes	1.18 (1.10-1.27)	<.001	1.07 (0.98-1.16)	.125	1.08 (0.99-1.17)	.088
Use of lipid-lowering agents (No)	Yes	1.06 (0.97-1.15)	.190	1.05 (0.96-1.15)	.275	1.05 (0.96-1.15)	.269
Triglyceride (mg/dL)	76.4	1.05 (1.02-1.09)	.002				
LDL cholesterol (mg/dL)	31.4	0.96 (0.92-0.99)	.018	0.98 (0.95-1.02)	.401	0.98 (0.95-1.02)	.429
HDL cholesterol (mg/dL)	16.7	0.94 (0.90-0.97)	<.001	1.01 (0.97-1.06)	.577	1.01 (0.97-1.05)	.704
Use of anti-diabetic agents (No)	Yes	1.03 (0.90-1.18)	.654	0.92 (0.81-1.05)	.217	0.93 (0.81-1.06)	.244
HbA1c (%)	1	1.01 (0.96-1.06)	.769				
AST (IU/L)	12.4	1.02 (1.01-1.03)	<.001				
ALT (IU/L)	14.3	1.03 (1.00-1.06)	.021				
GGT (IU/L)	47.1	1.05 (1.03-1.07)	<.001	1.04 (1.01-1.06)	.006	1.04 (1.01-1.06)	.007
Estimated GFR (mL/min/1.73 m ²)	15.7	0.97 (0.95-0.99)	.011	0.99 (0.95-1.03)	.637	0.99 (0.95-1.03)	.605

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; GFR, glomerular filtration rate; GGT, gamma-glutamyl transpeptidase; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein. *Bold type in the multivariate model indicates statistical significance. Because the Spearman's correlation coefficient between BMI and weight increment of ≥ 10 kg since the age of 20 years was -0.581 , multivariate model 1 included BMI but not weight increment of ≥ 10 kg since the age of 20 years; model 2 included weight increment of ≥ 10 kg since the age of 20 years but not BMI.

Table VII. Results of the multivariate model stratified by areas with 42 municipalities in Shizuoka Prefecture

Variable (reference), N = 487,719*	Category or unit	Multivariate model 3 [†]		Multivariate model 4 [†]	
		HR (95% CI)	P value	HR (95% CI)	P value
Age	10.8	1.11 (1.06-1.16)	<.001	1.11 (1.06-1.16)	<.001
Sex (women)	Men	1.11 (1.02-1.2)	.015	1.1 (1.02-1.2)	.019
BMI	3.4	1.09 (1.05-1.14)	<.001		
Current smoker (No)	Yes	1.47 (1.32-1.64)	<.001	1.46 (1.31-1.63)	<.001
Walking or exercise ≥1 h/wk (Yes)	No	1.12 (1.04-1.21)	.003	1.25 (1.15-1.35)	<.001
Weight increment ≥10 kg since the age of 20 y (No)	Yes			1.12 (1.04-1.2)	.004
Eats dinner within 2 h before bedtime ≥3 times/wk (No)	Yes	0.96 (0.86-1.08)	.499	0.96 (0.86-1.07)	.455
Use of hypotensive agents (No)	Yes	0.16 (1.06-0.98)	.158	1.07 (0.99-1.16)	.108
Use of lipid-lowering agents (No)	Yes	0.98 (0.94-1.02)	.319	0.98 (0.94-1.02)	.353
LDL cholesterol (mg/dL)	31.4	1.01 (0.97-1.05)	.601	1.01 (0.97-1.05)	.752
HDL cholesterol (mg/dL)	16.7	0.31 (1.05-0.96)	.313	1.05 (0.96-1.15)	.300
Use of antidiabetic agents (No)	Yes	0.16 (0.91-0.8)	.160	0.92 (0.8-1.04)	.184
GGT (IU/L)	47.1	1.04 (1.01-1.06)	.003	1.04 (1.01-1.06)	.004
Estimated GFR (mL/min/1.73 m ²)	15.7	0.98 (0.94-1.03)	.425	0.98 (0.94-1.02)	.396

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; GFR, glomerular filtration rate; GGT, gamma-glutamyl transpeptidase; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein.

*The categorical variable for area was missing in 116 cases.

[†]Multivariate models 3 and 4 included a categorical variable for area in models 1 and 2 (Table VI). The 42 municipalities (number of individuals [% against overall patients]) in Shizuoka Prefecture were, in descending order, Fuji (34,085 cases [7.06%]); Shimizu-ku, Shizuoka (33,708 cases [6.98%]); Aoi-ku, Shizuoka (32,781 cases [6.79%]); Naka-ku, Hamamatsu (32,686 cases [6.77%]); Numazu (30,917 cases [6.41%]); Suruga-ku, Shizuoka (25,395 cases [5.26%]); Fujieda (22,440 cases [4.65%]); Nishi-ku, Hamamatsu (16,704 cases [3.46%]); Higashi-ku, Hamamatsu (16,250 cases [3.37%]); Ito (15,034 cases [3.12%]); Hamakita-ku, Hamamatsu (14,402 cases [2.98%]); Fujinomiya (13,722 cases [2.84%]); Gotenba (13,640 cases [2.83%]); Iwata (13,488 cases [2.79%]); Minami-ku, Hamamatsu (13,465 cases [2.79%]); Kita-ku, Hamamatsu (13,409 cases [2.78%]); Mishima (13,347 cases [2.77%]); Kakegawa (10,680 cases [2.21%]); Shimada (10,166 cases [2.11%]); Izunokuni (9820 cases [2.03%]); Susono (7853 cases [1.63%]); Kosai (7772 cases [1.61%]); Izu (7726 cases [1.6%]); Atami (7177 cases [1.49%]); Tenryu-ku, Hamamatsu (6294 cases [1.3%]); Kannami-cho, Tagata-cho (5989 cases [1.24%]); Nagaizumi-cho, Sunto-gun (5367 cases [1.11%]); Shimizu-cho, Sunto-gun (4743 cases [0.98%]); Omaezaki (4371 cases [0.91%]); Kikugawa (4288 cases [0.89%]); Fukuroi (4225 cases [0.88%]); Shimoda (3894 cases [0.81%]); Oyama-cho, Sunto-gun (3581 cases [0.74%]); Yoshida-cho, Haibara (2793 cases [0.58%]); Higashiizu-cho, Kamo-gun (2656 cases [0.55%]); Yaizu (2480 cases [0.51%]); Mori-machi, Syuti-gun (2258 cases [0.47%]); Nishiizu-cho, Kamo-gun (1800 cases [0.37%]); Kawanehon-cho, Haibara-gun (1758 cases [0.36%]); Minamiizu-cho, Kamo-gun (1599 cases [0.33%]); Kawazu-cho, Kamo-gun (1503 cases [0.31%]); and Matsuzaki-cho, Kamo-gun (1349 cases [0.28%]).

Table VIII. A comparison of patient backgrounds among psoriasis patients by age

Variable	Psoriasis onset in cohort period (median 5.5 y)		P value
	≥60 y old	<60 y old	
	N = 2414	N = 379	
Age (y)	71.7 ± 7.6	51.7 ± 5.9	NE
Sex (male)	1164 (48.2)	167 (44.1)	.132
BMI	22.9 ± 3.3	23.6 ± 4.1	.030
Current smoker (Yes)	340 (14.1)	110 (29.0)	<.001
Walking or physical exercise ≥1 h/wk (No)	1183 (49.0)	148 (39.1)	<.001
Increment in weight ≥10 kg since the age of 20 y (Yes)	795 (32.9)	163 (43.0)	<.001
Eats dinner within 2 h before bedtime, ≥3 times/wk (Yes)	299 (12.4)	70 (18.5)	.001
Use of hypotensive agents	1215 (50.3)	88 (23.2)	<.001
Use of lipid-lowering agents	741 (30.7)	43 (11.3)	<.001
Triglyceride (mg/dL)	118.9 ± 69.7	127.0 ± 92.6	.913
LDL cholesterol (mg/dL)	122.9 ± 31.6	125.5 ± 32.3	.207
HDL cholesterol (mg/dL)	60.9 ± 16.6	63.4 ± 17.9	.013
Use of antidiabetic agents	236 (9.8)	22 (5.8)	.013
HbA1c (%)	5.8 ± 0.6	5.6 ± 0.7	<.001
AST (IU/L)	25.1 ± 13.4	24.6 ± 10.7	.045
ALT (IU/L)	20.3 ± 12.8	24.6 ± 15.9	<.001
GGT (IU/L)	36.0 ± 53.2	41.7 ± 44.3	.003
Estimated GFR (mL/min/1.73 m ²)	67.3 ± 15.6	77.6 ± 13.5	<.001

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GFR, glomerular filtration rate; GGT, gamma-glutamyl transpeptidase; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NE, not evaluate.

are thought to be extremely rare. Despite these limitations, we identified several factors associated with psoriasis onset in this study.

In conclusion, our data confirmed that increasing age, male sex, smoking, BMI, weight gain since the age of 20 years, low physical activity levels, and GGT are associated with the late-onset development of psoriasis in the Japanese population. Further research on the relationship between liver function disorders and the development of psoriasis are needed.

Comments and data management were provided by Dr Kiyoshi Tanaka (Kobe Gakuin University), Dr Yasuharu Tabara (Kyoto University), Dr Noriko Kojimahara, Yoshimi Iwasaki, Fumihiko Makita, and Junpei Minami (Shizuoka General Hospital). The manuscript was edited by Edanz Group (<https://en-author-services.edanzgroup.com/>).

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