



# BMJ Open Association between a History of herpes zoster and the risk of Sjögren's syndrome: a nationwide, population-based, case-control study

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## ABSTRACT

**Objective** Viral infection is an exogenous factor for Sjögren's syndrome (SS). The relationship between herpes zoster infection and the ensuing risk of SS has remained unclear. This study investigated the association between a history of herpes zoster infection and the risk of SS through a nationwide population-based case-control study.

**Design** Retrospective case-control study.

**Setting** General population of Taiwan.

**Data source** 2003–2013 National Health Insurance Research Database of Taiwan.

**Participants** We identified all patients with newly diagnosed SS between 1 January 2007 and 31 December 2012 without a history of rheumatoid arthritis or systemic lupus erythematosus as the SS group.

**Controls** We randomly selected patients without SS between 1 January 2003 and 31 December 2012 and matched 1:5 with controls based on index year, age and sex.

**Main outcome measure** Conditional logistic regression analysis to examine the association between a history of herpes zoster and the risk of SS.

**Results** The study included 5751 patients with SS and 28 755 matched controls. The risk of SS was significantly associated with a history of herpes zoster (model A (adjusted for Charlson Comorbidity Index (CCI) (excluding connective tissue disease, CTD)): OR 1.89; 95% CI 1.71 to 2.08; model B (adjusted for comorbidities used to calculate CCI (excluding CTD)): OR 1.90; 95% CI 1.72 to 2.10), in particular if the interval from the last visit for herpes zoster infection to the index date was <3 months (model A: OR 3.09; 95% CI 2.20 to 4.34; model B: OR 3.13; 95% CI 2.20 to 4.45). Such associations remained robust using various definitions of herpes zoster.

**Conclusion** This nationwide, population-based, case-control study revealed a significant association between a history of herpes zoster and the risk of SS.

## INTRODUCTION

Varicella zoster virus (VZV; human herpesvirus type 3) causes varicella (chickenpox) and herpes zoster. Chickenpox occurs during the acute, primary infection phase of the virus that is highly contagious. VZV is transmitted

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ We conducted a study based on nationwide population-based claims data adequately powered to minimise selection bias and detect an association between a history of herpes zoster and the Risk of Sjögren's syndrome (SS).
- ⇒ National Health Insurance Research Database of Taiwan does not provide information regarding individual habits, laboratory data, detailed information of disease severity and medication, and determination of SS diagnoses based on claims data, so misclassification is a possibility.
- ⇒ We cannot sufficiently infer a causal relationship between herpes zoster and SS risk because of observational non-randomisation.

through aerosol, air or direct contact, and its transmission is mediated by the innate immune system through antiviral cytokines and natural killer (NK) cell activation.<sup>1</sup> Activated NK cells are a substantial source of interferon- $\gamma$  and enhance the clonal expansion of antigen-specific T cells. Herpes zoster, an acute neurocutaneous disease characterised by severe pain (postherpetic neuralgia) and dermatomal rash, represents the reactivation of the VZV from its latent phase in the sensory root ganglia. Primary VZV infection elicits immunoglobulin (Ig)G, IgM and IgA antibodies, which bind to many classes of viral proteins. Herpes zoster can be treated with antiviral therapy, corticosteroids and analgesics to reduce pain, enable rapid healing and prevent complications.

Sjögren's syndrome (SS) is an autoimmune inflammatory disorder of the exocrine tissue. The incidence of SS peaks around 50 years of age, with female-to-male ratio reported in literature varies geographically and ethnicity from 7:1 to 27:1, which is stronger sex bias than in almost all other autoimmune diseases.<sup>2–4</sup> The incidence rate of SS

in Taiwan was 10.6 cases per 100 000 person-years from year 2000 to 2008.<sup>5</sup> SS can affect many body parts and cause xerostomia, xerophthalmia, fatigue, eye complications and oral infection. Although SS is identified to be a multifactorial disease, its risk factors and pathogenesis remain incompletely understood. However, its potential risk factors include endogenous genetic susceptibility with strongest association with the human leucocyte antigen locus,<sup>6–8</sup> exogenous infection and environmental stimuli such as cigarette smoking and diet.<sup>9–13</sup> B cell activation plays an important role in the pathogenesis of SS.<sup>14</sup> Given that varicella infection can drive specific and non-specific B cell activation,<sup>15</sup> we hypothesised that herpes zoster may be a risk factor for SS. However, the relationship between herpes zoster exposure and the risk of SS remains unclear.<sup>16 17</sup> Taiwan's National Health Insurance (NHI) Research Database (NHIRD) has been released for research purposes and facilitated population-based epidemiological studies. Therefore, this study examined the association of a history of herpes zoster and the risk of SS by using the NHIRD.

## MATERIALS AND METHODS

### Study design

This was a retrospective, population-based, case–control study.

### Patient and public involvement

There was no patient or public involvement in this study.

### Data source

Taiwan's NHI is a government, single-payer, compulsory programme launched in 1995. The NHIRD contains the detailed claims data of NHI beneficiaries including medical diagnoses, inpatient care received, outpatient physician visits and prescriptions. As of 2014, the NHI covered up to 99.9% of Taiwan's population of approximately 23 million people. For research purposes, the National Health Research Institute (NHRI) manages the NHIRD and releases comprehensive NHI-related claims data, including the files of ambulatory care expenditure by visits, ambulatory care orders, inpatient expenditure by admissions, inpatient orders, prescriptions, and registry for beneficiaries.

The Bureau of National Health Insurance established the Registry for Catastrophic Illness Patient (RCIP) database for patients with major illness or systemic autoimmune syndrome including SS, RA and systemic lupus erythematosus (SLE). Patients are issued a catastrophic illness certificate and enrolled in the RCIP after their diagnosis is confirmed by a clinical physician and permission is obtained from the Ministry of Health and Welfare's Health Promotion Administration. Patients with a catastrophic illness certificate are exempt from copayments for treatments related to the disease. In this study, patients with SS were identified from the RCIP database. SS was

diagnosed from clinical expert opinion by signs, clinical symptoms and laboratory data.

The NHRI established the Longitudinal Health Insurance Database 2000 (LHID2000), which contains all the original claims data of 1 million beneficiaries enrolled in 2000 who were randomly sampled from the 2000 Registry for Beneficiaries of the NHIRD; the registration data of all individuals who were beneficiaries of the NHI programme from 1 January 2000 to 31 December 2000, were drawn for random sampling. All the registration and claims data of these 1 million individuals collected through the NHI programme constitute the LHID2000. No significant difference was observed in the sex distribution between the LHID2000 and original NHIRD, and the representativeness of the LHID2000 was validated by the NHRI.<sup>18</sup> We selected age-matched, sex-matched and index year-matched controls from the LHID2000.

### Study subjects

The flow diagram of enrolment, categorisation and matching for the comparison of the study population is shown in figure 1.

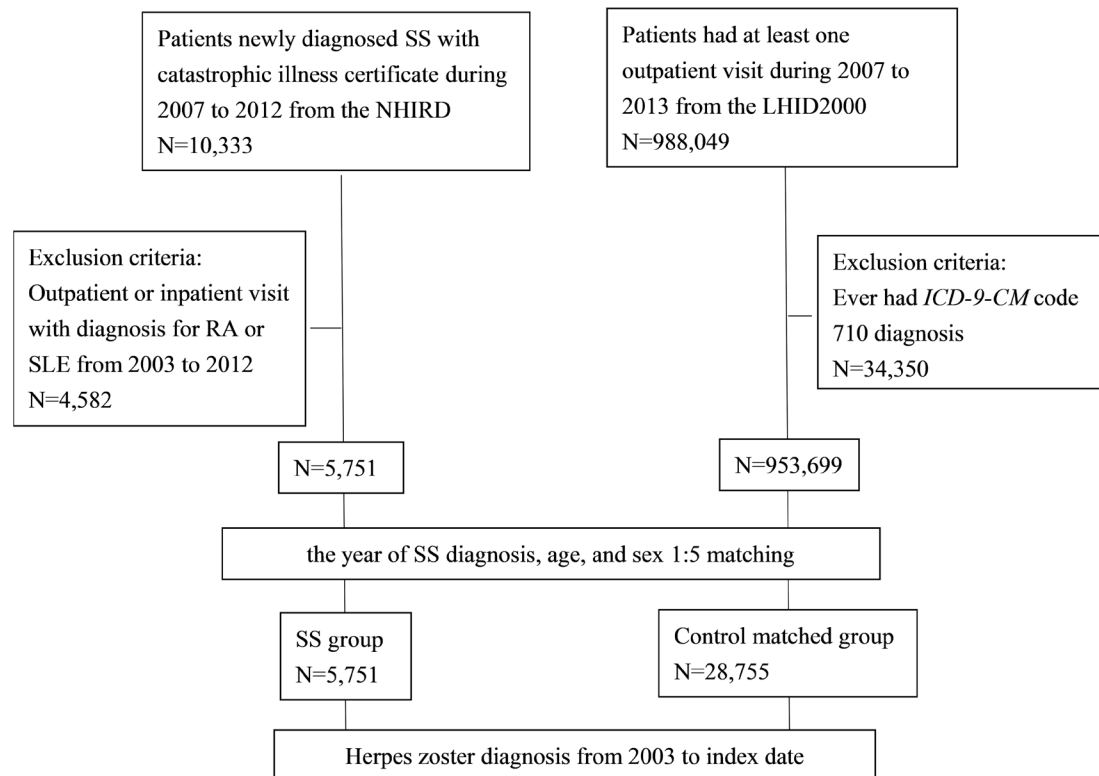
### Incident SS cases identified from the whole Taiwanese population

From the RCIP database, we identified patients with a catastrophic illness certificate for SS (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 710.2) who received their first diagnosis of SS between 2007 and 2012. SS was diagnosed based on clinical expert opinion. According to the patients' earliest SS diagnosis date (ie, index date), the incidence year of these patients was determined, and new patients with SS were identified each year. Patients who were diagnosed as having RA (ICD-9-CM code 714.0) or SLE (ICD-9-CM code 710.0) during 2003–2012 were excluded. The index date was defined as the date of the first diagnosis of SS, and the index year was the year of the index date.

### Matched non-SS controls selected from one million representative population

We used the LHID 2000 to select controls to sample outpatient visits from 1996 to 2012 after excluding codes for diffuse disease of the connective tissue (ICD-9-CM code 710) and original claims data with missing details regarding sex or age. The control group was matched for the index year, age and sex with the SS group at a 1:5 ratio. Under Gaussian model for matched sets, we used 1:5 ratio to produce good quality matching and a better sampling variability ( $1+1/\kappa=1+1/5=1.2$ ). The precision obtained by increasing  $\kappa$  decreased rapidly after 4. Therefore, we increased  $\kappa$  to 5 to maximise sample size of controls without losing sample size.<sup>19 20</sup>

Age, sex and race are often used to match cases and controls because they are typically strong confounders of disease.<sup>21</sup> On the basis of age and sex, the matching biological properties are the most similar. Most of SS patients were women, and women over the age of 40 when



**Figure 1** Flow chart of study patients. ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; LHID2000, Longitudinal Health Insurance Database 2000; NHIRD, National Health Insurance Research Database; RA, rheumatoid arthritis; SS, Sjögren syndrome; SLE, systemic lupus erythematosus.

they were first diagnosed. Women are more likely to get the disease than men.<sup>2-4 22</sup> Risk of herpes zoster increases with age, and women have a greater risk of developing herpes zoster than men.<sup>23</sup> Both age and sex are specific risk factors for SS and herpes zoster. The index date was defined as the first day of ambulatory visit for any reason in each year, and the index year was the year of the index date. Index year is because different years (calendar years) have different classification standards, so it is necessary to match the index year.

#### Definition of herpes zoster infection and methods to identify a history of herpes zoster infection

Herpes zoster infection was defined as the reactivation of VZV, which remains latent in the dorsal root ganglion after primary infection (chickenpox) and causes a painful, maculopapular rash and postherpetic neuralgia along with dermatome involvement.<sup>24</sup>

Patients were identified to have a history of herpes zoster infection if they had an inpatient visit or ambulatory visit with a diagnosis of herpes zoster (ICD-9-CM code 053) with a concurrent prescription of topical/systemic antiviral agents before the index date. Sensitivity analysis was conducted by using various methods to identify herpes zoster infection: (1) herpes zoster diagnosis made by any doctors, (2) herpes zoster diagnosis made by qualified dermatologists, (3) herpes zoster diagnosis with concurrent prescriptions of adjuvant medications and (4)

herpes zoster diagnosis with concurrent prescriptions of both antiviral agents and adjuvant medications.

#### Comorbidities as potential confounders

Because comorbidities may be associated with both herpes zoster and SS, they are considered as potential confounders for the association between herpes zoster and the risk of SS. We used the Charlson Comorbidity Index (CCI) as the general comorbidity index<sup>25 26</sup> after excluding connective tissue disease (CTD) to examine the presence of comorbidities including diabetes with diabetic complications, myocardial infarction, congestive heart failure, peripheral vascular disease,<sup>27 28</sup> chronic pulmonary disease,<sup>29-31</sup> ulcer disease,<sup>32</sup> mild liver disease,<sup>33 34</sup> moderate or severe liver disease, hemiplegia, moderate or severe renal disease, tumour<sup>35</sup> and solid metastatic tumour. Patients were considered to have any comorbidity when they had at least three outpatient visits or one hospitalisation with the corresponding ICD-9-CM code within 1 year before the index date. Because the first diagnosis may only be suspected, because it is an application for NHI database, if there is no corresponding diagnosis, relevant examinations and tests cannot be prescribed, and the second visit will report the examination. If confirmed, the third visit will remain diagnostic. Discharge diagnosis is usually included in the discharge diagnosis after relevant tests are carried out during hospitalisation to confirm the diagnosis.



Peripheral vascular diseases are included peripheral arterial disease, chronic venous insufficiency and deep vein thrombosis. Patients were considered to have mild liver disease if they had chronic hepatitis B or C or cirrhosis without portal hypertension. Patients were considered to have moderate liver disease if they had cirrhosis with portal hypertension but without bleeding. Patients were considered to have severe liver disease if they had ascites, chronic jaundice, portal hypertension or a history of variceal bleeding or liver transplant. Moderate renal insufficiency was defined as a serum creatinine level of  $>3$  mg/dL. Patients who required dialysis, underwent a transplant and had uraemia were considered to have severe renal disease.<sup>25</sup> The CCI was derived through the summation of the assigned weights of all comorbid conditions presented by patients.

### Statistical analysis

This investigation is a retrospective observational case control study for exploring the correlation of each variable and the dependent variable. Demographic data are presented as the mean $\pm$ SD for continuous variables and as the number (percentage) for categorical variables. We examined differences between groups by using Student's t-test for continuous variables with normal distribution, the Mann-Whitney U test for continuous variables without normal distribution, and Pearson's  $\chi^2$  test for categorical variables. We examined the association between a history of herpes zoster and the risk of SS by performing conditional logistic regression analysis after adjusting for potential confounders and calculating ORs with 95% CIs. Stratified analysis was conducted based on age (ie,  $<50$  years and  $\geq 50$  years), sex and CCI (ie, 0 and  $\geq 1$ ). The significance of the interaction effect of covariates (ie, age group, sex and CCI group) on the association of SS risk with herpes zoster was estimated by examining the p value associated with the product of each indicator of the covariate and the indicator of herpes zoster by using the Wald test. Statistical significance was considered when the p value was  $<0.05$ . Bonferroni correction of the probability value cut-off was applied to examine the association between the risk of SS and four category of cardiovascular events (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease;  $p<0.0125$ ), two category of liver disease (mild liver disease, moderate or severe liver disease;  $p<0.025$ ), two category of DM disease (DM, DM with end-organ disease;  $p<0.025$ ), two category of tumour (tumour, metastatic solid tumour;  $p<0.025$ ). All statistical analyses were performed using SAS, V.9.3 (SAS).

## RESULTS

### Selection and grouping of study population

From 1 January 2003 and 31 December 2012, we identified 10 333 cases with a new diagnosis of SS defined by a catastrophic illness certificate and those who diagnosis of RF or SLE in outpatient or inpatient visit ( $n=4582$ ) were

excluded. Ultimately, a total 5751 participants with a new diagnosis of SS defined by a catastrophic illness certificate between 2003 and 2012 were included, and 28 755 non-SS controls from the LHID 2000, matched for year of index date, age, and sex at a ratio of 1:5 (figure 1).

### Characteristics of the study population

Table 1 lists the distributions of demographic characteristics, comorbidities, and CCI scores for the SS and control cohorts. The mean ages at diagnosis of SS in study population were  $55\pm 14$  years and 66.9% were aged  $\geq 50$  years. The study population consisted of female patients mainly (87.8%). Although no significant differences were observed between the case and control groups in terms of age, sex distribution and the time interval ( $<3$  years) between the last visit for herpes zoster infection and index date. High percentage of patients with SS had comorbidities including peripheral vascular disease (0.7% vs 0.4%;  $p<0.001$ ), chronic pulmonary disease (7.2% vs 3.7%;  $p<0.001$ ), ulcer disease (11.8% vs 5.1%;  $p<0.001$ ), mild liver disease (6.5% vs 2.2%;  $p<0.001$ ), moderate or severe renal disease (2.4% vs 1.3%;  $p<0.001$ ); a history of herpes zoster (10.9% vs 6.1%;  $p<0.001$ ). Sensitivity analyses using various definition for herpes zoster was noted high percentage in SS patients, diagnosis of herpes zoster by a dermatologist (7.8% vs 3.9%;  $p<0.001$ ) and treatment of herpes zoster with antiviral agents (3.5% vs 1.8%;  $p<0.001$ ), adjuvant therapies, (9.0% vs 5.2%;  $p<0.001$ ) or combination therapies (9.6% vs 5.4%;  $p<0.001$ ). Low percentage of patients with SS had comorbidities including diabetes mellitus (6.5% vs 8.7%;  $p<0.001$ ), tumours (0.6% vs 2.8%;  $p<0.001$ ) and metastatic solid tumour (0.1% vs 0.3%;  $p<0.001$ ).

### Association between a history of herpes zoster and the risk of SS

The results of univariable analysis revealed a significant association between a history of herpes zoster and the risk of SS (OR 1.91; 95% CI 1.74 to 2.11; table 2). The association between herpes zoster exposure and SS risk remained significant after adjustment for  $CCI\geq 1$  (model A: OR 1.89; 95% CI 1.71 to 2.08) and comorbidities used to calculate CCI (model B: OR 1.90; 95% CI 1.72 to 2.10), but DM and tumours are exception. The relationship between herpes zoster and SS risk decreased significantly in DM (univariable OR 0.72; 95% CI 0.64 to 0.81; multivariable analyses, model B: OR 0.62; 95% CI 0.55 to 0.70) and tumours (univariable OR, 0.23; 95% CI 0.16 to 0.32; multivariable analyses, model B: OR 0.18; 95% CI 0.13 to 0.26) patients. The association of the risk of SS with a history of herpes zoster was the strongest when the interval between the last visit for herpes zoster infection and the index date was  $<3$  months (univariable OR 3.32; 95% CI 2.38 to 4.65; multivariable analyses, model A: OR 3.09; 95% CI 2.20 to 4.34; and model B: OR, 3.13; 95% CI, 2.20 to 4.45), followed by an interval of 3–6 months (univariable OR 1.95, 95% CI 1.35 to 2.82; multivariable analyses, model A: OR 1.92; 95% CI 1.32 to 2.79 and model B: OR 2.01;



**Table 1** Demographic data and clinical characteristics of the SS case and controls groups

	Control (n=28755)	SS (n=5751)	P value
Age, years (mean±SD)	55±14	55±14	1*
Age group			
<50 years	9520 (33.1)	1904 (33.1)	
≥50 years	19235 (66.9)	3847 (66.9)	
Sex			1*
Female	25255 (87.8)	5051 (87.8)	
Male	3500 (12.2)	700 (12.2)	
CCI (mean±SD) (exclude CTD)	0.4±1.0	0.5±0.9	<0.001
CCI group (exclude CTD)			
0	22378 (77.8)	3963 (68.9)	
≥1	6377 (22.2)	1788 (31.1)	
Myocardial infarction	58 (0.2)	15 (0.3)	0.373†
Congestive heart failure	279 (1.0)	76 (1.3)	0.016†
Peripheral vascular disease	100 (0.4)	42 (0.7)	<0.001†
Cerebrovascular disease	930 (3.2)	217 (3.8)	0.037†
Dementia	261 (0.8)	40 (0.7)	0.654
Chronic pulmonary disease	1067 (3.7)	416 (7.2)	<0.001
Ulcer disease	1464 (5.1)	677 (11.8)	<0.001
Mild liver disease	618 (2.2)	372 (6.5)	<0.001‡
Moderate or severe liver disease	17 (0.1)	6 (0.1)	0.225‡
DM	2495 (8.7)	374 (6.5)	<0.001‡
DM with end-organ damage	502 (1.8)	96 (1.7)	0.685‡
Hemiplegia	55 (0.2)	9 (0.2)	0.576
Moderate or severe renal disease	370 (1.3)	140 (2.4)	<0.001
Tumour	791 (2.8)	37 (0.6)	<0.001‡
Metastatic solid tumour	89 (0.3)	4 (0.1)	<0.001‡
Herpes zoster	1752 (6.1)	629 (10.9)	<0.001
Herpes zoster diagnosis made by dermatologist	1121 (3.9)	446 (7.8)	<0.001
Herpes zoster treated with topical/systemic antiviral agents§	508 (1.8)	199 (3.5)	<0.001
Herpes zoster treated with adjuvant therapies¶	1488 (5.2)	516 (9.0)	<0.001
Herpes zoster treated with both antiviral agents and adjuvant therapies	1560 (5.4)	553 (9.6)	<0.001
Time interval between the last herpes zoster-related visit and the index date, years	3.2±2.2	3.2±2.4	0.713
No herpes zoster	27003 (93.9)	5122 (89.1)	<0.001
Time interval <3 months	88 (0.3)	56 (1.0)	
3 months≤time interval <6 months	106 (0.4)	39 (0.7)	
0.5 year ≤time interval <1 year	137 (0.5)	48 (0.8)	
1 year ≤time interval <3 years	561 (2.0)	172 (3.0)	
3 years ≤time interval	860 (3.0)	314 (5.5)	

Continued

**Table 1** Continued

	Control (n=28755)	SS (n=5751)	P value
Data are shown as the number (percentage) unless specified otherwise.			
Comorbidity was identified within 1 year before the index date.			
*Age and sex are matched, p=1.000.			
†Bonferroni correction, p=0.05/4.			
‡Bonferroni correction, p=0.05/2			
§Antiviral agents for herpes zoster included acyclovir, valaciclovir and famciclovir.			
¶Adjuvant therapies included non-steroidal anti-inflammatory agents, tramadol, acetaminophen, gabapentin, pregabalin, duloxetine, and tricyclic antidepressants (amitriptyline (N06AA09), clomipramine (N06AA04), doxepin (N06AA12), imipramine (N06AA02), trimipramine (N06AA06), amoxapine (N06AA17), desipramine (N06AA01), nortriptyline (N06AA10) and protriptyline(N06AA11)).			
CCI, Charlson Comorbidity Index; CTD, connective tissue disease; DM, diabetes mellitus; SS, Sjögren syndrome.			

95% CI 1.38 to 2.94; [table 3](#)). The magnitude of this association did not change with various definitions of herpes zoster (diagnosis established by qualified dermatologists rather than by any physicians) and the application of antiviral medications, adjuvant therapies or combination therapies ([table 3](#)).

### Subgroup analysis

The positive association between a history of herpes zoster and the risk of SS remained consistently significant in all the subgroups based on age, sex and CCI exclude CTD ([table 4](#)). The CCI which exclude CTD exhibited a

significant interaction effect on the association between a history of herpes zoster and the risk of SS (p<0.001). The association between a history of herpes zoster and the risk of SS was significantly higher in the patients with a CCI of 0 (OR 2.24; 95% CI 1.77 to 2.82) than in those with a CCI of ≥1 (OR 1.71; 95% CI 1.21 to 2.41).

### DISCUSSION

The main finding of this study shows that a history of herpes zoster is associated with risk of SS after adjustment

**Table 2** Univariable and multivariable conditional logistic regression analyses for comorbidities associated with SS risk shown as ORs with 95% CIs (model A: adjusted CCI (exclude CTD); model B: adjusted comorbidities (exclude CTD))

Variable	Univariable OR (95% CI)	Multivariable	
		Model A OR (95% CI)	Model B OR (95% CI)
Herpes zoster	1.91 (1.74 to 2.11)	1.89 (1.71 to 2.08)	1.90 (1.72 to 2.10)
CCI ≥1 (exclude CTD)	1.70 (1.59 to 1.82)	1.69 (1.58 to 1.81)	
Myocardial infarction	1.30 (0.73 to 2.31)		1.24 (0.69 to 2.25)
Congestive heart failure	1.38 (1.06 to 1.79)		1.08 (0.82 to 1.43)
Peripheral vascular disease	2.11 (1.47 to 3.03)		2.21 (1.52 to 3.22)
Cerebrovascular disease	1.18 (1.01 to 1.38)		1.16 (0.98 to 1.37)
Dementia	0.92 (0.65 to 1.30)		0.75 (0.52 to 1.08)
Chronic pulmonary disease	2.07 (1.84 to 2.33)		1.93 (1.71 to 2.19)
Ulcer disease	2.53 (2.29 to 2.79)		2.27 (2.05 to 2.51)
Mild liver disease	3.14 (2.75 to 3.58)		3.02 (2.63 to 3.48)
Moderate or severe liver disease	1.77 (0.70 to 4.48)		0.64 (0.23 to 1.73)
DM	0.72 (0.64 to 0.81)		0.62 (0.55 to 0.70)
DM with end-organ damage	0.96 (0.77 to 1.19)		0.90 (0.71 to 1.14)
Hemiplegia	0.82 (0.40 to 1.66)		0.70 (0.33 to 1.46)
Moderate or severe renal disease	1.88 (1.55 to 2.29)		1.83 (1.49 to 2.26)
Tumour	0.23 (0.16 to 0.32)		0.18 (0.13 to 0.26)
Metastatic solid tumour	0.22 (0.08 to 0.61)		1.05 (0.36 to 3.05)

Comorbidity was identified within 1 year before the index date.  
CCI, Charlson Comorbidity Index; CTD, connective tissue disease; DM, diabetes mellitus; SS, Sjögren syndrome.

**Table 3** Conditional logistic regression analyses for herpes zoster associated with SS risk shown as ORs with 95% CIs (model A: adjusted CCI (exclude CTD); model B: adjusted comorbidities (exclude CTD))

	Multivariable		
	Univariable	Model A	Model B
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Time interval between the last herpes zoster-related visit and the index date, years			
No herpes zoster	1.00 (reference)	1.00 (reference)	1.00 (reference)
Time interval <3 months	3.32 (2.38 to 4.65)	3.09 (2.20 to 4.34)	3.13 (2.20 to 4.45)
3 months ≤time interval <6 months	1.95 (1.35 to 2.82)	1.92 (1.32 to 2.79)	2.01 (1.38 to 2.94)
0.5 year ≤time interval <1 year	1.86 (1.33 to 2.59)	1.86 (1.33 to 2.59)	1.89 (1.35 to 2.65)
1 year ≤time interval <3 years	1.64 (1.37 to 1.95)	1.62 (1.36 to 1.93)	1.58 (1.32 to 1.89)
3 year ≤time interval	1.94 (1.70 to 2.22)	1.93 (1.69 to 2.21)	1.96 (1.71 to 2.25)
Sensitivity analysis			
Herpes zoster			
No herpes zoster	1.00 (reference)	1.00 (reference)	1.00 (reference)
Herpes zoster diagnosed by any doctors	1.54 (1.31 to 1.83)	1.53 (1.29 to 1.81)	1.55 (1.31 to 1.85)
Herpes zoster diagnosed by dermatologists	2.12 (1.89 to 2.38)	2.09 (1.86 to 2.35)	2.09 (1.86 to 2.35)
Herpes zoster treated with topical/systemic antiviral agents*	2.00 (1.69 to 2.36)	1.95 (1.65 to 2.31)	1.98 (1.66 to 2.35)
Herpes zoster treated with adjuvant therapies†	1.83 (1.64 to 2.03)	1.80 (1.62 to 2.00)	1.81 (1.63 to 2.02)
Herpes zoster treated with both antiviral agents and adjuvant therapies	1.88 (1.69 to 2.08)	1.85 (1.67 to 2.06)	1.86 (1.67 to 2.07)
*Antiviral agents for herpes zoster included acyclovir, valaciclovir and famciclovir.			
†Adjuvant therapies include non-steroidal anti-inflammatory agents, tramadol, acetaminophen, gabapentin, pregabalin, duloxetine, and tricyclic antidepressants (amitriptyline, clomipramine, doxepin, imipramine, trimipramine, amoxapine, desipramine, nortriptyline and protriptyline).			
CCI, Charlson Comorbidity Index; CTD, connective tissue disease; SS, Sjögren syndrome.			

for potential confounders. Although adult patients with SS had been previously reported to have a higher risk of shingles than those without SS,<sup>16</sup> the association of SS with prior herpes zoster infection had not been completely

**Table 4** Subgroup analyses for the association between herpes zoster exposure and Sjogren syndrome risk based on age, sex and CCI (exclude CTD)

	OR (95% CI)	P value*
Age group		0.270
< 50 years	2.09 (1.67 to 2.61)	
≥50 years	1.84 (1.65 to 2.05)	
Sex		0.146
Female	1.94 (1.75 to 2.15)	
Male	1.50 (1.11 to 2.04)	
CCI group (exclude CTD)		0.001
0	2.13 (1.88 to 2.43)	
≥1	1.63 (1.32 to 2.02)	
Comorbidity was identified within 1 year before the index date.		
*P for interaction.		
CCI, Charlson Comorbidity Index; CTD, connective tissue disease.		

studied. This nationwide, population-based, case-control study was the first to demonstrate a significant relationship between herpes zoster exposure and SS risk, and the magnitude of this association was the strongest when the interval between the last visit for herpes zoster infection and the index date was <3 months. A possible explanation for our main finding was that herpes zoster infection may lead to a persistent B cell activation,<sup>14</sup> which further lead to the development of SS in genetically susceptible patients.<sup>15</sup> Though a misclassification bias may be introduced by using the ICD-9-CM code of herpes zoster with concurrent antiviral therapies to identify patients with a history of herpes zoster, analysis revealed that the results were not sensitive to the various definitions of herpes zoster. Also, if we can calculate the actual misclassification rate and assume that the misclassification rate for herpes zoster did not differ between the SS group and the non-SS group, the direction of this non-differential misclassification bias was always towards the null.<sup>36</sup>

Low percentage of patients with SS had dDM and lower risk between herpes zoster exposure and SS in DM patients. The result can be explained by metformin is regarded as the first-line therapy of type 2 DM and reduce the risk of developing SS in patients with DM through



anti-inflammatory effect, furthermore, it has been considered as the treatment strategy for SS in the manner of enhancing the immunomodulatory response.<sup>37–38</sup> Another finding is low percentage of patients with SS had tumours and metastatic solid tumour and lower risk between herpes zoster exposure and SS in tumours patients. There is inconsistent information about overall risk of cancer, and little information about the solid cancer in SS patients.<sup>39–41</sup> DM and tumours probably have protective effects between herpes zoster and SS. This aspect needs to more investigate to clarify. Another significant outcome in this study was that the association between herpes zoster and SS was strongest when the lag time of the last herpes zoster-related visit was <3 months. However, we cannot exclude the possibility that SS might have occurred before the last herpes zoster-related visit date when the lag time was <3 months. Therefore, reverse causality may explain the finding given that SS patients have an increased risk of herpes zoster<sup>16</sup> and the diagnosis of SS may be delayed frequently because the onset of SS clinical symptoms and relative autoantibodies may also present for up to several years before the onset of SS clinical symptoms and the diagnosis of primary SS, particularly anti-Ro/SSA and anti-La/SSB.<sup>42–44</sup> Thus, the best explanation for the comorbidities is long disease development and chronic inflammatory conditions in SS patients.

The study also revealed that SS was associated with several comorbidities, including peripheral vascular disease, chronic pulmonary disease, ulcer disease, mild liver disease and moderate to severe renal disease. Several extraglandular systems may be involvement in patients with SS, including musculoskeletal, pulmonary, cardiovascular, gastrointestinal, renal, urogenital and nervous systems.<sup>45</sup> Therefore, a possible explanation for the associations between these comorbidities with SS was that the diagnosis of SS was later than the disease related to extraglandular manifestations of SS. Also, prior studies also found a higher prevalence of *Helicobacter pylori* infection and higher serum levels of anti-*H. pylori* IgA and IgM in SS patients compared with controls,<sup>46–47</sup> and these findings might explain, at least in part, the association between ulcer disease and SS. Regarding the association between mild liver disease and SS, another explanation was that SS is one of the extrahepatic manifestations of hepatitis C virus infection.<sup>48–50</sup> Also, positive associations of SS with chronic pulmonary disease and peripheral vascular disease may be explained by shared risk factors, such as cigarette smoking.<sup>13</sup> We also found that the magnitude of the association between herpes zoster and SS was significantly higher among those without comorbidities compared with those with CCI  $\geq 1$ . It is possible that the influence of herpes zoster on SS was mitigated by the presence of competing risk factors as mentioned above among those with CCI  $\geq 1$  because of long development time before SS was diagnosed.

The strength of this study is that it used nationwide population-based claims data to minimise selection bias. However, this study has several limitations. First, the

determination of diagnoses based on claims data may not be accurate, many SS patients are initially and incorrectly diagnosed with either RA or SLE, because of positive ANA or RF. However, SS diagnosis may not be of a concern given that a catastrophic illness certificate was issued only if at least two qualified rheumatologists had confirmed SS diagnosis through the retrieval of original medical records. Moreover, the association between a history of herpes zoster and SS risk was even more robust when we considered herpes zoster diagnosis to be valid only if it was established by a qualified dermatologist. Furthermore, the non-differential misclassification bias related to herpes zoster diagnosis in the case and control groups could only underestimate the strength of the association between herpes zoster exposure and SS risk.

Second, the NHIRD does not provide information regarding individual habits, including smoking and self-paid medication, such as herpes zoster vaccination, which may be confounding factors. However, we adjusted for smoking-related comorbidities, namely chronic pulmonary disease<sup>51–52</sup> cardiovascular disease (myocardial infarction, congestive heart failure, peripheral vascular disease, and cerebrovascular disease), peptic ulcer<sup>53</sup> and tumour, which may serve as a proxy of the confounding effect of smoking. In addition, we adjusted for medications used for treating herpes zoster infection based on NHI payment guidelines. Third, the NHIRD does not provide laboratory data such as the autoantibody titre. Furthermore, given that physicians do not examine the autoantibody profile for individuals with asymptomatic SS, we could not exclude the possibility of reverse causality for the association between herpes zoster exposure and SS risk. Fourth, a case–control study cannot sufficiently infer a causal relationship between herpes zoster and SS risk because of observational non-randomisation. Fifth, claims data lacked detailed information regarding herpes zoster severity and medication, thus limiting the estimation of a dose–response relationship between a history of herpes zoster and the risk of SS. Finally, the results of this population-based study in Taiwan might not be generalisable to other populations.

## CONCLUSIONS

This nationwide, population-based dataset study revealed a significant association between a history of herpes zoster and the ensuring risk of SS, particularly among those without comorbidities. The need for screening for SS in patients with herpes zoster infection may be crucial, particularly among those with a CCI score of 0. While it remained unclear the molecular mechanism underlying the association between herpes zoster and SS, further studies need be investigated.

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