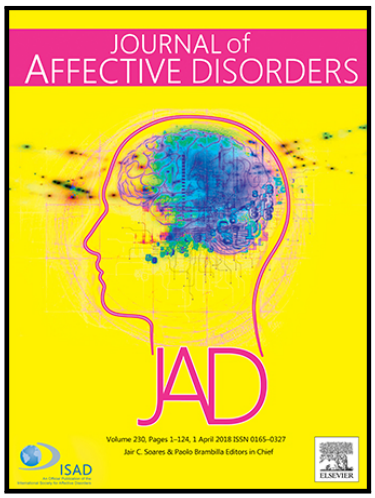

Bidirectional association between psoriasis and depression: Two longitudinal follow-up studies using a national sample cohort

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Highlights

- Two studies were conducted for the association between psoriasis and depression.
- The distributions were comparably matched between psoriasis and control I group.
- The distributions were comparably matched between depression and control II group.
- Depression occurred more frequently in psoriasis patients.
- Psoriasis occurred more frequently in younger and older males with depression.

Bidirectional association between psoriasis and depression:

Two longitudinal follow-up studies using a national sample cohort

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Abstract

Background: Few studies have investigated the bidirectional association between psoriasis and depression. The aim of our study was to identify the association between psoriasis and depression.

Methods: Data collected by the Korean Health Insurance Review and Assessment from 2002 to 2013 were used. In study I, psoriasis patients (n = 10,932) were matched 1:4 with control I group participants. In study II, depression patients (n = 60,383) were matched 1:4 with control II group participants. Matching was performed for age, sex, income, and region of residence. The stratified Cox-proportional hazard model was used to calculate the hazard ratio (HR) with crude and adjusted models.

Results: In study I, the adjusted HR for depression was 1.13 (95% confidence interval (CI) = 1.03-1.24) in the psoriasis group compared to the control I group. In study II, the adjusted HR for depression was 1.11 (95% CI = 1.00-1.22) in the depression group compared to the control II group. In the subgroup analyses, the adjusted HRs for depression were 1.24 (95% CI = 1.00 – 1.53) in females aged < 40 years and 1.31 (95% CI = 1.04 - 1.66) in males aged ≥ 60 years. In the subgroup analyses from study II, the adjusted HRs for psoriasis were 1.56 (95% CI = 1.15 – 2.12) in males aged < 40 years and 1.35 (95% CI = 1.04 – 1.75) in males aged ≥ 60 years.

Conclusions: We suggest that psoriasis and depression might have a bidirectional association.

Key words: psoriasis; depression; inflammation; immunity; bidirectional association

1. Introduction

Psoriasis is a chronic inflammatory disease characterized by skin with plaques and silvery scales (Kim et al., 2017). The prevalence of psoriasis is approximately 2%-3% worldwide (Christophers, 2001; Rachakonda et al., 2014) and approximately 0.3%-0.4% in the Asian population (Kubota et al., 2015; Lee et al., 2017; Yip, 1984). Psoriasis has a psychosocial effect on patients that can include stigmatization and social isolation that lead to a reduced quality of life (Krueger et al., 2001; Wahl et al., 2002). Relatedly, psoriasis has been associated with the development of psychiatric illness, including anxiety, depression, and suicidality (Kim et al., 2017; Kurd et al., 2010). The pathophysiologic mechanism of psoriasis is complex and includes immune disturbance and environmental factors (Boehncke, 2015; Kim and Krueger, 2015). Classical T helper (Th) 1 and Th17 cell immune responses and other types of innate and adaptive immune systems are believed to contribute to the development of psoriasis (Boehncke, 2015). Increasing evidence suggests that various immune-mediated and inflammatory diseases are associated with psoriasis, such as arthritis, cancer, and cardiovascular disease (Hu and Lan, 2017; Kim et al., 2017; Yang et al., 2011).

Depression is a complex disorder that results from biological, genetic, environmental, and psychological factors (Sullivan et al., 2000). Previous studies have suggested that the depression can be caused by disease in addition to psychological factors such as distress about an illness, awareness of oneself in society, or economic impacts (Cheng and Silverberg, 2019; Simanek et al., 2014; Wahl et al., 2002). Another possible cause of depression is inflammatory cytokines that affect cellular immunity (Han and Yu, 2014). Increasing evidence has shown that depression is associated with a reduced lymphocyte proliferation response and a decrease in the proportions of lymphocytes and T cells that are responsible for cell-mediated immunity (Zorrilla et al., 2001). Among inflammatory cytokines, C-reactive protein (CRP) and interleukin (IL)-6 are associated with the development of depression

(Valkanova et al., 2013; Young et al., 2014). In contrast, some studies have reported that depression predicted the presence of inflammatory cytokines, including IL-6 and CRP (Copeland et al., 2012; Deverts et al., 2010; Duivis et al., 2011; Matthews et al., 2010). Likewise, Tohid et al. suggested that psoriasis, as a systemic inflammation disease, and depression might be mutually causative through a possible bidirectional relationship (Tohid et al., 2016). Several cohort studies have reported that psoriasis was associated with a risk of depression (Dommasch et al., 2015; Jensen et al., 2016; Kurd et al., 2010; Tsai et al., 2011; Wu et al., 2017). However, few studies have investigated the risk of psoriasis in patients with depression.

The purpose of our study was to identify the association between psoriasis and depression using data from a Korean national sample cohort. To analyze the association between psoriasis and depression, we conducted two longitudinal follow-up studies. In study I, we selected psoriasis patients and 1:4-matched control participants and analyzed the risk of depression. In study II, we selected depression patients and 1:4-matched control participants and analyzed the risk of psoriasis.

2. Methods

Study Population and Data Collection

The Ethics Committee of Hallym University (2017-I102) approved the use of these data. The Institutional Review Board exempted the requirement for written informed consent.

This national cohort study used data from the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC). A detailed description of these data was provided in our previous studies (Kim et al., 2018; Min et al., 2019).

Participant Selection

Of 1,125,691 cases with 114,369,638 medical claim codes, we included patients who were diagnosed with psoriasis (ICD-10: L40) from 2002 through 2013. The patients were followed for up to 12 years. From these patients, we selected those who had been treated for psoriasis ≥ 2 times (n = 12,921). The date of psoriasis onset was defined as the day that psoriasis was diagnosed.

Depression was defined using ICD-10 codes F31 (bipolar affective disorder) through F39 (unspecified mood disorder) diagnosed by a psychiatrist from 2002 through 2013. From these patients, we selected those who had been treated for depression ≥ 2 times (n = 68,019). The date of the onset of depression was the day that depression was diagnosed.

Study I

In study I, the control I group was defined as participants who had never been diagnosed with psoriasis from 2002 through 2013. In addition, because we assumed that control participants had been seen at the same time as each matched psoriasis participant, the control participants were included if they had not died or had no history of depression before the index date of the matched psoriasis participants; the index date was the date of the diagnosis of psoriasis. The psoriasis participants were matched 1:4 with the control participants. The control participants were selected from the mother population (n = 1,112,770). The matches were processed for age group, sex, income group, and region of residence. To prevent selection bias when selecting the matched participants, the control I group participants were sorted using a random number order and selected from top to bottom. In the psoriasis group, 519 participants were excluded because they had a history of depression before the index date. Psoriasis patients for whom we could not identify enough matching participants were excluded (n = 33). We excluded participants who were under 20 years old (n = 1,437). The

mean follow-up time from the index date to the end date (Dec. 31, 2013) or the date of death was nearly similar for both the psoriasis (77.4 months, standard deviation [SD] = 43.4) and control I groups (77.6 months, SD = 43.5). Finally, 1:4 matching resulted in the inclusion of 10,932 psoriasis participants and 43,728 control I group participants (Fig. 1).

Study II

In study II, the control II group was defined as participants who had never been diagnosed with depression from 2002 through 2013. In addition, because we assumed the control participants had been seen at the same time as each matched depression participant, control participants were included if they had not died or had no history of psoriasis before the index date of the matched depression participants; the index date was the date of the diagnosis of depression. The depression participants were matched 1:4 with the control participants. They were selected from the mother population (n = 1,057,672). The two groups were matched for age group, sex, income group, and region of residence. As in study I, the control II group participants were sorted using another random number order and selected from the top. Depression patients were excluded if they had a history of psoriasis before the index date (n = 622) and if an inadequate number of matching controls could be identified (n = 597). Participants under the age of 20 years old were also excluded (n = 6,417). The mean follow-up time from the index date to the end date (Dec. 31, 2013) or the date of death was similar for both the depression (71.6 months, SD = 43.5) and control II groups (72.9 months, SD = 43.3). Finally, 1:4 matching resulted in the inclusion of 60,383 depression group participants and 241,532 control II group participants (Fig. 1).

Variables

The age groups were classified using 5-year intervals: 20-24, 25-29, 30-34…, and 85+ years old. A total of 14 age groups were designated. The income groups were initially divided into 41 classes (one health assistance class, 20 self-employment health insurance classes, and 20 employee health insurance classes). These groups were recategorized into 11 classes (class 1 [lowest income]-11 [highest income]). Region of residence was divided into 16 areas according to administrative district. These regions were regrouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

The Charlson comorbidity index (CCI) is widely used to measure disease burden based on 17 comorbidities, such as dementia, liver disease, rheumatologic disease, and any malignancy. As stated in previous studies regarding CCI, a score was given to each participant depending on the severity and number of diseases. CCI was measured as a continuous variable (0 [no comorbidities] through 29 [multiple comorbidities]) (Quan et al., 2011; Quan et al., 2005). Because both psoriasis and depression are associated with other diseases (Maes et al., 2011; Tsai et al., 2011), the CCI score was used to adjust the analyses.

Statistical Analyses

The chi-square test was used to compare the distribution of variables between the psoriasis and control I groups (study I) and between the depression and control II groups (study II).

In both studies, a stratified Cox-proportional hazard model was used to analyze the hazard ratio (HR) of psoriasis for depression (study I) and of depression for psoriasis (study II). Stratified analyses were performed according to matching variables such as age, sex, income, and region of residence. In these analyses, crude (simple) and adjusted (CCI) models were

used. The 95% confidence intervals (CIs) were calculated. Kaplan-Meier analysis and the log-rank test were used to analyze the cumulative probability of depression in the psoriasis group (study I) and of psoriasis in the depression group (study II) compared with the respective control groups.

For the stratification analyses, we classified the participants by age and sex (young [<40 years], middle aged [≥ 40 years and < 60 years], and old [≥ 60 years] males and females).

Two-tailed analyses were performed, and P values less than 0.05 were considered significant. The results were statistically analyzed using SPSS v. 22.0 (IBM, Armonk, NY, USA).

3. Results

Study I

The duration from the index date to the diagnosis of depression was 49.9 months (SD =35.9) in the psoriasis group and 49.2 months (SD = 35.9) in the control I group. The rate of depression was higher in the psoriasis group (5.2% [571/10,932]) than in the control I group (4.5% [1,945/43,728], P = 0.001, Table 1). The general characteristics (age, sex, income, and region of residence) of the participants were exactly the same due to the matching procedure (P = 1.000). The CCI score was higher in the psoriasis group than in the control I group (P < 0.001). The prevalence of depression was higher among male psoriasis patients compared to male control I group, but no such relationship was found for females (P = 0.003 in males; P = 0.050 in females, S1 Table).

The psoriasis group included a higher proportion of individuals with depression than the control I group (Fig. 2). The adjusted HR for depression was higher in the psoriasis group than in the control I group (adjusted HR =1.13, 95% CI = 1.03-1.24, P = 0.009, Table 2).

In the stratification analyses, the adjusted HRs for depression were higher in the following psoriasis subgroups: < 40-year-old females and ≥ 60-year-old males. The adjusted HRs were 1.24 (95% CI = 1.00-1.53, P = 0.046) for the < 40-year-old females and 1.31 (95% CI = 1.04-1.66, P = 0.021) for the ≥ 60-year-old males (Table 2).

Study II

The duration from the index date to the diagnosis of psoriasis was 43.4 months (SD =33.1) in the depression group and 43.7 months (SD = 34.6) in the control II group. The rate of psoriasis was higher in the depression group (0.8% [494/60,363]) than in the control II group (0.7% [1,733/241,532], P = 0.010, Table 1). The general characteristics (age, sex, income, and region of residence) of the participants were exactly the same due to the matching procedure (P = 1.000). The CCI score was higher in the depression group than in the control II group (P < 0.001). The prevalence of psoriasis was higher in male depression patients compared to the male control II group, but no such relationship was found for females (P = 0.015 in males; P = 0.182 in females, S1 Table).

The depression group showed a higher proportion of individuals with psoriasis than the control II group (Fig. 2). The adjusted HR for psoriasis was not significantly different between the depression group and the control II group (adjusted HR = 1.11, 95% CI = 1.00-1.22, P = 0.051, Table 3).

In the stratification analyses, the adjusted HR for psoriasis was higher in the depression subgroups of < 40-year-old males (adjusted HR = 1.56, 95% CI = 1.15 – 2.12, P = 0.005) and ≥ 60-year-old males (adjusted HR = 1.35, 95% CI = 1.04 -1.75, P = 0.024) compared with the control II group (Table 3).

4. Discussion

We conducted two studies to identify the direction of the association between psoriasis and depression. In study I, a higher risk of depression was shown in psoriasis patients than in the control I group. In study II, a higher risk of psoriasis was shown in depression patients than in the control II group in < 40-year-old males and ≥ 60-year-old males. In other words, an increased risk of depression was found among psoriasis patients, and an increased risk of psoriasis was found among male depression patients aged < 40 and ≥ 60 years old. Several studies have investigated the risk of depression in psoriasis patients, and the results were consistent with our findings from study I (Dommasch et al., 2015; Jensen et al., 2016; Kurd et al., 2010; Tsai et al., 2011; Wu et al., 2017); in contrast, few studies have investigated the risk of psoriasis in depression patients. Tsai et al. used 1:4 matching in their cohort study, which was similar to our study method. The authors reported that psoriasis was associated with an increased prevalence of depression (relative risk = 1.50, 95% CI = 1.39 – 1.61; Tsai et al., 2011). In our study, we performed 1:4 matching using various demographic factors, including age, sex, income, and region of residence. Moreover, we performed two studies to clarify the association between psoriasis and depression.

Several plausible mechanisms could link psoriasis and depression, including inflammatory cytokines, immunological changes, genetics, the psychological distress of illness and other possible mediating factors. Increasing evidence suggests that inflammation associated with immunity is closely related to both psoriasis and depression. Because psoriasis is a systemic inflammatory disease, one possible mechanism is that the activation of plasmacytoid dendritic cells (DCs) triggers psoriasis. This activation produces proinflammatory cytokines such as tumor necrosis factor (TNF)-α, IL-12, and IL-23, which lead to psoriasis (Furue et al., 2017). Another possible immunity-related mechanism for

psoriasis is CD 8+ T cell accumulation and Th17/T cytotoxic (Tc) 17-mediated inflammation amplification around the IL-23/IL-17 axis (Casciano et al., 2018).

Psychological distress is a possible cause of depression in psoriasis patients. One qualitative study that interviewed 22 psoriasis patients reported that the patients mainly suffered from views of their visible body as offensive, unattractive, and ugly. These types of body perceptions can be a source of emotional disorders, including depression (Wahl et al., 2002).

On the depression side, increasing evidence has demonstrated that depression could be caused by inflammatory cytokines that affect the neurotransmitter systems (Han and Yu, 2014). In particular, increased TNF-α could be associated with serotonin transporter gene (5-HTT) availability and could lead to depression (Krishnadas et al., 2016). Furthermore, Maes demonstrated that not only inflammatory cytokines but also cell-mediated immune activation are major components of depression. For example, serum-soluble CD8 concentrations are increased in depression patients compared with controls, leading to increased numbers and percentages of T cells bearing T cell activation markers (Maes, 2011).

In addition, Demirhan et al. reported the association between psoriasis and depression in terms of immunological changes and genetic factors. In a family study, they found an increased percentage of CD2+, CD4+, and CD8+ lymphocytes in the father, who had both psoriasis and depression; decreased CD4+ in the mother, who was normal; and increased CD8+ and decreased CD4+ in their son, who had the same symptoms as his father (Demirhan et al., 2012). The study found shared immunologic and genetic factors associated with both psoriasis and depression.

In summary, inflammatory cytokines and immunological changes can underlie both psoriasis and depression. Regarding the increased risk of depression in psoriasis, some previous studies have summarized that the inflammation of psoriasis lesions in psoriasis

patients could cause hypothalamic-pituitary-adrenal (HPA) axis activation. This activation reduces serotonergic (5-HT) neurotransmitter levels, which lead to mood disorders, including depression (Maes et al., 2011; Schiepers et al., 2005).

Regarding the increased risk of psoriasis in depression, Tohid et al. suggested in their review study that not only does psoriasis affect depression but depression affects psoriasis (Tohid et al., 2016). According to previous studies, depression can lead to psoriasis through diminishing melatonin levels (Carrillo-Vico et al., 2013; Kartha et al., 2014). In addition, depression could lead to psoriasis by increasing inflammatory cytokines. Specifically, some prospective studies have reported that the presence of depression predicts higher levels of IL-6 and CRP (Copeland et al., 2012; Deverts et al., 2010; Duivis et al., 2011; Matthews et al., 2010). However, one study reported that IL-6 and CRP levels did not differ significantly between depression patients and controls after adjustment for physical inactivity, body mass index (BMI), and smoking (Duivis et al., 2011). Inflammatory cytokine activity is influenced by stress, obesity, and diet (Lotrich, 2015). It is possible that these tertiary mediators might affect both depression and psoriasis. In other words, tertiary mediators could explain the bidirectional relationship between psoriasis and depression. Further studies should elucidate the specific associations among psoriasis, depression, and possible mediators.

In the stratification analyses of our study outcomes, each risk factor for depression and psoriasis was increased in ≥ 60-year-old males in both the psoriasis and depression groups. Previous reports indicated that patients over 60 years old had a higher prevalence of depression than 20- to 40-year-olds (Mirowsky and Ross, 1992) and that patients aged 57 to 60 years had a higher prevalence of psoriasis (Griffiths and Barker, 2007; Levine and Gottlieb, 2009). Additionally, males with psoriasis had a greater prevalence of self-medication with alcohol, which can lead to psychologic problems, including depression

(Kurd et al., 2010). Despite limited evidence, the increased risk of psoriasis in males with depression might also be affected by those risk factors.

In addition, in study II, the risk of psoriasis was increased among males < 40 years old in the depression group, but not among females of any age. These findings suggest that young and old males with depression could be more affected by psoriasis risk factors than females.

In the psoriasis group in study I, the risk of depression was increased in females < 40 years old. This finding was consistent with previous studies. One study reported that patients < 50 years old with severe psoriasis had a significantly higher risk of depression (Jensen et al., 2016). Moreover, other studies reported that young and female psoriasis patients had greater impairment in quality of life, which could influence psychological problems, including depression (Gelfand et al., 2004; Krueger et al., 2001).

The strengths of our study are as follows. First, we included large groups of both depression patients and psoriasis patients from a national cohort for higher statistical power. Second, our study had a long-term follow-up period so that we could identify the association between psoriasis and depression. Third, 1:4 matching was performed according to several confounding factors to independently identify the difference between patients and control participants. Fourth, the HR was adjusted for several confounding factors to investigate the independent association between psoriasis and depression. Finally, we conducted two studies that excluded control participants who were psoriasis patients prior to the index date in study I or were depression patients prior to the index date in study II. Hence, we could identify the directional association between psoriasis and depression.

Our study has several limitations. First, because our study was conducted using national cohort data collected by NHIS, we could not consider certain variables. For example, potential confounding factors related to the risk of depression, such as stress, BMI, and smoking status, were not included in the database. Second, although the study outcomes were

significant, the differences were minimal (in study I, the prevalence of depression was 13% higher in psoriasis patients in the adjusted model [Table 2]; in study II, the prevalence of psoriasis was 11% higher in depression patients in the adjusted model [Table 3]). A possible reason may be confounding factors that we did not consider. Thus, the results should be carefully interpreted. Third, the classification of psoriasis as mild or severe was not considered in our study. Finally, the ability to determine definitive causality was limited because our study had an observational design.

We suggest that psoriasis and depression might have a bidirectional association. Specifically, young females and older males with psoriasis might have an increased risk of depression. In addition, young males and older males with depression might have an increased risk of psoriasis.

Author contributions

Chanyang Min wrote the manuscript. Miyoung Kim analyzed and interpreted the data. Dong Jun Oh performed the data processing. Hyo Geun Choi conceptualized, wrote and reviewed the manuscript. The authors declare that we have no competing interests.

Declarations of interest

None.

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Figure legends

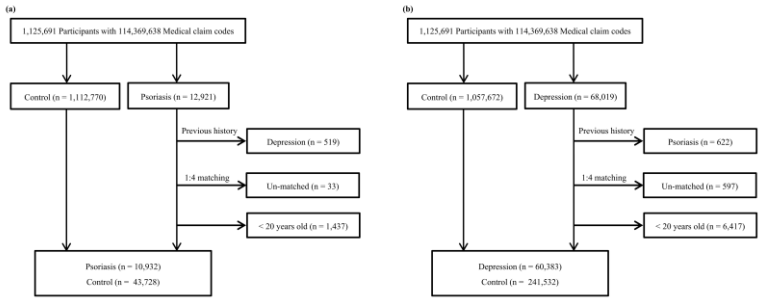

Fig. 1. A schematic illustration of the participant selection process used in the present study. (a) In study I, out of a total of 1,125,691 participants, 10,932 participants with psoriasis were matched with 43,728 control I group members for age group, sex, income group, and region of residence. (b) In study II, out of a total of 1,125,691 participants, 60,383 participants with depression were matched with 241,532 control II group members for age group, sex, income group, and region of residence.

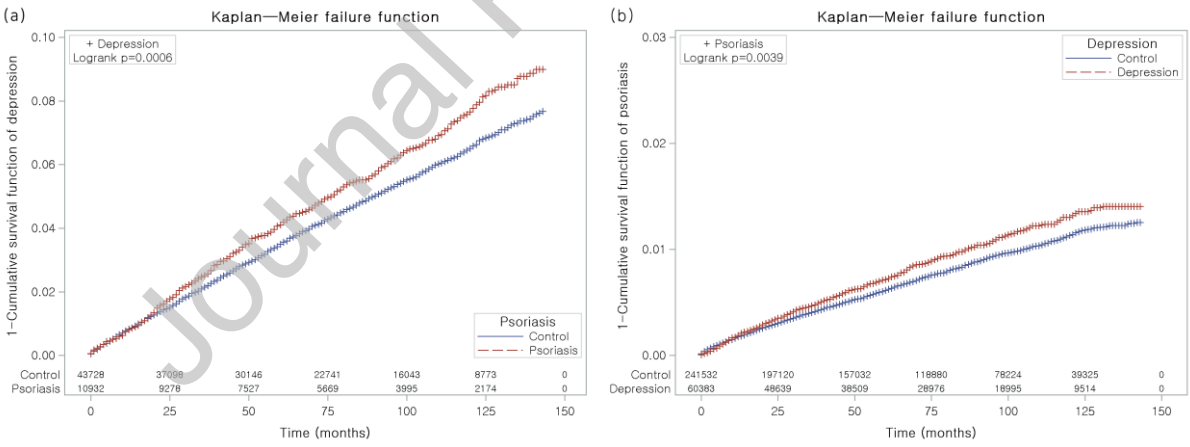

Fig. 2. Kaplan-Meier failure analyses. (a) The psoriasis group demonstrated a higher cumulative rate of depression than the control I group. (b) The depression group demonstrated a higher cumulative rate of psoriasis than the control II group.

Table 1 General characteristics of the participants

Characteristics	Study I			Study II		
	Psoriasis (n, %)	Control I (n, %)	P-value	Depression (n, %)	Control II (n, %)	P-value
Age (years)			1.000			1.000
20-24	782 (7.2)	3,128 (7.2)		3,829 (6.34)	15,316 (6.34)	
25-29	959 (8.8)	3,836 (8.8)		4,513 (7.47)	18,052 (7.47)	
30-34	1,100 (10.1)	4,400 (10.1)		5,216 (8.64)	20,864 (8.64)	
35-39	1,172 (10.7)	4,688 (10.7)		5,747 (9.52)	22,988 (9.52)	
40-44	1,190 (10.9)	4,760 (10.9)		6,121 (10.14)	24,484 (10.14)	
45-49	1,214 (11.1)	4,856 (11.1)		6,405 (10.61)	25,620 (10.61)	
50-54	1,133 (10.4)	4,532 (10.4)		6,137 (10.16)	24,548 (10.16)	
55-59	897 (8.2)	3,588 (8.2)		5,013 (8.30)	20,052 (8.30)	
60-64	758 (6.9)	3,032 (6.9)		4,684 (7.76)	18,736 (7.76)	
65-69	673 (6.2)	2,692 (6.2)		4,551 (7.54)	18,204 (7.54)	
70-74	538 (4.9)	2,152 (4.9)		3,814 (6.32)	15,256 (6.32)	
75-79	283 (2.6)	1,132 (2.6)		2,427 (4.02)	9,708 (4.02)	
80-84	159 (1.5)	636 (1.5)		1,280 (2.12)	5,120 (2.12)	
85+	74 (0.7)	296 (0.7)		646 (1.07)	2,584 (1.07)	
Sex			1.000			1.000
Male	6,167 (56.4)	24,668 (56.4)		20,511 (33.97)	82,044 (33.97)	
Female	4,765 (43.6)	19,060 (43.6)		39,872 (66.03)	159,488 (66.03)	

Income			1.000			1.000
1 (lowest)	1,644 (15.0)	6,576 (15.0)		9,468 (15.7)	37,872 (15.7)	
2	1,739 (15.9)	6,956 (15.9)		8,891 (14.7)	35,564 (14.7)	
3	2,075 (19.0)	8,300 (19.0)		10,395 (17.2)	41,580 (17.2)	
4	2,427 (22.2)	9,708 (22.2)		12,996 (21.5)	51,984 (21.5)	
5 (highest)	3,047 (27.9)	12,188 (27.9)		18,633 (30.9)	74,532 (30.9)	
Region of residence			1.000			1.000
Urban	5,228 (47.8)	20,912 (47.8)		27,620 (45.74)	110,480 (45.74)	
Rural	5,704 (52.2)	22,816 (52.2)		32,763 (54.26)	131,052 (54.26)	
CCI (score)†			<0.001*			<0.001*
0	4,583 (41.9)	20,286 (46.4)		17,871 (29.6)	104,263 (43.2)	
1	1,206 (11.0)	4,831 (11.1)		5,778 (9.6)	25,166 (10.4)	
2	1,348 (12.3)	5,043 (11.5)		7,947 (13.2)	28,739 (11.9)	
3	1,149 (10.5)	4,204 (9.6)		7,535 (12.5)	24,656 (10.2)	
4	0,806 (7.4)	3,104 (7.1)		6,248 (10.4)	19,000 (7.9)	
5	0,631 (5.8)	2,160 (4.9)		4,896 (8.1)	14,092 (5.8)	
≥ 6	1,209 (11.1)	4,100 (9.4)		10,108 (16.7)	25,616 (10.6)	
Depression	571 (5.2)	1,945 (4.5)	0.001*	60,383 (100.0)	0 (0.0)	<0.001*
Psoriasis	10,932 (100.0)	0 (0.0)	<0.001*	494 (0.8)	1,733 (0.7)	0.010*

*Chi-square test; significance at $P < 0.05$.

† CCI: Charlson comorbidity index.

Table 2 Crude and adjusted hazard ratios (95% confidence interval) for depression in psoriasis patients

Characteristics	Depression			
	Crude†	P-value	Adjusted†‡	P-value
Total (n = 54,660)				
Psoriasis	1.18 (1.07-1.29)	<0.001*	1.13 (1.03-1.24)	0.009*
Control I	1.00		1.00	
Age < 40 years, males (n = 10,335)				
Psoriasis	0.98 (0.72-1.33)	0.980	0.95 (0.70-1.29)	0.753
Control I	1.00		1.00	
Age < 40 years, females (n = 9,730)				
Psoriasis	1.29 (1.04-1.59)	0.019*	1.24 (1.00-1.53)	0.046*
Control I	1.00		1.00	
Age 40-59 years, males (n = 13,245)				
Psoriasis	1.27 (1.02-1.58)	0.036*	1.20 (0.96-1.49)	0.105
Control I	1.00		1.00	
Age 40-59 years, females (n = 8,925)				
Psoriasis	1.10 (0.91-1.34)	0.328	1.08 (0.89-1.31)	0.452
Control I	1.00		1.00	
Age ≥ 60 years, males (n = 7,255)				
Psoriasis	1.41 (1.12-1.78)	0.004*	1.31 (1.04-1.66)	0.021*
Control I	1.00		1.00	

Age ≥ 60 years, females (n = 5,170)				
Psoriasis	1.00 (0.78-1.28)	0.982	0.96 (0.75-1.24)	0.748
Control I	1.00		1.00	

* Cox proportional hazards regression model; significance at $P < 0.05$.

† Model stratified for age, sex, income, and region of residence.

‡ Model adjusted for Charlson comorbidity index.

Table 3 Crude and adjusted hazard ratios (95% confidence interval) for psoriasis in depression patients

Characteristics	Psoriasis			
	Crude†	P-value	Adjusted†‡	P-value
Total (n = 301,915)				
Depression	1.17 (1.05-1.29)	0.003*	1.11 (1.00-1.22)	0.051
Control II	1.00		1.00	
Age < 40 years, males (n = 33,235)				
Depression	1.56 (1.15-2.11)	0.004*	1.56 (1.15-2.12)	0.005*
Control II	1.00		1.00	
Age < 40 years, females (n = 63,290)				
Depression	1.21 (0.95-1.53)	0.127	1.12 (0.88-1.42)	0.355
Control II	1.00		1.00	
Age 40-59 years, males (n = 40,110)				
Depression	1.00 (0.78-1.27)	0.968	0.94 (0.73-1.21)	0.625

Control II	1.00		1.00	
Age 40-59 years, females (n = 78,270)				
Depression	1.03 (0.84-1.27)	0.765	0.99 (0.80-1.22)	0.887
Control II	1.00		1.00	
Age ≥ 60 years, males (n = 29,210)				
Depression	1.41 (1.10-1.83)	0.008*	1.35 (1.04-1.75)	0.024*
Control II	1.00		1.00	
Age ≥ 60 years, females (n = 57,800)				
Depression	1.11 (0.87-1.42)	0.396	1.03 (0.81-1.32)	0.799
Control II	1.00		1.00	

* Cox proportional hazards regression model; significance at $P < 0.05$.

† Model stratified for age, sex, income, and region of residence.

‡ Model adjusted for Charlson comorbidity index.