Japanese Dermatological Association
The Journal of Dermatology
doi: 10.1111/1346-8138.15052
Journal of Dermatology 2019; ●●: 1–8

ORIGINAL ARTICLE

Increased risk of atherosclerotic cardiovascular disease among patients with psoriasis in Korea: A 15-year nationwide population-based cohort study

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ABSTRACT

The association between psoriasis and risk of atherosclerotic cardiovascular disease has not been thoroughly evaluated in a large longitudinal cohort of an Asian population. We conducted a nationwide population-based retrospective cohort study encompassing more than 1.7 million Koreans with a 15-year follow-up period. The period prevalence of psoriasis was 0.33% among the baseline participants (1997–2000). In Cox proportional hazard analyses, the individuals with psoriasis had a higher adjusted hazard ratio (HR) for incidence of overall atherosclerotic cardiovascular disease (HR, 1.18; 95% confidence interval [CI], 1.09–1.27) compared with controls. Subgroup analyses revealed that the risk for myocardial infarction was commonly increased in both sexes with moderate to severe psoriasis (male: HR, 2.09; 95% CI, 1.35–3.24; female: HR, 3.23; 95% CI, 1.34–7.76), whereas the risk for ischemic stroke was specifically increased in female individuals with moderate to severe psoriasis (HR, 2.02; 95% CI, 1.24–3.30). Our data suggest that appropriate medical screening for possible cardiovascular comorbidities is warranted in Asian psoriatic patients according to disease severity and sex.

Key words: atherosclerotic cardiovascular disease, cohort study, epidemiology, Korea, psoriasis.

INTRODUCTION

Psoriasis is an immune-mediated inflammatory skin disorder characterized by erythematous scaly plaques of chronic nature.[1] It affects approximately 1–5% of the Western population, but its prevalence in the Asian population is reported to be lower than 1%.[2,3] The major underlying immunopathogenesis of psoriasis consists of the immune cell-derived interleukin (IL)-23–IL-17 cytokine axis which mediates dysregulated hyperproliferation and differentiation of keratinocytes.[4] In addition, other pro-inflammatory cytokines such as IL-1β, IL-6 and tumor necrosis factor-α are also highly expressed in the psoriatic lesions, which synergistically drive chronic psoriatic immune reactions in a "feed forward" manner.[5,6] Patients with psoriasis frequently present an increased level of inflammatory cytokines in sera, indicating that psoriatic inflammation may have systemic effects.[7–10] Indeed, psoriatic patients frequently demonstrated an increased level of circulating C-reactive protein which is a known marker of systemic inflammation.[11] Our group previously showed that several inflammation-associated markers, such as red blood cell distribution width,[12] mean platelet volume[13] and neutrophil-to-lymphocyte ratio[14] were commonly elevated in psoriatic patients, further supporting an underlying systemic inflammation in psoriasis. As a systemic disease, it has been extensively examined whether patients with psoriasis have an increased risk for cardiovascular and ischemic comorbidities.[15–17] Several studies involving population-based cohorts and meta-analysis have demonstrated that psoriasis is an independent risk factor for developing cardiovascular diseases, in which more severe psoriasis exhibits a higher risk rate.[18–23] However, currently most of the available studies were based on Caucasian populations and there has been relatively

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Received 18 April 2019; accepted 25 July 2019.

little evidence demonstrating a direct causal relationship between psoriasis and subsequent development of atherosclerotic cardiovascular diseases (ASCVD) in Asians. Lin *et al*.[24] reported an increased risk of acute myocardial infarction (MI) in Taiwanese patients with psoriasis using nationwide population-based data. However, they described relatively short 5-year follow-up outcomes with a lack of adjustment for some important risk factors for MI, which would be insufficient to conclude a solid association between psoriasis and an increased risk of MI.

Here, we demonstrate a 15-year nationwide retrospective cohort study comprising more than 1.7 million Korean adults to examine the risk of ASCVD in Korean psoriatic patients. We found that psoriasis is a strong independent risk factor for an overall incidence of ASCVD comprised of ischemic heart disease (IHD) such as angina pectoris and MI, ischemic stroke and hemorrhagic stroke after adjusting for major compounding variables. Intriguingly, our results show an increased risk for MI in both sexes with severe psoriasis, whereas the risk for ischemic stroke is specifically elevated in females with severe disease. Therefore, our study reveals that there is a differential risk for each ischemic event in Korean patients with psoriasis according to the disease severity and sex, which implicates a necessity of tailored screening strategies to prevent and control different ASCVD comorbidities in Asian psoriatic patients.

METHODS

Study population

The study design and baseline characteristics of The Korean Cancer Prevention Study (KCPS) have been described in our previous studies.[25,26] The National Health Insurance Service (NHIS) provides health insurance to government employees, teachers and their dependents. Approximately 96% of South Koreans are covered by the NHIS, through which all Korean citizens are eligible to participate in regular health examinations.

The baseline was between 1997 and 2000, with 1 838 570 people aged 20 years or older included in the initial cohort. All participants received a medical evaluation provided by the NHIS between 1997 and 2000. For participants who underwent two or more examinations, data at the first examination was used. We excluded 1190 persons whose records were missing information on body mass index (BMI), alcohol intake, blood pressure, fasting blood glucose levels or total cholesterol levels; 60 085 who self-reported having cancer or cardiovascular diseases (hypertension [HTN], heart disease or stroke) at or prior to the baseline survey; and 2227 with extremely low BMI ($<$15.0 kg/m^2) or extremely short stature ($<$1.3 m). Thus, we initially recruited 1 775 068 subjects from the national sample cohort. The institutional review board of Yonsei University approved the study (IRB no. 4-2001-0029).

Data collection

All participants underwent medical examinations at local hospitals. Enrollees underwent standardized biennial examinations with collection of the following information by standardized questionnaire and medical examination. The standardized questionnaire included the status of cigarette smoking (never, former, current), alcohol intake (g ethanol/day) and current participation in physical exercise (yes or no) using self-reported questions, while the medical examination collected data including total cholesterol and glucose levels assayed from a fasting serum specimen, and each participating hospital in the examination had external quality control procedures that were supervised by the Korean Association of Laboratory Quality Control. Height and weight were measured while the participants wore light clothing without shoes, and BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2).[25]

Ascertainment of diseases associated with psoriasis

We captured outpatient and inpatient records from 1997 through 2015 deposited in the NHIS database. Outpatient treatment and hospitalization for psoriatic diseases were identified according to the 10th revised codes of the International Classification of Diseases (ICD-10), code L40. Because our study was specifically aimed to assess the long-term risk for ASCVD among the patients with typical chronic psoriasis, we excluded 1282 individuals diagnosed with other clinical variants of psoriasis (L40.1, generalized pustular psoriasis; L40.2, acrodermatitis continua; L40.3, pustulosis palmaris et plantaris; and L40.4, Guttate psoriasis) and 40 166 individuals diagnosed with any type of psoriatic diseases beyond the baseline period. Thus, 1 733 620 individuals (692 226 female) were finally included in the study (Fig. 1). Then, psoriasis was defined using the ICD-10 codes L40.0 (psoriasis vulgaris) and L40.5 (arthropathic psoriasis [M07.0–M07.3]) registered by the responsible physicians. Psoriatic severity was defined as moderate to severe disease if the patients received treatment codes with systemic antipsoriatic therapy (cyclosporin, methotrexate, retinoids, azathioprine, phototherapy comprising narrowband ultraviolet B and psoralen plus ultraviolet A, and biologic agents) as described and validated previously.[18,27] A group with mild psoriasis was defined if the patients never received systemic treatment codes. The control group who never received a diagnostic code consistent with psoriasis was also defined.

Follow up and outcomes

Using computerized searches of data provided by the NHIS in Korea,[28] outcomes were ascertained from diagnosis listed on hospital discharge summaries. With rare emigration from South Korea,[28] follow up was likely to be close to 100% complete. The principal outcomes were ASCVD morbidities according to ICD-10 codes: (i) IHD (I20–I25) including angina pectoris (I20) and MI (I21–I23); (ii) stroke (I60–I69); and (iii) cardiovascular disease, which, in addition to (i) and (ii), included hypertensive disease (I10–I15), other diseases likely to be related to ASCVD (I44–I51), sudden death (R96) and other vascular disease (I70–I74). For individuals with more than one event recorded, we used the first event for analysis. The follow-up period was from January 2000 to December 2015. Members of an Event Validation Committee visited select hospitals to review medical records so as to assess the accuracy of medical insurance claims for IHD and stroke, by validating such events against

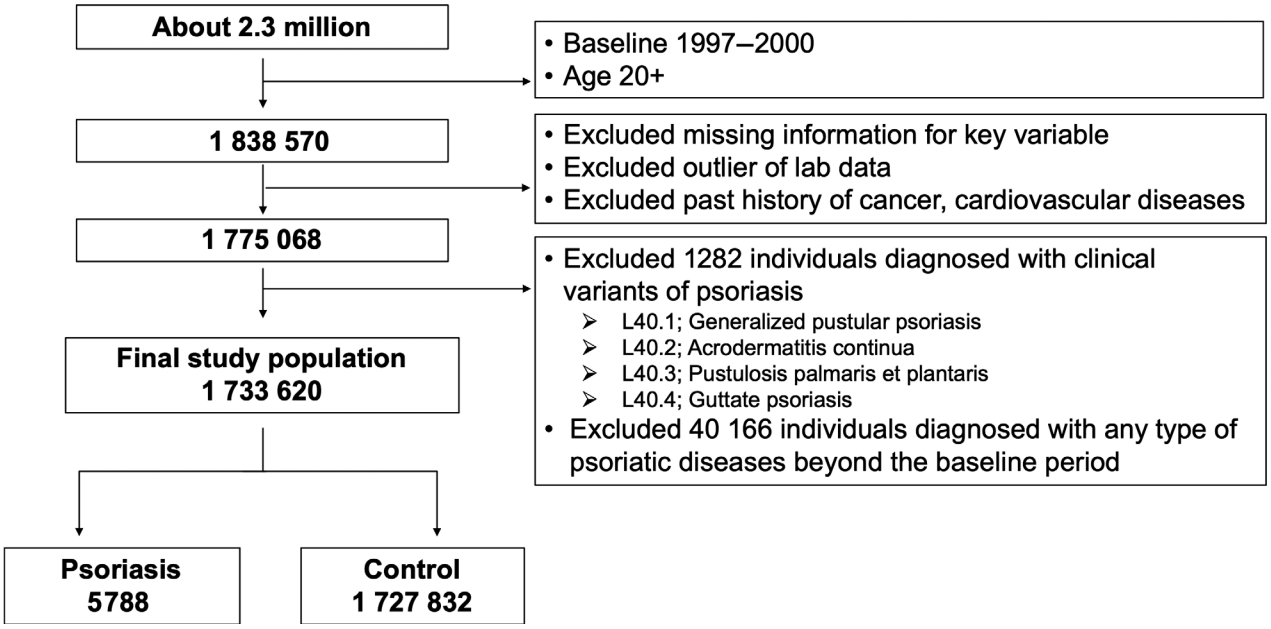

Figure 1. Flowchart of study cohort selection.

hospital records. Based on a sample of 673 IHD patients and 626 stroke patients, we found 73% and 83% accuracy, respectively.[29]

Statistical analysis

All analyses were conducted using SAS version 9.4 software (SAS Institute Inc, Cary, NC, USA). Analyses were stratified by sex and adjusted for age and other potential confounding factors. Cox proportional hazards models were used to evaluate the association of psoriasis with risk for various indicators of ASCVD. We used the PROC PHREG procedure, and calculated the *P*-value by Student's *t*-test for continuous variables and the χ^2-test for categorical variables (Table 1).

RESULTS

Baseline characteristics of the study cohort

A total of 1 733 620 Korean subjects who received health insurance from the NHIS were enrolled between 1997 and 2000. During the baseline period, a total of 5788 subjects were defined as a psoriatic group displaying 0.33% of period prevalence rate, which is consistently lower than that of Caucasian populations (Table 1). The point prevalence of psoriasis among male subjects was higher than that of female participants (0.36% vs 0.29%, respectively). Comparison of baseline characteristics between the control and psoriatic groups revealed that individuals with psoriasis had a significantly greater level of BMI, total cholesterol and systolic blood pressure. In addition, psoriatic individuals showed a higher coexistence of obesity, dyslipidemia and diabetes, collectively demonstrating an increased prevalence of multiple cardiovascular risk factors in

Table 1. Baseline characteristic of study participants between non-psoriasis and psoriasis

	Non-psoriasis (*n* = 1 727 832)	Psoriasis (*n* = 5788)	*P*
Mean (SD)			
Age, years	43.50 (12.89)	44.25 (12.82)	<0.0001
Body mass index, kg/m^2	23.20 (2.92)	23.29 (2.87)	0.013
Total cholesterol, mg/dL	190.11 (36.68)	192.70 (36.92)	<0.0001
Systolic blood pressure	121.45 (16.36)	122.08 (16.22)	0.003
Fasting glucose, mg/dL	91.72 (24.07)	92.34 (25.56)	0.062
% (*n*)			
Sex (female)	39.24 (680 320)	34.62 (2004)	<0.0001
Smoking status			
Ex-smokers	8.85	10.79	<0.0001
Current smokers	36.05	39.53	
Drinking (yes)	53.46	53.47	0.983
Exercise (yes)	49.93	50.26	0.615
Obesity*	25.90	27.71	0.002
Dyslipidemia#	9.35	10.45	0.004
Hypertension†	24.54	24.62	0.892
Diabetes‡	4.53	5.32	0.004

*Obesity was defined as body mass index of >25. #Dyslipidemia was defined as total cholesterol of ≥240. †Hypertension was defined as systolic blood pressure of ≥140 mmHg or a history of treatment for hypertension. ‡Diabetes was defined as fasting serum glucose of ≥126 mg/dL or a history of treatment for diabetes. SD, standard deviation.

Korean patients with psoriasis as similarly seen in other Western studies.[30–33]

Risk of ASCVD in Korean patients with psoriasis

Next, we analyzed the new-onset events of overall ASCVD during the 15 years of the observational study period (Table 2). The incidence rate for ASCVD was 864.0 and 729.6 per 100 000 person-years (PY) in the psoriatic and non-psoriatic groups, respectively. The psoriatic group showed a significantly increased hazard ratio (HR) for ASCVD as compared with non-psoriatic controls after stratifying by age and sex and adjusting for several known risk factors of ASCVD (HR, 1.18; 95% confidence interval [CI], 1.09–1.27). Both sexes with psoriasis demonstrated a commonly increased rick for ASCVD (males: HR, 1.17; 95% CI, 1.07–1.27; females: HR, 1.20; 95% CI, 1.04–1.37). These results indicate that psoriasis is an independent risk factor for an increased incidence of ASCVD in Koreans.

We subsequently examined the risk of each ASCVD among the patients with psoriasis. As previous reports showed that the risk for cardiovascular and cerebrovascular events was much greater in moderate to severe psoriasis as compared with mild disease,[18,19] we additionally classified the psoriatic group according to the disease severity determined by treatment codes for systemic therapies. The risk of IHD was significantly increased in male (HR, 1.33; 95% CI, 1.18–1.50), but not in female psoriatic patients (HR, 1.19; 95% CI, 0.95–1.49) (Table S1). Male psoriatic patients with moderate to severe disease displayed a slightly higher risk for IHD as compared with mild psoriasis (mild psoriasis: HR, 1.25; 95% CI, 1.10–1.44; moderate to severe psoriasis: HR, 1.67; 95% CI, 1.30–2.15) (Table 3). The risk of angina pectoris showed a similar trend for the sex-biased risk of IHD, which was significantly increased in male (HR, 1.40; 95% CI, 1.23–1.59) but not in female psoriasis (HR, 1.13; 95% CI, 0.89–1.46). Male patients with moderate to severe psoriasis had a slightly greater risk of angina pectoris than those with mild psoriasis (mild: HR, 1.36; 95% CI, 1.18–1.57; moderate to severe: HR, 1.58; 95% CI, 1.20–2.08). However, in contrast to angina pectoris, the risk for overall MI was not generally increased in both sexes of psoriasis as compared with the comparison group (Table S1). Notably, subgroup analysis revealed that the hazard of MI was 2.24-times greater (95% CI, 1.51–3.32) for patients with moderate to severe psoriasis than the comparison group. This trend was commonly observed in both sexes with more severe psoriasis (male: HR, 2.09; 95% CI, 1.35–3.24; female: HR, 3.23; 95% CI, 1.34–7.76), but not in mild psoriasis (Table 3). The incidence of total stroke was increased in female patients with psoriasis (HR, 1.23; 95% CI, 1.02–1.49), whereas psoriatic male patients did not demonstrate any increased risk for stroke (Table S1). According to the type of stroke, the risk of ischemic stroke, but not hemorrhagic stroke, was distinctly elevated in female patients with psoriasis (HR, 1.37; 95% CI, 1.08–1.74). Furthermore, we found that an increased risk for ischemic stroke in female psoriatic patients was principally conferred by the severe psoriatic subgroup (HR, 2.02; 95% CI, 1.24–3.30) (Table 3). Therefore, our data indicated that psoriasis is associated with an increased risk of ischemic cardiovascular events in both sexes with severe psoriasis, whereas the risk for ischemic cerebrovascular disease is specifically elevated in female patients with severe disease in Korea.

Next, we additionally performed subgroup analyses for the risk of MI and ischemic stroke in psoriatic patients according to the existence of complications. The significant effects of severe psoriasis on the risk of MI were even observed in subgroups without well-known MI risk factors (i.e. obesity, diabetes mellitus [DM], HTN and dyslipidemia) (Table 4). Interestingly, this trend was more clearly demonstrated in male psoriatic patients compared with female. The effects of psoriasis on the risk of ischemic stroke were observed in female patients with severe psoriasis without obesity and DM (Table 5). In addition, non-obese female patients with mild psoriasis showed an increased risk for ischemic stroke, which was more greatly increased in the severe group (mild: HR, 1.45; 95% CI, 1.05–2.02; moderate to severe: HR, 2.30; 95% CI, 1.27–4.15). Again, these results strongly indicated that psoriasis is an independent risk for MI and ischemic stroke in Korean patients with severe psoriasis.

DISCUSSION

In this 15-year nationwide cohort study, we found that psoriatic patients (n = 5788) had a significantly higher risk of having

Table 2. Incidence rate (per 100 000) and adjusted hazard ratios for ASCVD by psoriasis

	Person-years	ASCVD event	Incidence rate per 100 000 PY*	Hazard ratio (95% confidence interval)
Total				
Non-psoriasis	28 906 309	173 539	729.6	1.0
Psoriasis	95 335	719	864.0	1.18 (1.09–1.27)
Men				
Non-psoriasis	17 312 962	108 583	730.6	1.0
Psoriasis	61 331	510	849.8	1.17 (1.07–1.27)
Women				
Non-psoriasis	11 593 347	64 953	699.7	1.0
Psoriasis	34 004	209	828.7	1.20 (1.04–1.37)

*Incidences were standardized to the age distribution in the 2005 Korean population. Adjusted for age, sex, smoking status, alcohol consumption, exercise, body mass index, dyslipidemia, hypertension and diabetes. ASCVD, atherosclerotic cardiovascular disease; PY, person-years.

Table 3. Adjusted hazard ratios for ASCVD by psoriasis according to the disease severity

	ASCVD	IHD	Angina pectoris	MI	Total stroke	Ischemic stroke	Hemorrhagic stroke
Total							
Non-psoriasis	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Mild psoriasis*	1.16 (1.07–1.26)	1.25 (1.11 –1.41)	1.32 (1.17–1.50)	0.96 (0.72 –1.26)	1.09 (0.97–1.23)	1.08 (0.93–1.27)	0.92 (0.70–1.21)
Moderate to severe psoriasis†	1.23 (1.04–1.46)	1.52 (1.21–1.92)	1.38 (1.06–1.79)	2.24 (1.51–3.32)	1.23 (0.96–1.59)	1.27 (0.93–1.74)	1.00 (0.73–1.37)
Men							
Non-psoriasis	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Mild psoriasis*	1.16 (1.05–1.27)	1.25 (1.10–1.44)	1.36 (1.18–1.57)	0.95 (0.70–1.29)	1.06 (0.92–1.23)	1.02 (0.85–1.23)	1.00 (0.73–1.37)
Moderate-to-severe psoriasis†	1.22 (1.00–1.50)	1.67 (1.30–2.15)	1.58 (1.20–2.08)	2.09 (1.35–3.24)	1.03 (0.75–1.43)	1.00 (0.67–1.51)	0.95 (0.47–1.90)
Women							
Non-psoriasis	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Mild psoriasis*	1.19 (1.02–1.38)	1.23 (0.97–1.57)	1.21 (0.94–1.57)	1.05 (0.55–2.02)	1.14 (0.92–1.41)	1.25 (0.95–1.64)	0.76 (0.44–1.30)
Moderate-to-severe psoriasis†	1.24 (0.89–1.72)	0.99 (0.53–1.83)	0.69 (0.31–1.54)	3.23 (1.34–7.76)	1.71 (1.14–2.55)	2.02 (1.24–3.30)	1.19 (0.45–3.17)

*Mild psoriasis: no systemic treatment. †Moderate to severe psoriasis: conventional oral medication, phototherapy and biologic agent user. Adjusted for age, sex, smoking status, alcohol consumption, exercise, body mass index, dyslipidemia, hypertension and diabetes. ASCVD, atherosclerotic cardiovascular disease; IHD, ischemic heart disease; MI, myocardial infarction.

Table 4. Subgroup analyses for MI risk in psoriatic patients according to the existence of major comorbidities

	MI							
	Obesity (*n* = 449 052)	Non-obesity (*n* = 1 284 568)	DM (*n* = 78 632)	Non-DM (*n* = 1 654 988)	HTN (*n* = 425 484)	Non-HTN (*n* = 1 308 135)	Dyslipidemia (*n* = 162 091)	Non-dyslipidemia (*n* = 1 571 529)
Total								
Non-psoriasis	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Mild psoriasis*	1.20 (0.54–2.67)	0.89 (0.61–1.27)	0.42 (0.16–1.13)	1.07 (0.80–1.43)	1.10 (0.74–1.63)	0.85 (0.57–1.26)	1.32 (0.79–2.18)	0.86 (0.61–1.19)
Severe psoriasis†	3.09 (1.00–9.58)	2.30 (1.39–3.81)	1.18 (0.30–4.72)	2.41 (1.60–3.63)	2.52 (1.46–4.34)	1.94 (1.10–3.41)	2.50 (1.19–5.25)	2.12 (1.33–3.36)
Men								
Non-psoriasis	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Mild psoriasis*	1.07 (0.70–1.65)	0.84 (0.56–1.27)	0.40 (0.13–1.23)	1.06 (0.77–1.46)	0.96 (0.60–1.52)	0.95 (0.63–1.43)	1.22 (0.67–2.20)	0.88 (0.62–1.26)
Severe psoriasis†	2.15 (1.15–3.99)	2.17 (1.23–3.83)	1.44 (0.36–5.75)	2.18 (1.37–3.46)	2.29 (1.23–4.25)	1.86 (1.00–3.46)	2.01 (0.84–4.82)	2.08 (1.26–3.46)
Women								
Non-psoriasis	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Mild psoriasis*	1.13 (0.71–1.80)	1.20 (0.54–2.67)	0.52 (0.07–3.66)	1.22 (0.61–2.44)	1.85 (0.88–3.89)	0.41 (0.10–1.63)	1.99 (0.74–5.31)	0.76 (0.32–1.82)
Severe psoriasis†	1.98 (0.99–3.95)	3.09 (1.00–9.58)	–	3.73 (1.55–8.96)	3.94 (1.27–12.20)	2.44 (0.61–9.77)	5.92 (1.48–23.70)	2.41 (0.78–7.49)

*Mild psoriasis: no systemic treatment. †Moderate to severe psoriasis: conventional oral medication, phototherapy and biologic agent user. Adjusted for age, sex, smoking status, alcohol consumption, exercise, body mass index, dyslipidemia, hypertension and diabetes. DM, diabetes mellitus; HTN, hypertension; MI, myocardial infarction.

Table 5. Subgroup analyses for ischemic stroke risk in psoriatic patients according to the existence of major comorbidities

	Ischemic stroke							
	Obesity (n = 449 052)	Non-obesity (n = 1 284 568)	DM (n = 78 632)	Non-DM (n = 1 654 988)	HTN (n = 425 484)	Non-HTN (n = 1 308 135)	Dyslipidemia (n = 162 091)	Non-dyslipidemia (n = 1 571 529)
Total								
Non-psoriasis	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Mild psoriasis*	1.10 (0.85–1.42)	1.08 (0.89–1.31)	0.76 (0.50–1.17)	1.16 (0.98–1.37)	1.14 (0.92–1.42)	1.03 (0.83–1.28)	1.13 (0.78–1.64)	1.07 (0.91–1.27)
Severe psoriasis†	0.99 (0.56–1.74)	1.46 (1.00–2.12)	0.99 (0.41–2.38)	1.32 (0.94–1.85)	1.40 (0.92–2.12)	1.09 (0.68–1.76)	2.07 (1.14–3.74)	1.09 (0.75–1.58)
Men								
Non-psoriasis	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Mild psoriasis*	1.16 (0.86–1.57)	0.95 (0.75–1.20)	0.63 (0.37–1.09)	1.11 (0.91–1.35)	1.05 (0.81–1.36)	0.99 (0.76–1.30)	1.00 (0.62–1.61)	1.02 (0.84–1.26)
Severe psoriasis†	0.77 (0.37–1.62)	1.16 (0.71–1.89)	0.74 (0.24–2.29)	1.06 (0.68–1.64)	1.08 (0.63–1.86)	0.89 (0.48–1.65)	1.71 (0.82–3.60)	0.85 (0.52–1.38)
Women								
Non-psoriasis	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Mild psoriasis*	0.98 (0.61–1.57)	1.45 (1.05–2.02)	1.16 (0.58–2.32)	1.28 (0.95–1.71)	1.40 (0.96–2.06)	1.12 (0.77–1.63)	1.41 (0.78–2.56)	1.21 (0.90–1.64)
Severe psoriasis†	1.58 (0.66–3.79)	2.30 (1.27–4.15)	2.13 (0.53–8.54)	1.99 (1.18–3.35)	2.45 (1.28–4.71)	1.63 (0.77–3.41)	3.48 (1.31–9.25)	1.76 (1.00–3.10)

*Mild psoriasis: no systemic treatment. †Moderate to severe psoriasis: conventional oral medication, phototherapy and biologic agent user. Adjusted for age, sex, smoking status, alcohol consumption, exercise, body mass index, dyslipidemia, hypertension and diabetes. DM, diabetes mellitus; HTN, hypertension.

ASCVD (HR, 1.18) than control individuals (n = 1 727 832) in Korea. Upon subgroup analyses stratified by the severity of psoriasis, more severe disease was shown to be associated with a higher incidence of MI in men (HR, 2.09) and women (HR, 3.23), and the risk of ischemic stroke was specifically elevated in the severe group of female psoriasis (HR, 2.02). Furthermore, the risk of MI and ischemic stroke was also increased in subgroups of severe psoriasis with a lack of certain major cardiovascular risk factor. Overall, our data suggest that psoriasis is an independent risk for the development of ASCVD in the Asian adult population.

The chronic inflammatory nature of psoriasis has led to an extensive investigation of possible causal relationship between psoriasis and systemic comorbidities including cardiovascular events. Previous studies showed that patients with psoriasis were more likely to have multiple cardiovascular risk factors, including diabetes, HTN, hyperlipidemia, obesity and smoking than the control population, suggesting that accompanying cardiometabolic abnormalities in psoriatic patients may lead to ASCVD comorbidities.[30,31] However, several population-based studies primarily based on Western populations revealed that psoriasis is an independent risk factor for an increased incidence of MI and ischemic events after adjusting cardiovascular risk factors.[18,19,21,23] Highly increased levels of pro-inflammatory molecules and cytokine-activated leukocytes entering systemic circulation have been implicated in the resultant cardiovascular and metabolic comorbidities in psoriatic individuals.[34,35] Indeed, certain transgenic mouse models of psoriatic inflammation were shown to be prone to developing thrombotic comorbidity which was protected by inhibition of IL-23 or IL-17A.[36] However, to date, the long-term risk for ASCVD in Asian patients with psoriasis has not been sufficiently understood. Because Asian psoriasis exhibited different characteristics of inflammatory gene signatures as compared with those of Caucasian psoriasis,[37,38] systemic comorbidities in Asian psoriasis could not be directly estimated by results from a Caucasian population. Our current cohort study demonstrated that psoriasis is independently associated with an increased risk of ASCVD in Koreans. To the best of our knowledge, this is the first, largest and longest observational cohort study unveiling direct association between psoriasis and an increased risk of ASCVD comorbidities among Asians. Considering the relatively lower prevalence of psoriasis in Asian countries including Korea (0.3–0.4% prevalence rate),[2,3,39] the results from our large-scale cohort enabled us to assess the significant risk for ASCVD in Korean psoriatic patients from more than 1.7 million enrolled participants.

Previous studies from Asian populations determining the association between psoriasis and cardiovascular and ischemic comorbidities have mostly utilized national insurance claim data which largely lack information of major cardiovascular risk factors such as BMI, smoking status and numerical values of fasting glucose and cholesterol.[24,40] Our current study was designed to collect lifestyle information and basic laboratory values at biennial intervals which enabled us to determine more accurately the risk of ASCVD in Korean patients with psoriasis as reported in a previous Western study.[18] Primary

results revealed that overall risk for ASCVD was significantly increased both in male and female patients with psoriasis. When we analyzed each disease of ASCVD, risk for angina pectoris and total stroke was specifically observed in male and female psoriatic patients, respectively. Further subgroup analyses revealed that the risk of MI was equally increased both in male and female patients with severe psoriasis, whereas that of ischemic stroke was specifically elevated only in females with severe disease. For control individuals, we found a higher incidence of MI in male than female (77.0 vs 42.8 per 100 000 PY), whereas incidence of ischemic stroke was comparable between both sexes (225.0 vs 219.4 per 100 000 PY) (Table S1). Because the history of MI would further increase the risk of ischemic stroke,[41] it seems that the much greater risk for MI observed in female patients with severe psoriasis compared with male patients (female vs male: HR, 3.23 vs 2.09) would be associated with the female-biased risk for ischemic stroke. For coronary artery disease in female patients with severe psoriasis, we found the discrepant risk between angina pectoris (HR, 0.69) and MI (3.23). Although coronary artery disease-associated angina is a major risk factor for MI,[42] it has been shown that the frequency of MI without angina was significantly higher for women compared with men.[43] It is possible that psoriasis in women would not increase the risk of angina pectoris (i.e. transient ischemic events), but rather directly accelerates the rupture of vulnerable coronary plaques and subsequent development of overt MI which is closely associated with the status of systemic inflammation.[44]

In subgroup analyses according to the existence of comorbidities, the relative risk effects of psoriasis on MI and ischemic stroke were consistently observed in severe psoriatic patients even without known cardiovascular risk factors. Similar to our results, previous studies demonstrated that the relative risk for cardiovascular disease and thromboembolism was somewhat higher in psoriatic patients without certain traditional cardiovascular risk factors compared with the patients having risks.[40,45] These results suggest that the risk effect of psoriasis on cardiovascular diseases would be rather masked in patients with greater cardiovascular risk subgroups. Nevertheless, our data showed that psoriasis is associated with an increased risk of MI in severe male patients complicated with obesity and HTN. In addition, psoriasis also augmented the risk of MI and ischemic stroke in severe female patients with HTN and dyslipidemia. Therefore, psoriatic patients with severe disease are highly warranted to manage traditional cardiovascular risk factors to lower the risk of life-threatening ischemic comorbidities.

Our study has several limitations. First, the NHIS database may comprise incorrect diagnoses of the patients with psoriasis. However, clinical diagnosis of chronic plaque psoriasis based on the typical features is mostly unambiguous. Furthermore, to specifically define the group of typical psoriasis, we excluded psoriatic patients who were classified as the variants of psoriasis according to the diagnostic codes from the baseline participants. Second, detailed clinical information about psoriasis such as disease duration, family history and objective scores of disease severity are not eligible in the NHIS database. Thus, we could not examine some possible covariants affecting ASCVD outcomes. Third, the KCPS cohort is comprised of government employees, teachers and their dependents which might have resulted in selection bias of the study population. However, we consider that the risk of bias is too low to affect the results.

Nevertheless, this study has several clinical significances. We explored the 15-year ASCVD risk of exceptionally large numbers of Korean psoriatic patients and control individuals from the nationwide database in a retrospective manner. Our study design would clearly demonstrate the causal relationship between psoriasis and ASCVD outcomes in Asians. For the outcome measurements, we explored several kinds of cardiovascular and cerebrovascular events which encompass a major burden of comorbidities in psoriatic patients. This enabled us to dissect which ASCVD comorbidities were specifically associated with psoriasis in great detail.

In conclusion, our study revealed that psoriasis is an independent risk of ASCVD in Korean adult patients with psoriasis. More severe psoriasis was significantly associated with two to three times of an increased risk of MI in male and female patients, which emphasizes a rigorous counseling and physical examination in those patients. Furthermore, there is a differential risk for each ischemic event according to the sex, which implicates a necessity of tailored screening strategies to prevent and control different ASCVD comorbidities in Asian psoriatic patients in the future.

ACKNOWLEDGMENTS: This study was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health and Welfare (no. HI14C2686 to S. H. J. and HI17C1659 to M. G. L.), by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (no. NRF-2016R1A6A3A11933465 to K. J. J. and NRF-2017R1D1A1B03035571 to T. G. K), and by the NRF grant funded by the Korean Government (Ministry of Science and ICT (no. NRF-2018R1A2B6007818 to M. G. L.).

CONFLICT OF INTEREST: None declared.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Table S1. Incidence rate (per 100 000) and adjusted hazard ratios for individual comorbidity of atherosclerotic cardiovascular disease by psoriasis.