科技部補助

大專學生研究計畫研究成果報告

計畫名稱：	Association between endometriosis and the risk of Sjögren's Syndrome in a nationwide cohort-study

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Abstract

Objectives

We sought to determine whether endometriosis patients have higher risk of Sjögren's syndrome (SS).

Methods

We performed a retrospective cohort study of females with newly diagnosed endometriosis from 2000 to 2013 from the Longitudinal Health Insurance Dataset (LHID) of National Taiwan Insurance Research Database (NRIHD). Data on age, diagnosis code, history of comorbidities, the use of corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) were retrieved. We recruited cases (n = 15,947) of endometriosis and age-matched controls (n = 15,947) without endometriosis. Propensity score matching between endometriosis and non-endometriosis group was then conducted to exclude confounding factors including comorbidities and medications. A Cox proportional hazard model was developed to estimate the risk of SS in endometriosis patients. A cumulative probability model was adopted to assess the time-dependent effect of endometriosis on SS development, implying the casual link of the association. Sensitivity tests and subgroup analysis was conducted to confirm the risk of SS in endometriosis patients.

Results

The mean ± SD age (38.8 ± 8.8 y/o) was the same for patients with or without endometriosis (p = 0.309). Patients with endometriosis were more likely to have SS than non-endometriosis controls (adjusted hazard ratio 1.57, 95% confidence interval 1.29–1.91, P < 0.001), which persisted in sensitivity tests (adjusted HR=1.78, 95% CI = 1.28–2.47, P < 0.05).

Conclusions

Our findings suggest the association between endometriosis and higher risks of developing SS. Endometriosis may be a risk factor for, or share a common cause, with SS. Steroids and NSAIDs might reduce such association.

1. Introduction

Endometriosis is an estrogen-dependent disorder seen in up to 10% of women of reproductive age [1]. An estimated 50% to 60% of women with pelvic pain also have endometriosis [2]. Although not yet clear, the mechanism underlying endometriosis is thought to result from retrograde menstruation leading to implantation of endometrial tissue outside of the uterus [1, 3]. Dysfunction of the immune system may contribute to this disorder as endometrial tissues that should have otherwise been eliminated from ectopic sites remain uncleared by the immune system [4]. Such theory has prompted speculation that endometriosis may be linked to autoimmune disorders [5].

Supporting immunological studies have demonstrated that endometriosis is associated with increased levels of cytokines [6], abnormalities in B and T cell functions [7], and increased amounts of circulating auto-antibodies [5, 8]. In contrast, epidemiological studies have produced varying and inconclusive results. A cross-sectional survey of 3,680 women with surgically-diagnosed endometriosis reported significantly increased risk of multiple sclerosis (MS) and systemic lupus erythematosus (SLE) [9].Other studies based on national registry data found that patients with endometriosis have only mildly elevated risk of autoimmune disorders [10-13].

Sjögren syndrome (SS) is a common autoimmune disease, affecting predominantly young and middle-aged females. Earlier studies had reported the risk for SS in endometriosis patients to range from no significant risk to up to 24-fold [9, 10, 14].Given the discrepancies of results from previous studies, we conducted this long-term population-based cohort study to investigate the association between endometriosis and SS using a nationwide health insurance database in Taiwan. We also estimated the incidence of SS in the entire female population and in females with endometriosis in Taiwan.

2. Materials and Methods

2.1 Study design

Using the National Health Insurance Research Database (NHIRD) in Taiwan, we conducted a cohort study in adult with newly diagnosed endometriosis patients (ICD9-CM=617) and age matched controls without endometriosis during 2000-2013.

2.2 Data sources

In Taiwan, a single-payer National Health Insurance (NHI) program was instituted in 1995 and covered approximately 99% of Taiwan's population by the end of 2008 [15]. The NHIRD consists of data on reimbursement claims sourced from the NHI program. In the present study, we utilized the Longitudinal Health Insurance Database (LHID), a subset of NHIRD that contains the original claim data for 1 million randomly sampled individuals in the NHI.

2.3 Case definition

The index date was defined as the year that endometriosis was diagnosed. Patients were considered for analysis if they were female and aged 20 years or older before the index date. Patients were determined as study subjects if they met the following definition of endometriosis: at least 3 outpatient or 1 inpatient discharge diagnosis specifying endometriosis (ICD9-CM=617). Patients who did not meet these criteria were placed under the control group, i.e. non-endometriosis. Patients were considered to have SS if they met the following criteria: at least 3 outpatient or 1 inpatient discharge diagnosis specifying SS (ICD9-CM=710.2). Description of the case definition employed in this study can be found in Supplementary Table 1.

2.4 Study sample

A total of 16,214 patients were identified to have endometriosis. Two hundred and sixty-five patients received a diagnosis of SS before the index date and were excluded. The remaining 15,949 patients were age-matched (1:6) with control patients without a history of endometriosis. Propensity score matching between endometriosis and non-endometriosis group was then conducted to exclude potential confounding factors including comorbidities and

medications to derive the final cohort (endometriosis, n=15,947; non-endometriosis, n=15,947) (**Figure 1**).

2.5 Study variables

Data on age, history of underlying comorbidities such as hypertension, hyperlipidemia, chronic liver disease, diabetes, coronary artery disease, cerebrovascular disease, autoimmune disease, and cancer were retrieved from the LHID. Data on the prescriptions of corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and progestin/estrogen drugs (oral contraceptives) were also recorded. The list of ICD9-CM and condition adopted to specify the underlying comorbidities can be found in **Supplementary Table 1**.

2.6 Statistical analysis

Propensity score matching using the following factors: age, hypertension, hyperlipidemia, chronic liver disease, diabetes, coronary artery disease, autoimmune disease, cancer, corticosteroids, NSAIDs, and oral contraceptives were chosen to select controls for patients with endometriosis. A Cox proportional hazard model was adopted to estimate the risk of SS in patients with endometriosis, with a confidence interval of 95%. A cumulative probability model was also applied to assess the time-dependent effect of endometriosis on the development of SS. Sensitivity analysis was conducted to further confirm the risk of SS in endometriosis patients. Results with P-value less than 0.05 were considered statistically significant. All analyses were conducted using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

2.7 Ethical considerations

The study procedure was approved by the Institutional Review Board of Chung Shan Medical University Hospital (CS15134).

3. Results

3.1 Basic demographics of the study subjects

A total of 15,947 patients newly diagnosed with endometriosis were identified from the NHI database. Patients with endometriosis were associated with higher risk for several systemic diseases, including chronic hepatitis C, autoimmune disease, hypertension, hyperlipidemia and coronary artery disease (Table 2). After propensity score matching for potentially confounding factors, 15,947 control subjects were selected with mean age of 38.9 years (**Figure 1 and Table 2**).

3.2 Risk of SS in endometriosis

A total of 411 cases of SS were identified over 261,378 observed person-years, and 240 of these cases were associated with endometriosis. The incidence density of SS in patients with endometriosis was significantly higher than that among the general cohort (1.9 vs 1.2 per 1000 person-years) ($P < 0.001$) (**Table 3**). The Cox proportional hazard model revealed that patients with endometriosis had a significantly higher risk of SS compared to patients without endometriosis (adjusted HR=1.57, 95% CI = 1.29-1.91) after adjusting for possible confounding variables (**Table 3**). Cumulative probability of SS was found to be significantly higher for patients with endometriosis over a 14-year period of follow-up (Log-rank test, $p < 0.001$) (**Figure 2**).

Patients with hyperlipidemia, autoimmune diseases and diabetes were associated with higher risk of SS (adjusted HR = 1.84, 95% CI = 1.08-3.14; adjusted HR = 9.45, 95% CI = 5.51-16.21; adjusted HR = 2.50, 95% CI = 1.57-3.99) (**Table 3**). Use of nonsteroidal anti-inflammatory drugs (NSAIDs) was associated with a lower risk of SS (adjusted HR = 0.41, 95% CI = 0.32-0.53) (**Table 3**).

Subgroup analysis showed that there was no difference in the risk of SS in endometriosis patients aged above 55 and those between 20 and 55 (p-value for interaction = 0.550). The risk of SS in endometriosis patients who did not use corticosteroids was significantly higher than that in patients who used corticosteroids (p-value for interaction = 0.009). Similarly, endometriosis

patients who did not use NSAID or PE drugs had a higher mean risk of SS compared to those who used, although the elevated risk was not statistically significant (p-value for interaction = 0.332 and 0.671, respectively) (**Table 4**).

3.3 Sensitivity analysis

To confirm the association between SS and endometriosis, we further conducted a sensitivity analysis by restricting the cases of SS to patients who were prescribed at least 30 days of disease-modifying anti-rheumatic drugs (DMARD). Patients with endometriosis still had a significantly greater risk of SS compared to patients without endometriosis (adjusted HR = 1.78, 95% CI = 1.28-2.47) (**Table 5**). Patients with alcoholic liver disease and autoimmune disease had higher risk of SS (adjusted HR = 28.66, 95% CI = 3.45-283.32; adjusted HR 21.95, 95% CI = 11.73-41.08). NSAID use was associated with lower risk of SS (adjusted HR = 0.48, 95% CI = 0.32-0.73).

4. Discussion

In this population-based retrospective cohort study from Taiwan NHIRD, we found that patients with endometriosis present a higher risk of SS as compared to those without endometriosis (adjusted HR=1.57). Subgroup analysis suggests that endometriosis patients who use NSAIDs were associated with a lower risk of SS.

A previous cross-sectional survey-based study found markedly elevated risk (HR=24) of SS in patients with endometriosis [9]. However, such a markedly elevated SS risk might have resulted from methodological flaws such as disease self-reporting, which have been shown to be highly misclassified [13]. Our data were more consistent with two later studies that showed only slightly elevated risk of SS in patients with endometriosis [10, 14]. Nielson et al's study based on the Danish Hospital Discharge Register reported that patients with endometriosis have a significant increased risk of SS (SIR= 1.6; 95% CI = 1.3-2.0). However, when the analysis was restricted to patients with laparoscopy or laparotomy confirmed endometriosis, this association became non-significant (SIR = 1.4; 95% CI = 0.9–2.3). Matorras et al reported no significant difference in the prevalence of SS in women with endometriosis (n = 22) compared to controls (n = 501) (OR = 2.17) [14].

Using Cox proportional hazard analysis, we showed that patients with endometriosis have an approximately 57% higher risk of SS. The risk remained significant even when we restricted the analysis to more severe SS cases requiring DMARD. Overall, our results support the theory that patients with endometriosis have a modestly elevated risk of SS. Moreover, the same Cox proportional hazard analysis on comorbidities suggested that patients with hyperlipidemia and diabetes have higher risks of SS, which were consistent with previous studies showing that common comorbidities of SS include hyperlipidemia [16, 17] and type 2 diabetes [18].

Steroids and NSAIDs are sometimes given to relieve symptoms of parotid swelling and arthritis in SS [19]. Our subgroup analysis showed a higher risk of SS in endometriosis patients who did not use corticosteroids and lower risk of SS in endometriosis patients who use NSAIDs. This finding seems to suggest that steroid or analgesic medication may attenuate the risk of SS in endometriosis patients. It is possible that the use of steroid and analgesics suppresses the inflammatory cytokines that are central to both endometriosis and SS [20-22]. Since we could

not eliminate possible confounding factors such as severity of disease in the two populations, this observation should be validated in further studies.

Immunology evidence may support the link between endometriosis and SS. Defective B-, T-, and natural killer (NK) cell activity have been observed in patients with endometriosis [5, 23]. Similarly, patients with SS also have abnormal B- and T- cell activity leading to lymphocytic infiltration and glandular dysfunction [24-26]. Such alterations in humoral responses have also resulted in generation of autoantibodies in both groups of patients [27, 28]. Furthermore, increased pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) in patients with endometriosis [22, 29, 30] were also seen in the SS population [31]. These evidence suggest that endometriosis and SS may share a common pathogenic pathway that warrants further investigation.

Increasing number of association studies have shown that endometriosis is linked to autoimmune disorders. Patients with endometriosis have been found to have increased risk of SLE [10, 13], MS [10], rheumatoid arthritis [13], inflammatory bowel disease [11], and celiac disease [12].These findings further implicate the autoimmune etiology of endometriosis. From a therapeutic standpoint, whether or not endometriosis could be managed as an autoimmune disease by immunomodulation, disparate from conventional medical and surgical modalities is an intriguing question. GnRH agonists have already been shown to exert its beneficial effects through immunomodulation, particularly by increasing the NK cell count and T cell activity [32]; progesterone may help by suppressing cytokine release and action [33]. A similar approach to that for the treatment of ovarian failure resulting from polycystic ovary syndrome may be considered for endometriosis in light of the similarity between the disease and autoimmune disorders.

There are several limitations that should be considered while interpreting the data. First, our analysis was based on claims data from Taiwan's NHIRD, and identification of both exposure (endometriosis) and outcome (SS) was based solely on discharge codes endorsed by physicians. As a result, overestimation of both exposure and outcome could not be avoided. Furthermore, because data on clinical symptoms and laboratory data were not available, we were unable to compare the association between exposure and outcome based on disease severity. Second, we did not mandate surgery as part of the criteria for endometriosis, and this might have

resulted in inclusion of non-endometriosis cases. However, we utilized rigorous definition (3 outpatient or 1 inpatient discharge) to identify cases of endometriosis, and as such selection bias should be minimized. This approach also increases our external validity because milder cases of endometriosis were also included as part of the analysis. Thus, our results are also relevant to endometriosis patients who are managed conservatively without surgery. One major strength of our study is the larger sample size as compared to previous studies [10, 14].We also used propensity score matching to remove confounding factors for robust comparison between patients with endometriosis and those without. By utilizing Taiwan's NHIRD which includes data from 99% of the population, we were able to include patients for analysis regardless of economic, social or ethnic status. By requiring hospitalization as part of the definition of SS, we ensured that patients with only mild cases of SS were not included as part of the analysis. Thus, employing stringent criteria of SS makes the association between endometriosis and SS more conclusive.

In conclusion, our findings suggest that patients with endometriosis present a modestly elevated risk of SS. Steroid and NSAID use might reduce this risk association. Further studies could be conducted to ascertain the relationship between endometriosis and SS, as well as other types of autoimmune disorders.

6. Conflict of interest disclosure

The authors report no conflicts of interest.

7. References

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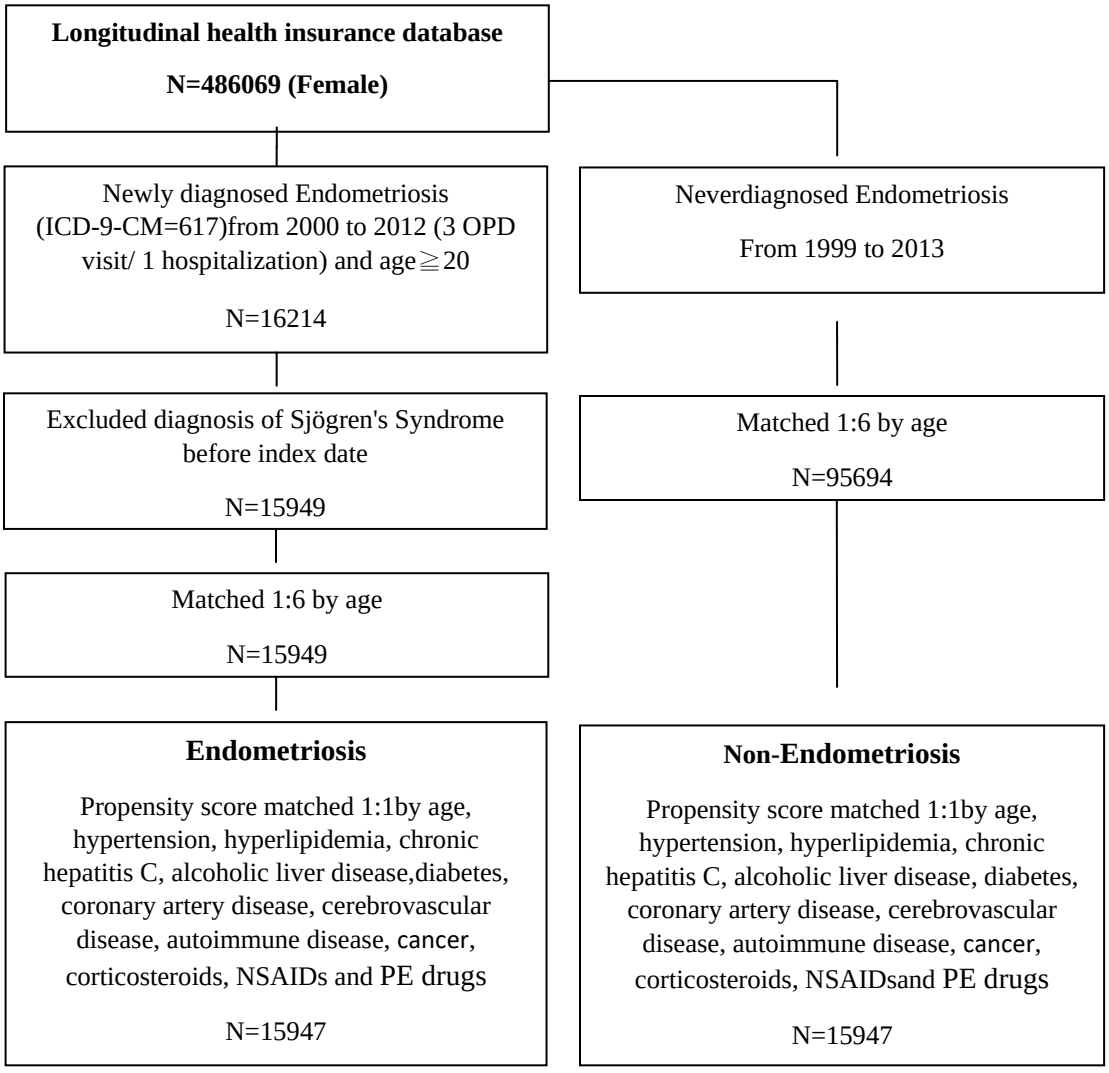
8. Appendix and Data Supplements

Figure 1. Flow-chart of patient selection



PE drugs: Progestin and estrogen.

Table 1. Variables and definition

Variable	Definition
Dependent variable	
Sjögren's Syndrome	Newly diagnosedSjögren's Syndrome(ICD-9-CM=710.2) (Outpatient visit≧3 or Admission≧1)
Sjögren's Syndrome (for sensitivity analysis)	Newly diagnosedSjögren's Syndrome(ICD-9-CM=710.2) (Outpatient visit≧3 or Admission≧1) and use of DMARDs ≧30 days DMARDs include: 1.Methotrexate 2.Sulfasalazine 3.Hydroxychloroquine
Survival_year	Ending point date - Starting point date
Starting point of the observation (index_date)	Date diagnosed endometriosis
Ending point of the observation (end_date)	1. Sjögren's Syndromedate 2. Dec. 31th, 2013 3.Dropped out the research
Independent variable	
Cohort duration	Jan. 1st, 2000 - Dec. 31th, 2013
Endometriosis	Newly diagnosed ICD-9-CM 617 Endometriosis from 2000 to 2012 (Outpatient visit≧3 or Admission≧1)
Gender	0 = Female ; 1= Male
Age	Age of index date
Hypertension	Complied with the definition of visiting the hospital within 1 year before (including) the observation starting point (Outpatient visit≧3 or Admission≧1) 0 = none ; 1 = yes ICD-9-CM=401-405
Hyperlipidemia	Complied with the definition of visiting the hospital within 1 year before (including) the observation starting point (Outpatient visit≧3 or Admission≧1)0 = none ; 1 = yes ICD-9-CM=272.0-272.4
Chronic liver disease	Complied with the definition of visiting the hospital within 1 year before (including) the observation starting point (Outpatient visit≧3 or Admission≧1) 0 = none ; 1 = yes

	ICD-9-CM=571
Chronic hepatitis C	Complied with the definition of visiting the hospital within 1 year before (including) the observation starting point (Outpatient visit≧3 or Admission≧1) 0 = none ; 1 = yes 070.44 Chronic hepatitis C with hepatic coma 070.54 Chronic hepatitis C without mention of hepatic coma V02.62 Hepatitis C carrier
Autoimmune hepatitis (0 case)	Complied with the definition of visiting the hospital within 1 year before (including) the observation starting point (Outpatient visit≧3 or Admission≧1) 0 = none ; 1 = yes 571.42 Autoimmune hepatitis
Alcoholic liver disease	Complied with the definition of visiting the hospital within 1 year before (including) the observation starting point (Outpatient visit≧3 or Admission≧1) 0 = none ; 1 = yes 571.0 Alcoholic fatty liver 571.1 Acute alcoholic hepatitis 571.2 Alcoholic cirrhosis of liver 571.3 Alcoholic liver damage, unspecified
Diabetes	Complied with the definition of visiting the hospital within 1 year before (including) the observation starting point (Outpatient visit≧3 or Admission≧1) 0 = none ; 1 = yes ICD-9-CM=250
Coronary artery disease	Complied with the definition of visiting the hospital within 1 year before (including) the observation starting point (Outpatient visit≧3 or Admission≧1) ICD-9-CM codes=410–414
Cerebrovascular disease	Complied with the definition while visiting the hospital within 1 year before (including) the observation starting point (Outpatient visit≧3 or Admission≧1) ICD-9-CM codes=430–438
Autoimmune disease	Complied with the definition of visiting the hospital within 1 year before (including) the observation starting point (Outpatient visit≧3 or Admission≧1) RA(ICD-9-CM codes=714.0) Ankylosing spondylitis (ICD-9-CM codes=720.0) SLE (ICD-9-CM codes=710.0)
Cancer	Complied with the definition of visiting the hospital within 1 year before (including) the observation starting point (Outpatient visit≧3 or Admission≧1) ICD-9-CM codes= 140–208

Corticosteroids	Usage during the research observation period ≧30 days
NSAIDs	Usage during the research observation period ≧30 days (Non-Steroidal Anti-Inflammatory Drug)
Progestin/Estrogen.	Usage oral dosage during the research observation period ≧30 days

Table 2. Demographic characteristics of Endometriosis and Non-Endometriosis

	Before propensity score matched					After propensity score matched				
	Endometriosis (N =15949)		Non-Endometriosis (N = 95694)			Endometriosis (N =15947)		Non-Endometriosis (N =15947)		
	N	%	n	%	p-value	n	%	n	%	p-value
Age					1					0.902
20-55	15644	98.1	93864	98.1		15643	98.1	15646	98.1	
≧55	305	1.9	1830	1.9		304	1.9	301	1.9	
Mean ± SD	38.8 ± 8.8		38.8 ± 8.8		1	38.8 ± 8.8		38.9 ± 8.8		0.309
Hypertension	825	5.2	3577	3.7	**<0.001**	823	5.2	814	5.1	0.819
Hyperlipidemia	337	2.1	1420	1.5	**<0.001**	335	2.1	325	2.0	0.694
Chronic hepatitis C	17	0.1	46	0.05	**0.004**	16	0.1	18	0.1	0.731
Alcoholic liver disease	5	0.03	20	0.02	0.391†	5	0.03	3	0.02	0.727†
Diabetes	363	2.3	1680	1.8	**<0.001**	362	2.3	342	2.1	0.446
Coronary artery disease	169	1.1	580	0.6	**<0.001**	167	1.0	170	1.1	0.870
Cerebrovascular disease	77	0.5	285	0.3	**<0.001**	77	0.5	73	0.5	0.743
Autoimmune disease	71	0.4	327	0.3	**0.042**	71	0.4	66	0.4	0.669
Cancer	363	2.3	897	0.9	**<0.001**	361	2.3	363	2.3	0.940
Corticosteroids	9387	58.9	41286	43.1	**<0.001**	9385	58.9	9382	58.8	0.973
NSAIDs	12328	77.3	55960	58.5	**<0.001**	12326	77.3	12332	77.3	0.936
PE drugs	3926	24.6	7038	7.4	**<0.001**	3924	24.6	3917	24.6	0.927

Bold font represents statistical significance ($p < 0.05$).

NSAIDs: Non-steroidal anti-inflammatory drugs.

PE drugs: Progestin and estrogen.

†Fisher's exact test

Figure 2. Cumulative probability of SS for patients with and without endometriosis

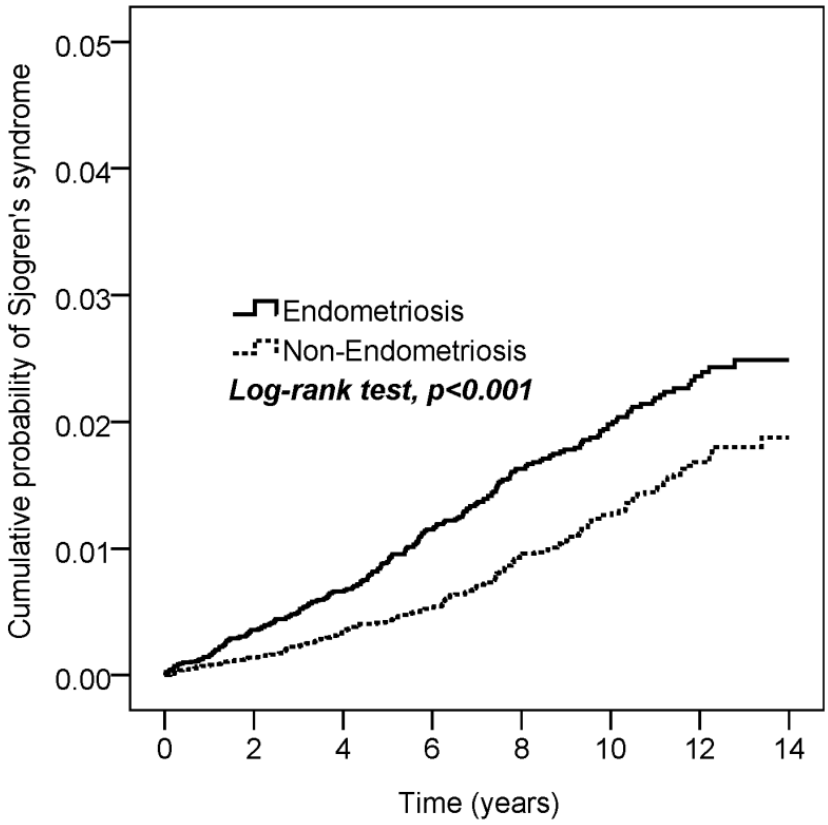


Table 3. Cox proportional hazard model

	No. of Sjogren's Syndrome	Observed Person-Years	Incidence Density (Per 1000 Person-Years)	Crude HR	95% C.I.	Adjusted HR†	95% C.I.
Endometriosis							
No	171	137140	1.2	1		1	
Yes	240	124237	1.9	**1.57**	**1.29-1.91**	**1.57**	**1.29-1.91**
Age							
20-55	397	256979	1.5	1		1	
≧55	14	4399	3.2	**2.09**	**1.23-3.57**	1.58	0.89-2.79
Hypertension	25	11877	2.1	1.39	0.92-2.08	0.87	0.55-1.37
Hyperlipidemia	18	4354	4.1	**2.79**	**1.74-4.48**	**1.84**	**1.08-3.14**
Alcoholic liver disease	1	56	18.0	**11.79**	**1.66-83.89**	6.58	0.87-49.50
Diabetes	24	4971	4.8	**3.27**	**2.16-4.93**	**2.50**	**1.57-3.99**
Coronary artery disease	8	2664	3.0	**1.94**	**0.96-3.90**	1.21	0.58-2.55
Cerebrovascular disease	3	1114	2.7	1.75	0.56-5.44	1.13	0.35-3.62
Autoimmune disease	14	910	15.4	**10.35**	**6.07-17.64**	**9.45**	**5.51-16.21**
Cancer	11	5009	2.2	1.44	0.79-2.62	1.30	0.71-2.38
Corticosteroids	277	173920	1.6	0.99	0.81-1.22	1.15	0.91-1.44
NSAIDs	306	221268	1.4	**0.48**	**0.39-0.61**	**0.41**	**0.32-0.53**
PE drugs	132	76421	1.7	1.11	0.90-1.37	1.15	0.93-1.43

Bold font represents statistical significance ($p < 0.05$).

†Adjusted for age, hypertension, hyperlipidemia, alcoholic liver disease, diabetes, coronary artery disease, cerebrovascular disease, autoimmune disease, cancer, corticosteroids, NSAIDs and PE drugs.
NSAIDs:Non-Steroidal Anti-Inflammatory Drugs.

PE drugs: Progestin and estrogen.

Table 4. Subgroup analysis of Cox proportional hazard model

	Endometriosis		Non-Endometriosis			
	N	No. of Sjogren's Syndrome	N	No. of Sjogren's Syndrome	HR	95% CI
Age						
20-55	15643	233	15646	164	**1.59**	**1.3-1.94**
≧55	304	7	301	7	1.16	0.41-3.30
						p for interaction = 0.550
Corticosteroids						
No	6562	88	6565	46	**2.16**	**1.51-3.08**
Yes	9385	152	9382	125	**1.33**	**1.05-1.68**
						p for interaction =0.009
NSAIDs						
No	3621	63	3615	42	**1.73**	**1.17-2.56**
Yes	12326	177	12332	129	**1.53**	**1.22-1.92**
						p for interaction =0.332
PE drugs						
No	12023	164	12030	115	**1.59**	**1.26-2.02**
Yes	3924	76	3917	56	**1.50**	**1.06-2.12**
						p for interaction =0.671

Bold font represents statistical significance ($p < 0.05$).

Hazard ration (HR) was estimated by univariate Cox proportional hazard model.

PE drugs: Progestin and estrogen.

Table 5. Sensitivity analysis

	No. of Sjogren's Syndrome	Observed Person-Years	Incidence Density (Per 1000 Person-Years)	Crude HR	95% C.I.	Adjusted HR†	95% C.I.
Endometriosis							
No	58	137617	0.4	1		1	
Yes	94	124968	0.8	**1.81**	**1.30-2.51**	**1.78**	**1.28-2.47**
Age							
20-55	148	258144	0.6	1		1	
≧55	4	4441	0.9	1.59	0.59-4.29	1.63	0.58-4.58
Hypertension	6	11973	0.5	0.87	0.39-1.98	0.52	0.21-1.28
Hyperlipidemia	6	4405	1.4	**2.49**	**1.10-5.63**	1.95	0.78-4.86
Alcoholic liver disease	1	56	18.0	**32.37**	**4.53-231.37**	**28.66**	**3.45-238.32**
Diabetes	6	5060	1.2	2.13	0.94-4.81	1.58	0.65-3.86
Coronary artery disease	2	2683	0.7	1.30	0.32-5.25	0.97	0.23-4.15
Autoimmune disease	11	926	11.9	**22.54**	**12.2-41.65**	**21.95**	**11.73-41.08**
Cancer	2	5042	0.4	0.69	0.17-2.80	0.64	0.16-2.60
Corticosteroids	109	174617	0.6	1.23	0.86-1.75	1.38	0.94-2.04
NSAIDs	118	222057	0.5	**0.59**	**0.40-0.87**	**0.48**	**0.32-0.73**
PE drugs	46	76824	0.6	1.02	0.72-1.44	0.98	0.68-1.40

The definition of Sjögren syndrome in this sensitivity test was defined by at least 3 outpatient visits or 1 inpatient plus DMARDs use ≧30 days after diagnosis of Sjögren syndrome.

Bold font represents statistical significance ($p < 0.05$).

†Adjusted for age, hypertension, hyperlipidemia, alcoholic liver disease, diabetes, coronary artery disease, autoimmune disease, cancer, corticosteroids, NSAIDs and PE drugs.

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs.

PE drugs: Progestin and estrogen.