High Prevalence of Herpes Zoster in Patients With Depression

Chun-Hui Liao, MD, MSPH[a,b]; Chen-Shu Chang, MD[e,f]; Chih-Hsin Muo, MSc[c]; and Chia-Hung Kao, MD[b,d,*]

ABSTRACT

Objective: Patients diagnosed with depression are at an elevated risk of physical illness. Researchers have noted that depression negatively affects immune function and leads to increased susceptibility to infection, including herpes zoster. Few epidemiologic studies have been conducted on whether patients with depression are at a higher risk of herpes zoster. We conducted a retrospective population-based cohort study to investigate whether depression is associated with an increased risk of herpes zoster.

Method: We identified 22,886 patients with depression (*ICD-9*: 296.2, 296.3, 300.4, and 311) in 2000–2005 from National Health Insurance (Taiwan) claims and selected 91,542 controls, frequency matched by sex, age, and index year. We calculated the risk of herpes zoster (*ICD-9*: 053) between the 2 cohorts in Cox proportional hazards regression.

Results: Incidence of herpes zoster was 1.3 times higher in patients with depression than in controls (4.58 vs 3.54 per 1,000 person-years, respectively), with an adjusted hazard ratio (HR) of 1.11 (95% CI, 1.01–1.21). In subjects aged 45–54 years, those with depression had a significantly higher risk than controls (HR = 1.44; 95% CI, 1.19–1.73). In multivariable analysis, malignant conditions (HR = 1.41; 95% CI, 1.15–1.72), rheumatic diseases (HR = 1.28; 95% CI, 1.14–1.44), hyperlipidemia (HR = 1.24; 95% CI, 1.14–1.36), renal diseases (HR = 1.21; 95% CI, 1.08–1.36), anxiety (HR = 1.21; 95% CI, 1.07–1.38), sleep disorder (HR = 1.20; 95% CI, 1.09–1.31), and hypertension (HR = 1.11; 95% CI, 1.02–1.21) were potential risk factors for herpes zoster.

Conclusions: Patients diagnosed with depression are at an elevated risk of herpes zoster, particularly those aged 45 to 54 years and those with comorbidities, including renal diseases, hyperlipidemia, malignant conditions, rheumatic diseases, hypertension, anxiety, and sleep disorder.

J Clin Psychiatry 2015;76(9):e1099–e1104
dx.doi.org/10.4088/JCP.14m09311

[a]Department of Psychiatry, [b]School of Medicine, College of Medicine, [c]Management Office for Health Data, and [d]Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan
[e]Department of Neurology, Changhua Christian Hospital, Changhua, Taiwan
[f]Department of Medical Laboratory Science and Biotechnology and Medical Imaging and Radiological Sciences, Central Taiwan University of Science and Technology, Taichung, Taiwan
**Corresponding author:* Chia-Hung Kao, MD, Graduate Institute of Clinical Medical Science and School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan, No. 2, Yuh-Der Rd, Taichung 404, Taiwan (d10040@mail.cmuh.org.tw).

Depression, characterized by pervasive and persistent depressive mood, decreased confidence, and loss of interest in generally agreeable activities, can lead to withdrawal from social interaction and influence the subsequent development of physical illnesses; it is a biological, psychological, and social illness. Depression has also been observed to increase patients' risk of physical illness.[1] The World Health Organization (WHO) indicated that depressive disorders were the third leading cause of disease in 2004, and they are expected to rank the highest by 2030.[2]

Many hypotheses support the interactions between the central nervous system and the immune system in chronic stress response and in depression. In these interactions, consistent activation of the hypothalamic-pituitary-adrenal (HPA) axis potentially impairs immune response and contributes to the development and progression of numerous medical disorders.[3] Depression and anxiety have been observed to affect immune function negatively and lead to increased susceptibility to infection.[4,5] Furthermore, Irwin et al[6,7] demonstrated that patients with major depression have lower levels of varicella-zoster virus (VZV)–specific cell-mediated immunity, resulting in impaired cellular immunity and increased susceptibility to herpes zoster.

Herpes zoster, a painful neurocutaneous syndrome, results from the reactivation and replication of latent VZV in the dorsal root and cranial nerve ganglia.[7] A higher risk of occurrence was reported among patients with depressive disorders.[8] Despite providing evidence supporting depression as a risk factor for herpes zoster, the study had a cross-sectional design and the sample size was limited to 250 patients with herpes zoster, which precludes causal inference.

To date, limited longitudinal cohort studies have been conducted on the association between depression and herpes zoster. One epidemiologic study[9] revealed that psychiatric diseases are associated with herpes zoster. It revealed that patients aged 60 years or younger with affective psychosis and either neurotic illness or personality disorders are at a higher risk of developing herpes zoster. Hata et al[10] revealed a slight association between herpes zoster and depression in a hospital-based study, but the association was nonsignificant. On the basis of these findings, the long-term presence of depressive disorders seems to be associated with herpes zoster, but the relationship between depression and herpes zoster remains unclear. Therefore, we conducted a 12-year follow-up, population-based cohort study to evaluate the risk factors for developing herpes zoster in patients with depression in comparison with a control group of patients without depression. The results of this study can provide an evidenced-based plan for a more comprehensive approach to the long-term care of patients diagnosed with depression, which incorporates the prevention of herpes zoster.

METHOD

Study Population

In this retrospective cohort study, we used the Longitudinal Health Insurance Database (LHID), which is released by the Bureau of

Clinical Points

- Depression has been observed to affect immune function negatively and lead to increased susceptibility to infection, including herpes zoster.
- Patients with depression may have higher risk of developing herpes zoster than nondepressed patients, and if they have unusual neuralgia, clinicians should consider whether herpes zoster could be the cause, even in patients younger than 55 years.

National Health Insurance (BNHI) of Taiwan. The BNHI instituted a National Health Insurance (NHI) program on March 1, 1995, and this program covers nearly 99% of the population of Taiwan (http://www.nhi.gov.tw). The LHID covers 1 million insurants randomly selected from the 2000 registry and contains all medical records of each insurant from 1996 to 2011. The LHID identifies diseases based on the *International Classification of Diseases, Ninth Revision* (*ICD-9*).[11] The insurant's personal information is encrypted to protect his or her identity before being sent to researchers. This study was also approved by the institutional review board of China Medical University Hospital.

Study Participants

Participants in the study were patients diagnosed with depressive disorders (*ICD-9*: 296.2, 296.3, 300.4, and 311) from 2000 to 2005. Those with a history of herpes zoster (*ICD-9*: 053) after the date of depressive disorder diagnosis were excluded. The entry date was defined as the date of depression diagnosis. The 22,886 patients with depression were assigned to a depression cohort. For each patient in the depression cohort, we selected approximately 4 control patients from those without a history of depression or herpes zoster before the entry date. They were frequency matched with patients in the depression cohort based on age (in 5-year bands) and sex. Control patients were assigned the same index date as depression cohort patients. All patients were followed from the index date until herpes diagnosis, withdrawal from the program, or the end of 2011, whichever occurred first.

Baseline Comorbidities

Comorbidities were identified before the index date. We considered the following comorbidities in this study: anxiety (*ICD-9*: 300.00), sleep disorders (*ICD-9*: 307.4 and 780.5), diabetes (*ICD-9*: 250), hyperlipidemia (*ICD-9*: 272), hypertension (*ICD-9*: 401–405), renal diseases (*ICD-9*: 580–589), malignant conditions (*ICD-9*: 140–208), rheumatic diseases (*ICD-9*: 710, 714, and 725), autoimmune diseases (*ICD-9*: 245.2, 250.01, 340, 358, 555.9, 556.9, 579, 696.0, 696.1, 710.1, and 710.2), and organ transplants (*ICD-9*: 11.6, 33.5, 33.6, 37.5, 50.5, 52.8, and 55.6). All comorbidities were identified based on outpatient or inpatient claims data, except malignant conditions. Malignant conditions were identified using the Catastrophic Illness Patient Registry (http://www.nhi.gov.tw/English/webdata/webdata.aspx?menu=11&menu_id=596&WD_ID=596&webdata_id=3180), which contains information on patients who have received pathological treatment, or computed tomography or magnetic resonance imaging scans. Antidepressant use was a confounder for developing herpes zoster. A patient who received an antidepressant for more than 90 days within 180 days before the end point was defined as a user. Antidepressants were tricyclics (including amitriptyline, clomipramine, doxepin, and imipramine), selective serotonin reuptake inhibitors (including fluoxetine, paroxetine, sertraline, citalopram, escitalopram, and etoperidone), monoamine oxidase inhibitors (including selegiline and moclobemide), heterocyclic antidepressants (including trazodone), and others (including bupropion, venlafaxine, duloxetine, and mirtazapine).

Table 1. Distribution of Demographic Characteristics and Baseline Comorbidity Between Cohorts With and Without Depression

	With Depression (n = 22,886)		Without Depression (n = 91,542)		
Characteristic	n	%	n	%	*P* Value
Gender[a]					.96
Men	8,773	38.3	35,090	38.3	
Women	14,113	61.7	56,452	61.7	
Age, y[a]					.96
< 25	3,077	13.4	12,308	13.5	
25–34	3,767	16.5	15,068	16.5	
35–44	4,526	19.8	18,104	19.8	
45–54	4,371	19.1	17,484	19.1	
55–64	2,886	12.6	11,544	12.6	
≥ 65	4,259	18.6	1,7034	18.6	
Overall[b]	46.3[c]	17.9[d]	46.2[c]	18.0[d]	.18
Baseline comorbidity[a]					
Anxiety	3,925	17.2	2,832	3.09	< .0001
Sleep disorder	8,853	38.7	9,341	10.2	< .0001
Hypertension	7,046	30.8	20,523	22.4	< .0001
Diabetes	2,473	10.8	7,236	7.90	< .0001
Hyperlipidemia	4,520	19.8	11,762	12.9	< .0001
Renal disease	1,937	8.46	4,688	5.12	< .0001
Malignant conditions	568	2.48	1,526	1.67	< .0001
Rheumatic diseases	1,921	8.39	4,385	4.79	< .0001
Autoimmune diseases	476	2.08	1,127	1.23	< .0001
Organ transplants	98	0.43	235	0.26	< .0001
Antidepressant use[e]	4,683	20.5	1,450	1.58	< .0001

[a] χ^2 Test.
[b] *t* Test.
[c] Indicates mean.
[d] Indicates SD.
[e] Antidepressant use was defined as use of an antidepressant for > 90 days within 180 days before end point. Antidepressants included tricyclics (amitriptyline, clomipramine, doxepin, and imipramine), selective serotonin reuptake inhibitors (fluoxetine, paroxetine, sertraline, citalopram, escitalopram, and etoperidone), monoamine oxidase inhibitors (selegiline and moclobemide), heterocyclic antidepressants (trazodone), and others (bupropion, venlafaxine, duloxetine, and mirtazapine).

Statistical Analysis

The difference in distribution between the 2 cohorts was analyzed using a χ^2 test and a *t* test for categorical and continuous variables. We calculated the incidence of herpes zoster (per 1,000 person-years) for the 2 cohorts, and also assessed the risk for herpes zoster development

Table 2. Incidence and Hazard Ratios for Herpes Zoster and Herpes Zoster–Associated Risk Factor in Cox Proportional Hazard Regression

Variable	Herpes Zoster, n	Incidence[a]	Hazard Ratio (95% CI) Crude	Hazard Ratio (95% CI) Multivariable
Depression				
No	2,358	3.54	1.00	1.00
Yes	774	4.58	1.30 (1.19–1.41)***	1.11 (1.01–1.21)*
Gender				
Women	1,974	3.80	1.04 (0.97–1.12)	1.05 (0.97–1.13)
Men	1,158	3.66	1.00	1.00
Age, y				
<25	116	1.00	1.00	1.00
25–34	149	1.06	1.06 (0.83–1.35)	1.03 (0.81–1.31)
35–44	302	1.74	1.73 (1.39–2.14)***	1.62 (1.31–2.01)***
45–54	733	4.44	4.40 (3.62–5.36)***	3.87 (3.17–4.71)***
55–64	699	6.59	6.54 (5.37–7.96) ***	5.33 (4.35–6.52)***
≥65	1,133	8.39	8.46 (6.99–10.2)***	6.49 (5.31–7.94)***
Baseline comorbidity				
Anxiety				
No	2,830	3.58	1.00	1.00
Yes	302	6.71	1.92 (1.70–2.16)***	1.21 (1.07–1.38)**
Sleep disorder				
No	2,388	3.34	1.00	1.00
Yes	744	6.12	1.87 (1.72–2.03)***	1.20 (1.09–1.31)***
Hypertension				
No	2,830	3.58	1.00	1.00
Yes	302	6.71	1.92 (1.70–2.16)***	1.11 (1.02–1.21)*
Diabetes				
No	2,689	3.48	1.00	1.00
Yes	443	7.04	2.05 (1.85–2.26)***	0.98 (0.88–1.09)
Hyperlipidemia				
No	2,294	3.18	1.00	1.00
Yes	838	7.34	2.33 (2.15–2.52)***	1.24 (1.14–1.36)***
Renal disease				
No	2,781	3.51	1.00	1.00
Yes	351	8.22	2.37 (2.12–2.65)***	1.21 (1.08–1.36)**
Malignant condition				
No	3,034	3.68	1.00	1.00
Yes	98	8.51	2.36 (1.93–2.89)***	1.41 (1.15–1.72)***
Rheumatic disease				
No	2,771	3.50	1.00	1.00
Yes	361	8.27	2.37 (2.13–2.65)***	1.28 (1.14–1.44)***
Autoimmune disease				
No	3,061	3.71	1.00	1.00
Yes	71	6.81	1.88 (1.48–2.38)***	1.12 (0.88–1.42)
Organ transplants				
No	3,123	3.75	1.00	1.00
Yes	9	3.90	1.05 (0.55–2.02)	0.56 (0.29–1.08)
Antidepressant				
No	2,911	3.67	1.00	1.00
Yes	221	5.31	1.45 (1.27–1.67)***	1.05 (0.91–1.21)

[a]Per 1,000 person-years.
*P<.05. **P<.01. ***P<.001.

and herpes zoster–associated risk factors by using a Cox proportional hazards regression model, controlling for age, sex, and comorbidities. We used this multivariable model to estimate age-, sex-, and comorbidity-specific incidence and risk of herpes zoster. We examined the joint effect of herpes zoster and herpes zoster–associated top 3 risk factors on depression, hyperlipidemia, rheumatic diseases, and malignant conditions. The association between depression and antidepressant in herpes zoster was also assessed. The cumulative incidences of herpes zoster in the 2 cohorts were plotted using Kaplan-Meier analysis, and the difference was calculated using the log-rank test. We performed all statistical analyses using SAS 9.3 (SAS Institute Inc; Cary, North Carolina). A significance level of P<.05 was determined using a 2-tailed test.

RESULTS

Baseline Characteristics of the 2 Cohorts

We included 114,428 patients in this study, who were divided into 2 cohorts. The depression cohort contained 22,886 patients, and the control cohort contained 91,542 patients. The majority of the depression cohort were women (61.7% vs 38.3%), and the mean age was 46.3 years (SD = 17.9). Patients in the depression cohort had more comorbidities than did patients in the control cohort, particularly anxiety (17.2% vs 3.09%) and sleep disorders (38.7% vs 10.2%; Table 1). About 20.5% of patients with depression and 1.58% of controls had received an antidepressant for more than 90 days within 180 days before the end point.

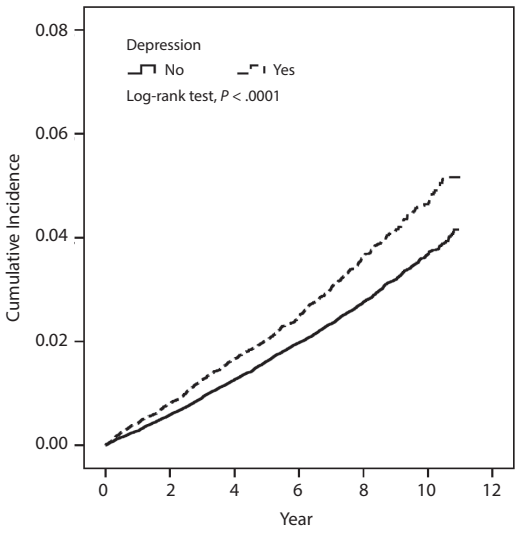
Incidence Rate and Hazard Ratios for Herpes Zoster and Herpes Zoster–Associated Risk Factors

During the study period, 774 patients with depression and 2,358 control patients developed herpes zoster. As compared to control patients, depressed patients had 1.30 times higher incidence of herpes zoster (4.58 in patients with depression vs 3.54 in control patients per 1,000 person-years) and, in the multivariable model, had 1.11 times higher incidence (95% CI, 1.01–1.21) (Table 2). At the 11-year follow-up, the cumulative incidence of herpes zoster in the depression cohort was approximately 1% higher than in the control cohort (log-rank P<.0001; Figure 1). Incidence of herpes zoster increased with age, from 1.00 to 8.39 per 1,000 person-years, and, in the multivariable model, the risk increased from 1.03 in patients aged 25–34 years to 6.49 in patients aged 65 years and older. In the multivariable model, patients with malignant conditions had the highest risk of developing herpes zoster (hazard ratio [HR] = 1.41; 95% CI, 1.15–1.72), followed by patients with rheumatic diseases (HR = 1.28; 95% CI, 1.14–1.44), hyperlipidemia (HR = 1.24; 95% CI, 1.14–1.36), renal diseases (HR = 1.21; 95% CI, 1.08–1.36), anxiety (HR = 1.21; 95% CI, 1.07–1.38), sleep disorder (HR = 1.20; 95% CI, 1.09–1.31), and hypertension (HR = 1.11; 95% CI, 1.02–1.21).

Incidence and Risk of Herpes Zoster in the Depression Cohort Versus the Control Cohort Based on Age, Sex, and Comorbidity

In a sex-specific analysis, incidence of herpes zoster in the depression cohort was higher than in the control cohort, but risk was significantly different in men (HR = 1.26; 95% CI, 1.09–1.47; Table 3). Only patients aged 45 to 54 years showed

Figure 1. Cumulative Incidence for Herpes Zoster Between Depression and Comparison Cohort



significant changes in incidence and risk of herpes zoster (HR = 1.44; 95% CI, 1.19–1.73). Patients with depression and without any comorbidity had a significantly higher risk than controls without any comorbidity (HR = 1.29; 95% CI, 1.07–1.56).

Joint Effect of Herpes Zoster and Herpes Zoster–Associated Risk Factors

Compared with study subjects without depression, rheumatic diseases, and malignant conditions, a 1.27-fold risk for herpes zoster was found in subjects with only depression (95% CI, 1.14–1.42; Table 4) in the age- and sex-adjusted model. Patients with depression had an increased risk with hyperlipidemia or rheumatic disease compared with patients with only depression (data not shown). Compared with subjects not receiving antidepressant treatment, subjects who received antidepressant treatment had a decreased risk (HR = 0.66; 95% CI, 0.47–0.93), but patients with depression who were taking antidepressant treatment had an increased risk (HR = 1.28; 95% CI, 1.09–1.49). Furthermore, we also found the patients with depression had higher risk of postherpetic neuralgia after herpes zoster infection. Depressive patients without antidepressants had more risk to suffer from the complaints (see Supplementary eTable 1 at Psychiatrist.com).

DISCUSSION

The results of this retrospective, population-based cohort study indicate that the incidence of herpes zoster in patients with depression is 1.30 times higher than in patients without depression. A significantly increased risk of herpes zoster in depressed patients, with an HR of 1.11 (95% CI, 1.01–1.21), was observed after adjusting for potential confounding factors, including demographic factors and potential risk factors for herpes zoster. Further analysis revealed that

Table 3. Incidence and Hazard Ratios for Herpes Zoster in Depression Cohort Compared to Control Cohort Stratified by Age, Gender, Comorbidity, and Antidepressant Use

	Depression		No Depression		
Variable	n	Incidence[a]	n	Incidence[a]	Hazard Ratio (95% CI)[b]
Gender					
Women	476	4.49	1,498	3.62	1.03 (0.92–1.16)
Men	298	4.74	860	3.39	1.26 (1.09–1.47)**
Age, y					
<25	29	1.24	87	0.94	1.20 (0.75–1.91)
25–34	35	1.21	114	1.2	0.95 (0.60–1.49)
35–44	85	2.42	217	1.57	1.07 (0.79–1.45)
45–54	212	6.41	521	3.94	1.44 (1.19–1.73)***
55–64	164	7.68	535	6.31	1.00 (0.82–1.22)
≥65	249	9.19	884	8.19	1.00 (0.85–1.17)
Baseline comorbidity					
No	138	2.17	902	2.05	1.29 (1.07–1.56)**
Yes	636	6.04	1,456	6.38	1.08 (0.98–1.20)

[a]Per 1,000 person-years.
[b]Manually adjusted for age, gender, comorbidity, and antidepressant use.
**P < .01. ***P < .001.

the increased risk of herpes zoster was significant among patients aged 45 to 54 years.

Research has proven that reactivation of the latent VZV causes herpes zoster.[12,13] Researchers have also revealed that the decline of cellular immunity to VZV predisposes patients to developing herpes zoster.[14–17] One study[18] indicated that depression is associated with infection because it causes immunosuppression. Irwin et al[6,7] suggested that patients with major depression had lower VZV-specific cell-mediated immunity. The results of our study provide epidemiologic evidence that depression is positively associated with herpes zoster. Furthermore, our analysis indicates that the prevalence of anxiety and sleep problems is greater among patients with depression. Previous research has revealed that patients with insomnia are more susceptible to infection.[19] Anxiety can also cause vulnerability to infection.[20] This could partially explain why patients with depression in our study had a higher risk of herpes zoster.

Moreover, research has linked depression to nutritional deficiencies.[21–23] Nutritional deficiencies might decrease specific immune response to VZV.[24–26]

This research is supported by the results of our study, and is consistent with the hypothesis that patients with depression are prone to developing herpes zoster because of impaired cellular immunity or nutritional deficiencies.

We also observed that the risk of developing herpes zoster increased significantly with age. This finding also correlates with previous studies[27,28] that have indicated that VZV-specific cell-mediated immunity declines with age. Forbes et al[29] found that patients with depression who were younger than 50 years had higher risk of herpes zoster than a control group in UK Clinical Practice Research Datalink primary care data. Our age-specific analysis determined that patients diagnosed with depression and aged 45 to 54 years had a significantly higher risk of developing herpes zoster. Frank et al[30] revealed that early onset depression might be associated with a reduction in natural killer cell activity and number, negatively affecting antiviral defense mechanisms.[31]

Table 4. Joint Effect Between Herpes Zoster and Herpes Zoster–Associated Risk Factor

Depression	Hyperlipidemia	Rheumatic Diseases	Malignant Condition	Cases, n	Population, n	Hazard Ratio (95% CI)
Model 1[a]						
No	No	No	No	1,573	75,771	1.00
No	Yes	No	No	477	9,995	1.46 (1.31–1.62)***
No	No	Yes	No	153	2,801	1.69 (1.43–2.00)***
No	No	No	Yes	42	1,106	1.46 (1.07–1.98)*
No	Yes	Yes	No	82	1,449	1.56 (1.24–1.95)***
No	Yes	No	Yes	18	288	2.10 (1.32–3.34)**
No	No	Yes	Yes	10	102	3.52 (1.89–6.57)***
No	Yes	Yes	Yes	3	30	3.13 (1.01–9.73)*
Yes	No	No	No	434	16,842	1.27 (1.14–1.42)***
Yes	Yes	No	No	206	3,627	1.76 (1.51–2.04)***
Yes	No	Yes	No	68	1,101	1.98 (1.55–2.53)***
Yes	No	No	Yes	12	373	1.41 (0.80–2.50)
Yes	Yes	Yes	No	41	748	1.41 (1.03–1.93)*
Yes	Yes	No	Yes	9	123	2.33 (1.21–4.50)*
Yes	No	Yes	Yes	2	50	1.46 (0.36–5.84)
Yes	Yes	Yes	Yes	2	22	2.84 (0.71–11.4)
Model 2[b]						
Depression	Antidepressant					
No	No			2,325	90,092	1.00
No	Yes			33	1,450	0.66 (0.47–0.93)*
Yes	No			586	18,203	1.06 (0.97–1.17)
Yes	Yes			188	4,683	1.28 (1.09–1.49)***

[a]Adjusted for age, gender, and antidepressant use.
[b]Adjusted for age, gender, and comorbidity.
*P < .05. **P < .01. ***P < .001.
Abbreviations: HR = hazard ratio.

However, this hypothesis could not explain why patients with depression aged 45 to 54 years were more sensitive to herpes zoster infection in our cohort study. Further investigation is required to answer this question. The result also indicates that patients aged 45 to 54 years with depression might need vaccination for herpes zoster.

We determined that patients diagnosed with depression are more likely to have comorbid chronic medical diseases than control patients[32]; after controlling for potential confounding effects caused by comorbidities, the results still indicate a significantly increased risk of developing herpes zoster in patients with depression. Our data also reveal that patients with malignant conditions, rheumatic diseases, hyperlipidemia, renal diseases, anxiety, sleep disorder, and hypertension have a significantly higher risk of developing herpes zoster. In addition to renal diseases, malignant conditions, rheumatic diseases, and autoimmune diseases, other medical conditions can also induce the reactivation of VZV, causing herpes zoster to develop.[10] We also observed that patients with hyperlipidemia have a higher incidence of herpes zoster. Our epidemiologic study links hyperlipidemia to herpes zoster; diminished cellular immunity caused by hyperlipidemia might have increased patients' susceptibility to reactivation of cells causing VZV infection.[33] Several studies have indicated that obesity causes a potential risk for infection.[34–38] Obesity and hyperlipidemia have a close positive correlation.[39] A more thorough investigation is required to evaluate the incidence of herpes zoster among the patients with hyperlipidemia.

The main strengths of our study are the large sample size, length of the longitudinal follow-up, and a large control cohort with stratified age and sex. This cohort study allows for prospective reporting of depression and herpes zoster to validate cases, thus reducing recall bias caused by events that occurred prior to the time of enrollment.

This study also has several limitations. First, although we controlled for several potential confounding factors in the statistical analysis, numerous possible confounding variables associated with herpes zoster, including smoking, alcohol use, diet, body weight, and presence of human immunodeficiency virus (HIV), were not included in our database. Information on these variables is not available for patients; therefore, it could not be controlled for directly in our analysis. The association among depression, HIV, and herpes zoster must be further evaluated. Second, we did not consider risk factors such as immunosuppressant drug use because of the complexity of this information. Additionally, the depression cohort exhibited a high risk of comorbidities causing immunodeficiency diseases, but the influence of immunodeficiency diseases (if any) most likely decreased after treatment. However, we might have underestimated the association between immunodeficiency diseases and the development of herpes zoster, because not all patients with such diseases received persistent drug treatment. Third, we could not evaluate the severity or status of depression because of the limited data provided by the NHI. Therefore, the correlation between severity of depression and herpes zoster was not within the scope of this study. Nonetheless, on the basis of statistical significance of our results, we do not believe that these limitations adversely affected our study.

In conclusion, this national cohort study indicated that depression is associated with an increased risk for developing

herpes zoster, particularly in patients aged 45 to 54 years and patients with comorbidities, including malignant conditions, rheumatic diseases, hyperlipidemia, renal diseases, anxiety, sleep disorder, and hypertension. Further investigation is required to identify the underlying causes of this association and determine whether appropriate treatment of depression can decrease the risk for developing herpes zoster and decrease the risk of postherpetic neuralgia. Indeed, a vaccination policy by the Centers for Disease Control and Prevention[40] suggested that only adults 60 years and older receive the vaccination. This research raises the question of whether younger patients with depression, especially those aged 45 to 54 years, might benefit from vaccination.

Submitted: June 13, 2014; accepted September 23, 2014.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), doxepin (Silenor and others), duloxetine (Cymbalta and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), selegiline (Eldepryl, Zelapar, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

Author contributions: Drs Liao and Chang contributed equally to the article.

Potential conflicts of interest: None reported.

Funding/support: This study was supported in part by a grant (DMR-101-083) from China Medical University Hospital; Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW104-TDU-B-212-113002); China Medical University Hospital, Academia Sinica Taiwan Biobank, Stroke Biosignature Project (BM104010092); NRPB Stroke Clinical Trial Consortium (MOST 103-2325-B-039-006); Tseng-Lien Lin Foundation, Taichung, Taiwan; Taiwan Brain Disease Foundation, Taipei, Taiwan; Katsuzo and Kiyo Aoshima Memorial Funds, Japan; and CMU under the Aim for Top University Plan of the Ministry of Education, Taiwan.

Role of the sponsors: The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding was received for this study.

Supplementary material: See accompanying pages.

REFERENCES

1. Howk C, Bennett M. Immune function and health outcomes in women with depression. *Biopsychosoc Med*. 2010;4(1):3.
2. WHO. *The Global Burden of Disease: 2004 Update*. Geneva, Switzerland: World Health Organization; 2008:51
3. Nunes SO, Reiche EM, Morimoto HK, et al. Immune and hormonal activity in adults suffering from depression. *Braz J Med Biol Res*. 2002;35(5):581–587.
4. Stein M, Miller AH, Trestman RL. Depression, the immune system, and health and illness: findings in search of meaning. *Arch Gen Psychiatry*. 1991;48(2):171–177.
5. Herbert TB, Cohen S. Depression and immunity: a meta-analytic review. *Psychol Bull*. 1993;113(3):472–486.
6. Irwin M, Costlow C, Williams H, et al. Cellular immunity to varicella-zoster virus in patients with major depression. *J Infect Dis*. 1998;178(suppl 1):S104–S108.
7. Irwin MR, Levin MJ, Carrillo C, et al. Major depressive disorder and immunity to varicella-zoster virus in the elderly. *Brain Behav Immun*. 2011;25(4):759–766.
8. Lasserre A, Blaizeau F, Gorwood P, et al. Herpes zoster: family history and psychological stress-case-control study. *J Clin Virol*. 2012;55(2):153–157.
9. Yang YW, Chen YH, Lin HW. Risk of herpes zoster among patients with psychiatric diseases: a population-based study. *J Eur Acad Dermatol Venereol*. 2011;25(4):447–453.
10. Hata A, Kuniyoshi M, Ohkusa Y. Risk of herpes zoster in patients with underlying diseases: a retrospective hospital-based cohort study. *Infection*. 2011;39(6):537–544.
11. Slee VN. The International Classification of Diseases: Ninth Revision (ICD-9). *Ann Intern Med*. 1978;88(3):424–426.
12. Arvin A. Aging, immunity, and the varicella-zoster virus. *N Engl J Med*. 2005;352(22):2266–2267.
13. Thomas SL, Hall AJ. What does epidemiology tell us about risk factors for herpes zoster? *Lancet Infect Dis*. 2004;4(1):26–33.
14. Hope-Simpson RE. The nature of herpes zoster: a long-term study and a new hypothesis. *Proc R Soc Med*. 1965;58:9–20.
15. Levin MJ, Smith JG, Kaufhold RM, et al. Decline in varicella-zoster virus (VZV)-specific cell-mediated immunity with increasing age and boosting with a high-dose VZV vaccine. *J Infect Dis*. 2003;188(9):1336–1344.
16. Brisson M, Edmunds WJ, Law B, et al. Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. *Epidemiol Infect*. 2001;127(2):305–314.
17. Chapman RS, Cross KW, Fleming DM. The incidence of shingles and its implications for vaccination policy. *Vaccine*. 2003;21(19–20):2541–2547.
18. Blume J, Douglas SD, Evans DL. Immune suppression and immune activation in depression. *Brain Behav Immun*. 2011;25(2):221–229.
19. Gamaldo CE, Shaikh AK, McArthur JC. The sleep-immunity relationship. *Neurol Clin*. 2012;30(4):1313–1343.
20. Linn BS, Linn MW, Jensen J. Anxiety and immune responsiveness. *Psychol Rep*. 1981;49(3):969–970.
21. Fereshtehnejad SM, Ghazi L, Shafieesabet M, et al. Motor, psychiatric and fatigue features associated with nutritional status and its effects on quality of life in Parkinson's disease patients. *PLoS ONE*. 2014;9(3):e91153.
22. Pan WH, Chang YP, Yeh WT, et al. Co-occurrence of anemia, marginal vitamin B6, and folate status and depressive symptoms in older adults. *J Geriatr Psychiatry Neurol*. 2012;25(3):170–178.
23. Davison KM, Kaplan BJ. Vitamin and mineral intakes in adults with mood disorders: comparisons to nutrition standards and associations with sociodemographic and clinical variables. *J Am Coll Nutr*. 2011;30(6):547–558.
24. Smith JG, Levin M, Vessey R, et al. Measurement of cell-mediated immunity with a Varicella-Zoster Virus-specific interferon-gamma ELISPOT assay: responses in an elderly population receiving a booster immunization. *J Med Virol*. 2003;70(suppl 1):S38–S41.
25. Kuvibidila SR, Gardner R, Velez M, et al. Iron deficiency, but not underfeeding reduces the secretion of interferon-gamma by mitogen-activated murine spleen cells. *Cytokine*. 2010;52(3):230–237.
26. Sandstead HH, Prasad AS, Penland JG, et al. Zinc deficiency in Mexican American children: influence of zinc and other micronutrients on T cells, cytokines, and antiinflammatory plasma proteins. *Am J Clin Nutr*. 2008;88(4):1067–1073.
27. Benson S, Janssen OE, Hahn S, et al. Obesity, depression, and chronic low-grade inflammation in women with polycystic ovary syndrome. *Brain Behav Immun*. 2008;22(2):177–184.
28. Schleifer SJ, Bartlett JA, Keller SE, et al. Immunity in adolescents with major depression. *J Am Acad Child Adolesc Psychiatry*. 2002;41(9):1054–1060.
29. Forbes HJ, Bhaskaran K, Thomas SL, et al. Quantification of risk factors for herpes zoster: population based case-control study. *BMJ*. 2014;348(2):g2911.
30. Frank MG, Wieseler Frank JL, Hendricks SE, et al. Age at onset of major depressive disorder predicts reductions in NK cell number and activity. *J Affect Disord*. 2002;71(1–3):159–167.
31. Biron CA, Brossay L. NK cells and NKT cells in innate defense against viral infections. *Curr Opin Immunol*. 2001;13(4):458–464.
32. Chapman DP, Perry GS, Strine TW. The vital link between chronic disease and depressive disorders. *Prev Chronic Dis*. 2005;2(1):A14.
33. Guilford T, Morris D, Gray D, et al. Atherosclerosis: pathogenesis and increased occurrence in individuals with HIV and Mycobacterium tuberculosis infection. *HIV AIDS (Auckl)*. 2010;2:211–218.
34. Karjala Z, Neal D, Rohrer J. Association between HSV1 seropositivity and obesity: data from the National Health and Nutritional Examination Survey, 2007–2008. *PLoS ONE*. 2011;6(5):e19092.
35. Adams KF, Schatzkin A, Harris TB, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *N Engl J Med*. 2006;355(8):763–778.
36. Myles TD, Gooch J, Santolaya J. Obesity as an independent risk factor for infectious morbidity in patients who undergo cesarean delivery. *Obstet Gynecol*. 2002;100(5, pt 1):959–964.
37. Fernández-Real JM, Ferri MJ, Vendrell J, et al. Burden of infection and fat mass in healthy middle-aged men. *Obesity (Silver Spring)*. 2007;15(1):245–252.
38. Thjodleifsson B, Olafsson I, Gislason D, et al. Infections and obesity: a multinational epidemiological study. *Scand J Infect Dis*. 2008;40(5):381–386.
39. Haslam DW, James WP. Obesity. *Lancet*. 2005;366(9492):1197–1209.
40. Harpaz R, Ortega-Sanchez IR, Seward JF. Prevention of herpes zoster: recommendations of the advisory committee on immunization practices (ACIP). Centers for Disease Control and Prevention. MMWR Recommendations and Reports. 57(05):1–30. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5705a1.htm. Published June 6, 2008. Accessed August 4, 2015.

Supplementary material follows this article.

THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: High Prevalence of Herpes Zoster in Patients With Depression

Authors: Chun-Hui Liao, MD, MSPH; Chen-Shu Chang, MD; Chih-Hsin Muo, MSc; and Chia-Hung Kao, MD

DOI Number: 10.4088/JCP.14m09311

List of Supplementary Material for the article

1. eTable 1 The risk for postherpetic neuralgia in herpes patients

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplemental Table. The risk for postherpetic neuralgia in herpes patients

	N	Post-herpetic neuralgia no. (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Comparison	2358	777 (33.0)	1.00	
Depression	774	294 (38.0)	1.25 (1.05-1.48)*	1.29 (1.07-1.57)**
Comparison without anti-depression	2327	762 (32.8)	1.00	1.00
Comparison with anti-depression	31	15 (48.4)	1.93 (0.95-3.92)	1.50 (0.75-3.03)
Depression without anti-depression	594	234 (39.4)	1.34 (1.11-1.61)**	1.35 (1.11-1.65)**
Depression with anti-depression	180	60 (33.3)	1.03 (0.74-1.42)	0.94 (0.67-1.30)

Postherpetic neuralgia, ICD-9-CM 053.1 and 053.2

* $p < 0.05$, ** $p < 0.01$