Increased utilization of eye disorder-related ambulatory medical services prior to the diagnosis of Sjögren syndrome in female patients: a longitudinal population-based study in Taiwan

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Title: Increased utilization of eye disorder-related ambulatory medical services prior to the diagnosis of Sjögren syndrome in female patients: a longitudinal population-based study in Taiwan

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ABSTRACT

Objectives: To investigate the utilization of eye disorder-related ambulatory medical services prior to the diagnosis of primary Sjögren syndrome in female Taiwanese patients

Design: A nationwide, population-based case-control study

Setting: Taiwan's National Health Insurance Research Database.

Participants: A total of 347 patients with a diagnosis of primary Sjögren syndrome from 2005 to 2010 and 1735 controls frequency-matched on 10-year age interval and index year were identified from the Taiwan's National Health Insurance Research Database. Diagnoses of eye disorder (ICD-9-CM codes from 360 to 370) were retrospectively screened to 1997.

Main outcome measure: The utilization of eye disorder-related medical service use over different intervals prior to diagnosis of Sjögren syndrome between the cases and controls were compared using generalized linear models with negative binomial distribution.

Results: A significantly higher proportion of patients with Sjögren syndrome (7.5%) utilized eye disorder-related ambulatory medical services over an eight-year interval prior to the diagnosis of the disease compared with controls (4.8%). Utilization of services related to disorders of lacrimal

system, keratitis, disorders of eyelids, and disorders of conjunctiva were significantly greater in the cases compared with controls two years prior to the diagnosis of Sjögren syndrome.

Conclusions: An increase in the utilization of eye disorder-related ambulatory medical services was observed in patients with Sjögren syndrome several years prior to the diagnosis of the disease. General practitioners and ophthalmologists can play an important role by including Sjögren's syndrome in the diagnostic evaluation of their patients afflicted with relevant symptoms.

ARTICLE SUMMARY

Article focus

- Dry eyes is a common manifestation of Sjögren's syndrome.
- To examine the utilization of eye disorder-related ambulatory medical services prior to the diagnosis of primary Sjögren syndrome in females in a nationwide setting.

Key messages

- An increase in the utilization of eye disorder-related ambulatory medical services was observed in patients with Sjögren's syndrome several years predating the diagnosis of the disease.
- Delays in diagnosis of Sjögren's syndrome may be minimized through recognizing the early manifestations of the disease.

Strengths and limitations

- Major strengths of the study are the population-based design, based on a nationwide claim database, which could minimize recall and selection bias.
- Limitations include the possibility of misclassification because the diagnosis of eye disorders was based solely on ICD-9-CM codes and the identification of patients was based on the registry for catastrophic illness.

INTRODUCTION

Dry eye, or xerophthalmia, is a common ophthalmological condition. However, persistent dry eye not only is associated with symptoms of discomfort and visual disturbance, it can lead to damage to the ocular surface with serious consequences such as cornea inflammation.[1] Dry eye symptoms can be caused by increased tear evaporation, insufficient tear production, or tear film instability and these conditions are, in turn, can be attributed to a numbers of factors such aging, environment of low humidity, hormonal changes in women, pollution, video display terminal use, contact lens wear, and adverse effect of medications.[2-4] Aqueous tear deficient dry eye syndrome can be classified into two major subclasses, namely, Sjögren's syndrome (SS) dry eye and non-SS dry eye syndrome.[5] Sjögren's syndrome (SS), a progressive systemic autoimmune disorder characterized by dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia).[6] In SS, lymphocytic infiltration of the lacrimal gland can lead to a destruction of the acinar structures and impair glandular function.[7] Meibomian gland dysfunction had also been suggested to partly contribute to the increased evaporation of tears in patients with SS.[8] Since patients may seek medical care because of their visual disturbance and ocular discomfort caused by dry eye, medical professionals can play an important role in identifying that the visual and ocular symptoms may be secondary to the underlying

SS in some of the cases. In a prospective cohort of 327 patients with aqueous-deficient dry eye, 11.6% of the patients were found to have SS. The authors concluded that ophthalmologists should consider the likelihood of underlying SS in patients with clinically significant dry eye. [9] Although there is no known cure for SS,[10] early management of the sicca manifestations may help to reduce further ocular complications and their negative impact on the quality of life.[11,12]

A population-based study using the National Health Insurance Research Database in Taiwan revealed that patients with dry eye disease had significantly higher prevalences in 25 of the 34 comorbidities examined. Among the comorbidities, systemic lupus erythematosus (odds ratio, OR = 4.0, 95% confidence interval, 95%CI = 2.9-5.4) and rheumatoid arthritis (OR = 2.9, 95%CI = 2.6-3.1) showed the strongest associations in patients with dry eye disease compared with the controls.[13] However, SS was not included in the list of comorbidites in the study and other eye disorders were not investigated. Therefore, the aim of the present study was to evaluate the utilization of eye disorder-related ambulatory care services by female patients prior to the diagnosis of primary SS through the use of a longitudinal population-based health claims database in Taiwan.

MATERIALS AND METHODS

Study design and data source

This case-control study is a secondary data analysis using claims data from the National Health Insurance Research Database (NHIRD) maintained by the National Health Research Institute, Taiwan. The NHIRD contains comprehensive administrative and claim data from the National Health Insurance program, which is a mandatory single-payer social health insurance system implemented in 1995. As of the end of 2011, 23.20 million out of 23.22 million (99.9%) residents were enrolled in the system.[14,15]

The ambulatory care expenditures by visits files (CD) from the Longitudinal Health Insurance Database (LHID2000), the catastrophic illness files (HV), and the beneficiaries files (ID) were used in the present study to identify cases, controls, and their use of ambulatory medical care services. Details of the structure of the claims data sets are described on the NHIRD website.[16] Since the NHIRD files contain only de-identified secondary data, the need for informed consent from individual subjects was waived. The study protocol was reviewed and approved by the Institutional Review Board of the Buddhist Dalin Tzu Chi Hospital, Taiwan (No. A10104020).

Study samples

Cases were defined as female patients newly diagnosed with primary SS (International Classification of Diseases, Ninth Revision, clinical modification [ICD-9-CM] code 710.2) who had applied for a certificate of catastrophic illness between January 1, 2005 and December 31, 2010. In Taiwan, SS is one of the 30 major categories of conditions that are recognized as catastrophic illness or injury covered under the National Health Insurance scheme. Holders of the catastrophic illness certificates are exempted from co-payment of medical cost related to the catastrophic illness. The application of catastrophic illness certificates are formally reviewed by the Bureau of NHI according to the criteria of the American-European Consensus Group for SS published in 2002.[17] Patients with catastrophic illness certificates of other autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, other connective tissue diseases, were excluded. Since SS occurs less commonly in children and adolescents, patients younger than 20 years of age were excluded from the study. The date of application of the catastrophic illness certificate was used as the index date for cases.

Controls were randomly selected from the LHID2000 at a ratio of 1:5 on frequency of 10-year age interval and year of index date (index year). The date of a randomly selected ambulatory visit during the index year (2005 to 2010) was selected

as the index date for the controls. Both the cases and controls were linked to the LHID2000 to obtain data for their utilization of ambulatory care services from 1997 to 2010.

Eye disorders

To evaluate the utilization of eye disorders-related ambulatory medical care use prior to index date, both the cases and controls were retrospectively screened to 1997. Eye disorders were defined as any diagnosis of ICD-9-CM codes from 360 to 379. Additional subgroup analyses were conducted on disorder of conjunctive (ICD-9-CM: 372), inflammation of eyelids (ICD-9-CM: 373) or other disorders of eyelids (ICD-9-CM: 374), disorders of lacrimal system (ICD-9-CM: 375), cataract (ICD-9-CM: 366), and keratitis (ICD-9-CM: 370).

Statistical analysis

Summary statistics are expressed as frequency and percentage for categorical data and mean ± standard deviation (SD) or median with minimum and maximum for continuous variables, as appropriate. Pearson Chi-square tests or Fisher's exact test were used to compare categorical data between cases and controls. To account for the substantial positive skewness and excess zeros present in the count data, generalized

linear models with a negative binomial distribution and a log link function were used compared the differences in eye disorder-related medical services use between the cases and controls. Generalized estimating equations (GEEs) with negative binomial distribution and log link function was used to estimate the incidence rate ratios and to assess the linear trend of eye disorder-related medical services use across the eight annual intervals, taking into account the within-subject correlation over time. A two-sided p-value < 0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics software package, version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total 347 cases with primary SS and 1735 controls frequency-matched on 10-year age interval and index year of the cases were included in the analysis of the study. The mean age of both groups was 53.8 years (median = 54.0, range = 20-89). Table 1 shows the utilization of eye disorder-related ambulatory medical care services in the cases and controls. The proportion of eye disorder-related visits over all medical visits was significantly higher in the cases (7.5%) compared with controls (4.8%). In terms of the number of patients who had eye disorder-related visits, they were all significantly greater in the cases compared with controls, both over the 8-year

interval and for each of the eight annual intervals. Furthermore, the counts of eye disorder-related visits between the cases and controls for each of the eight time intervals were compared using generalized linear models. Except for the 7-8 year interval, the numbers of eye disorder-related visits were significantly higher in the cases over all the intervals.

Table 1

Utilization of eye disorder-related ambulatory medical services in female patients with primary Sjögren syndrome and matched controls

Variable	Frequency (%) or Mean ± SD (median, minimum - maximum)		p value
	Case (n= 347)	Control (n = 1735)	
Eye disorder-related visits/all visits over the 8-year period	5609 / 74583 (7.5)	18914 / 393105 (4.8)	<0.001
Number of patients with eye disorder-related visits prior to index date by time interval (year)			
0 – 1	254 (73.2)	754 (43.5)	<0.001

1 – 2	190 (54.8)		745 (43.0)		<0.001
2 – 3	193 (55.6)		744 (42.9)		<0.001
3 – 4	177 (51.0)		676 (39.0)		<0.001
4 – 5	171 (49.3)		680 (39.2)		<0.001
5 – 6	163 (47.0)		695 (40.1)		0.020
6 – 7	157 (45.3)		643 (37.1)		0.005
7 – 8	135 (38.9)		559 (32.2)		0.018
Overall 0 – 8	325 (93.7)		1414 (81.5)		<0.001
Number of eye disorder-related visits / patient prior to index date by time interval (year)					
0 – 1	3.23 ± 4.55	(2, 0 – 33)	1.71 ± 3.39	(0, 0 – 26)	<0.001
1 – 2	2.38 ± 4.01	(1, 0 – 29)	1.68 ± 3.64	(0, 0 – 33)	0.001
2 – 3	2.08 ± 3.72	(1, 0 – 25)	1.56 ± 3.36	(0, 0 – 37)	0.009
3 – 4	2.15 ± 4.05	(1, 0 – 32)	1.44 ± 3.34	(0, 0 – 42)	0.001
4 – 5	2.08 ± 4.32	(0, 0 – 32)	1.32 ± 2.88	(0, 0 – 33)	<0.001
5 – 6	1.73 ± 3.21	(0, 0 – 23)	1.30 ± 2.86	(0, 0 – 28)	0.013
6 – 7	1.70 ± 3.81	(0, 0 – 42)	1.14 ± 2.84	(0, 0 – 38)	0.004
7 – 8	1.11 ± 2.60	(0, 0 – 26)	0.92 ± 2.36	(0, 0 – 24)	0.177

Table 2 presents the incidence rate ratios of annual frequency of eye disorder-related visits using the 7-8 year interval as the reference category. The incidence rate ratios, for both cases and controls, were all significantly higher in intervals closer to the index date that the reference category. A significant linear trend of increasing incident rate ratios over time was also observed in both groups.

Table 2

Trends of the annual frequency of utilization of eye disorder-related ambulatory medical services over different time intervals prior to index date

Time interval between eye disorder-related visits and index date (year)	Case			Control		
	IRR	95% CI	P	IRR	95% CI	p value
7 – 8	1.00			1.00		
6 – 7	1.51	1.24-1.84	<0.001	1.23	1.10-1.37	<0.001
5 – 6	1.59	1.27-2.00	<0.001	1.39	1.24-1.57	<0.001
4 – 5	1.91	1.46-2.51	<0.001	1.43	1.26-1.61	<0.001
3 – 4	2.00	1.54-2.61	<0.001	1.52	1.34-1.73	<0.001
2 – 3	1.90	1.47-2.45	<0.001	1.66	1.47-1.89	<0.001
1 – 2	2.18	1.69-2.81	<0.001	1.80	1.57-2.05	<0.001
0 – 1	3.02	2.37-3.84	<0.001	1.92	1.68-2.19	<0.001

Trend test	<0.001	<0.001

IRR: incidence rate ratio

CI: confidence interval

Generalized estimating equations with negative binomial distribution, log link function, and Huber/White/sandwich correlation matrix estimator, adjusted for age.

Results from the subgroup analysis of eye disorders are summarized in Table 3. The utilization of ambulatory medical care service for disorders of lacrimal system and keratitis were significantly higher in the cases compared with controls (rate ratio = 4.59, 95% CI = 3.23-6.36 and rate ratio = 4.16, 95% CI = 2.61-6.61, respectively). The medical utilization for disorder of conjunctive and eyelids were also significantly higher in the cases but with slightly lower rate ratios. No significant differences were observed in the rate ratios between the two groups for cataract.

Table 3

Number of utilization of five subgroups of eye disorder-related ambulatory medical services in female patients with primary Sjögren syndrome and matched controls two years prior to index date

Diagnosis (ICD-9-CM code)	Total number of visits Mean ± SD (median, minimum - maximum)		Rate ratio (95% CI)	p value
	Case	Control		
Disorders of lacrimal system (375)	2.09 ± 4.63 (1, 0 – 42)	0.46 ± 2.19 (0, 0 – 26)	4.59 (3.32 – 6.36)	<0.001
Keratitis (370)	1.19 ± 5.23 (0, 0 – 38)	0.29 ± 1.86 (0, 0 – 43)	4.16 (2.61 – 6.61)	<0.001
Inflammation of eyelids (373) and other disorders of eyelids (374)	0.72 ± 3.01 (0, 0 – 38)	0.31 ± 1.48 (0, 0 – 32)	2.33 (1.42 – 3.82)	0.001
Disorder of conjunctive (372)	3.37 ± 5.06 (1, 0 – 31)	2.20 ± 4.68 (0, 0 – 53)	1.53 (1.27 – 1.85)	<0.001
Cataract (366)	1.09 ± 3.66 (0, 0 – 45)	0.91 ± 3.45 (0, 0 – 53)	1.20 (0.81 – 1.79)	0.363

ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

CI: confidence interval

Generalized linear models estimation with negative binomial distribution, log link function, and Huber/White/sandwich correlation matrix estimator.

DISCUSSION

To the best of our knowledge, this study is the first to use nationwide, population-based longitudinal administrative data to investigate the utilization of eye disorder-related ambulatory medical services prior to the diagnosis of primary SS. The main finding of this study was the significant increase in utilization of eye disorder-related ambulatory medical services in patients with primary SS compared with controls. This pattern was clearly reflected all the comparisons made in this study including the proportion of utilization of ambulatory medical services that were eye disorder-related over the 8-year interval prior to the index date, the proportions of patients who had used eye disorder-related ambulatory medical services in all of the annual intervals, and the numbers of annual eye disorder-related visits in all of the annual intervals except the 7-8 year interval prior to the index date.

Regarding the trends of annual frequency of eye disorder-related ambulatory services use over the 8-year intervals, both the cases and controls had higher rate ratios in the intervals closer to the index date. The increase in rate ratios in the controls could partly be explained by aging and low copayment of medical services in Taiwan. It often costs less for a patient to visit a physician and obtain a prescription than to purchase over-the-counter medicine. Nonetheless, the rate ratio of the cases at 0-1 year interval was 3.02 compared to the reference intervals whereas that of the

controls was only 1.92, suggesting a greater upward trend of eye disorder-related ambulatory services use in patients with primary SS over time.

Results from the subgroup analysis of ambulatory medical services use over a two-year period prior to the index date for common eye disorders revealed a significant increase in four of the five eye disorders. The increase in the number of visits in disorders of lacrimal system and keratitis in the cases compared with controls two years prior to diagnosis of primary SS was associated with a rate ratio of 4.59 and 4.16, respectively. The risks of disorders of the eyelids (rate ratio = 2.33) and conjunctiva (rate ratio = 1.53) were also significantly higher in the cases compared with controls. The increase in these disorders was as expected because of the strong association between lacrimal dysfunction and the physiopathology of primary SS. A prospective cohort study on patients with clinically significant aqueous-deficient dry eye, increased staining in the corneal inferior zone was found in patients with primary SS. The authors hypothesized that it could be the result of constant direct contact between the inferior cornea and the tear meniscus, which contains inflammatory mediators.[9] In addition, results from the Sjögren's Syndrome International Registry revealed that the most common lid and conjunctival diseases were the presence of a pingueculum (28%) followed by meibomitis (15%) and blepharitis (11%). [18] Conversely, the lack of significant difference in the number of visits related to cataract

between the cases and controls was also as expected since there is no evidence suggesting an association between cataract and primary SS.

Furthermore, previous studies have shown that other rheumatologic diseases are often associated with ophthalmic manifestations.[19] In a medical record review study of 220 patients with a primary diagnosis of dry eye syndrome from a tertiary care ophthalmology clinic, 25 (11.4%) had rheumatoid arthritis and 24 (10.9%) had primary SS. The authors concluded that primary SS appeared to be underdiagnosed in patients with dry eye syndrome and therefore, primary SS should be included in the diagnostic evaluation of these patients. [20] In a cross-sectional study on 61 Thai patients with rheumatoid arthritis, the prevalence of dry eyes measured by Ocular Surface Disease Index scores was significantly higher in patients with secondary SS.[21] In addition, patients with systemic lupus erythematosus, another common and complex systemic autoimmune disease, also have a high incidence of dry eye. A hospital based cross-sectional study on 91 Nepalese patients reported that dry eye were present in 39.5% of the patients. [22] Therefore, ophthalmologists can play an important role in the care of patients with various underlying rheumatoid disorders including SS.

Several potential limitations of the present study should be noted. First, the identification of patients with primary SS was based on the registry for catastrophic

illness and therefore, patients with minor manifestations of the disease and those who did not require exemption from copayment of medications might not have applied for a catastrophic illness certificate. However, this is not a common situation based on our clinical experience. Second, the diagnosis of eye disorders was based solely on ICD-9-CM codes. Nevertheless, the National Health Insurance Bureau of Taiwan routinely audits the validity of diagnosis. Third, the Classification criteria for SS proposed by the American-European Consensus Group in 2002 [17] was used for the diagnosis of primary SS in our study. The adoption of the 2012 American College of Rheumatology classification criteria [23] might affect the duration between the onset of eye disorders to the diagnosis of primary SS.

Despite these limitations, the findings of this study are compelling. An increase in the utilization of eye disorder-related ambulatory medical services was observed in patients with SS several years prior to the diagnosis of the disease. Thus, early diagnosis of SS may be possible through the recognition by ophthalmologists that the ocular manifestations are manifestations of SS. Not only further ocular complications can be reduced by proper management of eye symptoms. Patients can also be referred to specialist care for a more comprehensive approach to treatment of SS.

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COMPETING INTERESTS: None

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STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation
Title and abstract	1✓	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2✓	Explain the scientific background and rationale for the investigation being reported
Objectives	3✓	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4✓	Present key elements of study design early in the paper
Setting	5✓	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6✓	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls
		(*b*) For matched studies, give matching criteria and the number of controls per case
Variables	7✓	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*✓	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9✓	Describe any efforts to address potential sources of bias
Study size	10✓	Explain how the study size was arrived at
Quantitative variables	11✓	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12✓	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how matching of cases and controls was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*✓	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*✓	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*✓	Report numbers in each exposure category, or summary measures of exposure
Main results	16✓	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17✓	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18✓	Summarise key results with reference to study objectives
Limitations	19✓	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20✓	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21✓	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22✓	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Increased utilization of eye disorder-related ambulatory medical services prior to the diagnosis of Sjögren syndrome in female patients: a longitudinal population-based study in Taiwan

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Title: Increased utilization of eye disorder-related ambulatory medical services prior to the diagnosis of Sjögren syndrome in female patients: a longitudinal population-based study in Taiwan

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ABSTRACT

Objectives: To investigate the utilization of eye disorder-related ambulatory medical services prior to the diagnosis of primary Sjögren syndrome in female Taiwanese patients

Design: A nationwide, population-based case-control study

Setting: Taiwan's National Health Insurance Research Database.

Participants: A total of 347 patients with a diagnosis of primary Sjögren syndrome from 2005 to 2010 and 1735 controls frequency-matched on 10-year age interval and index year were identified from the Taiwan's National Health Insurance Research Database. Diagnoses of eye disorder (ICD-9-CM codes from 360 to 370) were retrospectively screened to 1997.

Main outcome measure: The utilization of eye disorder-related medical service use over different intervals prior to diagnosis of Sjögren syndrome between the cases and controls were compared using generalized linear models with negative binomial distribution.

Results: A significantly higher proportion of patients with Sjögren syndrome (7.5%) utilized eye disorder-related ambulatory medical services over an eight-year interval prior to the diagnosis of the disease compared with controls (4.8%). Utilization of services related to disorders of lacrimal

system, keratitis, disorders of eyelids, and disorders of conjunctiva were significantly greater in the cases compared with controls two years prior to the diagnosis of Sjögren syndrome.

Conclusions: An increase in the utilization of eye disorder-related ambulatory medical services was observed in patients with Sjögren syndrome several years prior to the diagnosis of the disease. General practitioners and ophthalmologists can play an important role by including Sjögren's syndrome in the diagnostic evaluation of their patients afflicted with relevant symptoms.

Article summary:

Article focus:

- Dry eyes is a common manifestation of Sjögren's syndrome.
- To examine the utilization of eye disorder-related ambulatory medical services prior to the diagnosis of primary Sjögren syndrome in females in a nationwide setting.

Key messages:

- An increase in the utilization of eye disorder-related ambulatory medical services was observed in patients with Sjögren's syndrome several years predating the diagnosis of the disease.
- Delays in diagnosis of Sjögren's syndrome may be minimized through recognizing the early manifestations of the disease.

Strengths and limitations:

- Major strengths of the study are the population-based design, based on a nationwide claim database, which could minimize recall and selection bias.
- Limitations include the possibility of misclassification because the diagnosis of eye disorders was based solely on ICD-9-CM codes and the identification of patients was based on the registry for catastrophic illness.

INTRODUCTION

Dry eye, or xerophthalmia, is a common ophthalmological condition. However, persistent dry eye not only is associated with symptoms of discomfort and visual disturbance, it can damage the ocular surface with serious consequences such as cornea inflammation.[1] A number of factors could contribute to dry eye such as aging, environment of low humidity, hormonal changes in women, pollution, video display terminal use, contact lens wear, adverse effect of medications, meibomium gland dysfunction, and Sjögren's syndrome (SS).[2-5]

SS is a progressive systemic autoimmune disorder characterized by secretory gland dysfunction including dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia).[6, 7] In patients with SS, lymphocytic infiltration of the lacrimal gland can lead to a destruction of the acinar structures and impair glandular function.[8] Meibomian gland dysfunction had also been suggested to partly contribute to the increased evaporation of tears in patients with SS.[9]

Since patients may seek medical care because of their visual disturbance and ocular discomfort caused by dry eye, medical professionals can play an important role in identifying that the visual and ocular symptoms may be secondary to the underlying SS in some of the cases. In a prospective cohort of 327 patients with aqueous-deficient dry eye, 11.6% of the patients were found to have SS. The authors

concluded that ophthalmologists should consider the likelihood of underlying SS in patients with clinically significant dry eye. [10] Although there is no known cure for SS,[11] early diagnosis of the disease should help to reduce the negative impact on the quality of life and the development of other associated complications such as intersitial lung diseases, neuropathy, renal tubular acidosis, autoimmune hepatitis, and primary bililary cirrhosis. [12,13]

A population-based study using the National Health Insurance Research Database in Taiwan revealed that patients with dry eye disease had significantly higher prevalences in 25 of the 34 comorbidities examined. Among the comorbidities, systemic lupus erythematosus (odds ratio, OR = 4.0, 95% confidence interval, 95%CI = 2.9-5.4) and rheumatoid arthritis (OR = 2.9, 95%CI = 2.6-3.1) showed the strongest associations in patients with dry eye disease compared with the controls.[14] However, SS was not included in the list of comorbidites in the study and other eye disorders were not investigated. Therefore, the aim of the present study was to evaluate the utilization of eye disorder-related ambulatory care services by female patients prior to the diagnosis of primary SS through the use of a longitudinal population-based health claims database in Taiwan.

MATERIALS AND METHODS

Study design and data source

This case-control study is a secondary data analysis using claims data from the National Health Insurance Research Database (NHIRD) maintained by the National Health Research Institute, Taiwan. The NHIRD contains comprehensive administrative and claim data from the National Health Insurance (NHI) program, which is a mandatory single-payer social health insurance system implemented in 1995. [15] As of the end of 2011, 23.20 million out of 23.22 million (99.9%) residents were enrolled in the system.[16,17]

The ambulatory care expenditures by visits files (CD) from the Longitudinal Health Insurance Database (LHID2000), the catastrophic illness files (HV), and the beneficiaries files (ID) were used in the present study to identify cases, controls, and their use of ambulatory medical care services. Details of the structure of the claims data sets are described on the NHIRD website.[18] Since the NHIRD files contain only de-identified secondary data, the need for informed consent from individual subjects was waived. The study protocol was reviewed and approved by the Institutional Review Board of the Buddhist Dalin Tzu Chi Hospital, Taiwan (No. A10104020).

Study samples

Cases were defined as female patients newly diagnosed with primary SS (International Classification of Diseases, Ninth Revision, clinical modification [ICD-9-CM] code 710.2) who had applied for a certificate of catastrophic illness between January 1, 2005 and December 31, 2010. In Taiwan, SS is one of the 30 major categories of conditions that are recognized as catastrophic illness or injury covered under the National Health Insurance scheme. These are conditions that require long term medical treatment and therefore, could put heavy economic burden on afflicted individuals. Holders of the catastrophic illness certificates are exempted from co-payment of medical cost related to the catastrophic illness. The application of catastrophic illness certificates are formally reviewed by the Bureau of NHI according to the criteria of the American-European Consensus Group for SS published in 2002.[19] Therefore, the presence of certificate of catastrophic illness of SS is a reliable indicator of its definitive diagnosis. Patients with catastrophic illness certificates of other autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, other connective tissue diseases, were excluded. Since SS occurs less commonly in children and adolescents, patients younger than 20 years of age were excluded from the study. The date of application of the catastrophic illness certificate was used as the index date for cases.

Controls were selected from the LHID2000 at a ratio of 1:5 frequency-matched on 10-year age interval and year of index date (index year). The index date for the controls was assigned by randomly selected an ambulatory visit within the matched index year (2005 to 2010). Both the cases and controls were linked to the LHID2000 to obtain data for their utilization of ambulatory care services from 1997 to 2010.

Eye disorders

To evaluate the utilization of eye disorders-related ambulatory medical care use prior to index date, both the cases and controls were retrospectively screened to 1997. Eye disorders were defined as any diagnosis of ICD-9-CM codes from 360 to 379. Additional subgroup analyses were conducted on disorder of conjunctive (ICD-9-CM: 372), inflammation of eyelids (ICD-9-CM: 373) or other disorders of eyelids (ICD-9-CM: 374), disorders of lacrimal system (ICD-9-CM: 375), cataract (ICD-9-CM: 366), and keratitis (ICD-9-CM: 370).

Statistical analysis

Summary statistics are expressed as frequency and percentage for categorical data and mean ± standard deviation (SD) or median with minimum and maximum for continuous variables, as appropriate. Pearson Chi-square tests or Fisher's exact test

were used to compare categorical data between cases and controls. Mann-Whitney U-test were used to compare continuous data between cases and controls.

Urbanization of levels of the residence of cases and controls were constructed according to a published categorization scheme, which is based on a combination of population density, percentage of residents with college level or higher education, percentage of residents 65 years and older, percentage of residents who were agriculture workers, and the number of physicians per 100000 people.[20] In addition, we also calculated payroll-related insured amount as a proxy measure to represent socioeconomic status. The variable was categories into tertiles with the lower and upper cut-points at 18300 and 24000 New Taiwan dollar, respectively.

To account for the substantial positive skewness and excess zeros present in the count data, generalized linear models with a negative binomial distribution and a log link function were used compared the differences in eye disorder-related medical services use between the cases and controls. The positively-skewed frequency distribution of medical services utilization was consistent with a previous study on ambulatory care utilization patterns in Taiwan.[21]

Generalized estimating equations (GEEs) with negative binomial distribution and log link function were used to estimate the incidence rate ratios and assess the linear trend of eye disorder-related medical services use across the eight annual intervals,

taking into account of within-subject correlation over time.[22] In addition, incidence rate ratios of frequency of utilization of eye disorder-related medical services were calculated for each time interval. A two-sided p-value < 0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics software package, version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total 347 cases with primary SS and 1735 controls frequency-matched on 10-year age interval and index year of the cases were included in the analysis of the study. The mean age of both groups was 53.8 years (median = 54.0, range = 20-89). Table 1 shows the utilization of eye disorder-related ambulatory medical care services in cases and controls. The proportion of eye disorder-related visits over all medical visits was significantly higher in the cases (7.5%) compared with the controls (4.8%). In terms of the number of patients who had eye disorder-related visits, they were all significantly greater in the cases compared with controls, both over the 8-year interval or for each of the eight annual intervals. Furthermore, the counts of eye disorder-related visits between cases and controls for each of the eight time intervals were compared using generalized linear models. Except for the 7-8 year interval, the numbers of eye disorder-related visits were significantly higher for the cases in all the

intervals. No significant differences were observed in levels of urbanization between the cases and controls (p = 208) but the distribution of tertiles of insured amount were significantly different (p = 0.016) with a higher proportion of cases in the upper tertile compared with controls.

Table 1

Utilization of eye disorder-related ambulatory medical services and urbanization levels, and income levels in female patients with primary Sjögren syndrome and frequency matched controls

Variable	Frequency (%) or Mean ± SD (median, minimum - maximum)		p value
	Case (n= 347)	Control (n = 1735)	
Eye disorder-related visits/all visits over the 8-year period	5609 / 74583 (7.5)	18914 / 393105 (4.8)	<0.001
Number of patients with eye disorder-related visits prior to index date by time interval (year)			

Overall 0 – 8	325 (93.7)		1414 (81.5)		<0.001
7 – 8	135 (38.9)		559 (32.2)		0.018
6 – 7	157 (45.3)		643 (37.1)		0.005
5 – 6	163 (47.0)		695 (40.1)		0.020
4 – 5	171 (49.3)		680 (39.2)		<0.001
3 – 4	177 (51.0)		676 (39.0)		<0.001
2 – 3	193 (55.6)		744 (42.9)		<0.001
1 – 2	190 (54.8)		745 (43.0)		<0.001
0 – 1	254 (73.2)		754 (43.5)		<0.001
Number of eye disorder-related visits / patient prior to index date by time interval (year)					
7 – 8	1.11 ± 2.60	(0, 0 – 26)	0.92 ± 2.36	(0, 0 – 24)	0.177
6 – 7	1.70 ± 3.81	(0, 0 – 42)	1.14 ± 2.84	(0, 0 – 38)	0.004
5 – 6	1.73 ± 3.21	(0, 0 – 23)	1.30 ± 2.86	(0, 0 – 28)	0.013
4 – 5	2.08 ± 4.32	(0, 0 – 32)	1.32 ± 2.88	(0, 0 – 33)	<0.001
3 – 4	2.15 ± 4.05	(1, 0 – 32)	1.44 ± 3.34	(0, 0 – 42)	0.001
2 – 3	2.08 ± 3.72	(1, 0 – 25)	1.56 ± 3.36	(0, 0 – 37)	0.009
1 – 2	2.38 ± 4.01	(1, 0 – 29)	1.68 ± 3.64	(0, 0 – 33)	0.001
0 – 1	3.23 ± 4.55	(2, 0 – 33)	1.71 ± 3.39	(0, 0 – 26)	<0.001
Urbanization level of					0.208

patient's residence*			
1 (most urbanized)	109 (32.4)	553 (32.8)	
2	117 (34.8)	527 (31.3)	
3	33 (9.8)	240 (14.2)	
4	42 (12.5)	215 (12.8)	
5 (least urbanized)	35 (10.4)	150 (8.9)	
Tertile of insured amount*			0.016
1 (lowest)	100 (29.1)	614 (35.8)	
2	112 (32.6)	568 (33.1)	
3 (highest)	132 (38.4)	535 (31.2)	

*11 cases and 50 controls had missing information on urbanization levels and 3 cases and 18 controls had missing information on insured amount.

Table 2 presents the incidence rate ratios of annual frequency of eye disorder-related visits using the 7-8 year interval as the reference category. The incidence rate ratios, for both cases and controls, were all significantly higher in intervals closer to the index date that the reference category. A significant linear trend of increasing incident rate ratios over time was also observed in both groups. In addition, the incidence rate ratios of annual frequency of eye disorder-related visits for each of the eight time interval between the cases and controls are shown in Table 2.

The incidence rate ratios of eye disorder-related visits were significant for all time intervals except for that in the 7-8 year interval. The group effect comparing cases with controls over the whole 8-year period was also significant (incidence rate ratio = 1.58, 95% CI = 1.36-1.84), $p < 0.001$).

Table 2

Trend of incidence rate ratio of the annual frequency of utilization of eye disorder-related ambulatory medical services over different time intervals prior to index date and incidence rate ratio comparing cases and controls for each time interval.

Time interval between eye disorder-related visits and index date (year)	Case			Control			Case vs control		
	IRR	95% CI	p value*	IRR	95% CI	p value*	IRR	95% CI	p value†
7 – 8	1.00	-	-	1.00	-	-	1.22	0.95-1.57	0.116
6 – 7	1.49	1.22-1.82	<0.001	1.22	1.10-1.36	<0.001	1.49	1.18-1.90	0.001
5 – 6	1.58	1.25-1.99	<0.001	1.36	1.20-1.53	<0.001	1.46	1.18-1.82	0.001
4 – 5	1.88	1.42-2.49	<0.001	1.39	1.23-1.57	<0.001	1.63	1.26-2.09	<0.001
3 – 4	1.96	1.51-2.56	<0.001	1.47	1.29-1.67	<0.001	1.65	1.31-2.08	<0.001
2 – 3	1.88	1.47-2.41	<0.001	1.62	1.43-1.84	<0.001	1.43	1.17-1.76	0.001

1 – 2	2.22	1.72-2.88	<0.001	1.76	1.54-2.02	<0.001	1.51	1.23-1.86	<0.001
0 – 1	3.05	2.39-3.89	<0.001	1.90	1.67-2.17	<0.001	1.92	1.62-2.28	<0.001
Trend test	-	-	<0.001	-	-	<0.001	-	-	

* p values for comparisons between IRR within each column using the 7-8 year IRR as the reference category

† p values for comparisons between IRR within each row using the IRR of the control as the reference category

Group effect (case versus control overall the whole 8-year interval), IRR = 1.58 (95% CI = 1.36-1.84), p < 0.001.

IRR: incidence rate ratio

CI: confidence interval

Generalized estimating equations with negative binomial distribution, log link function, and Huber/White/sandwich correlation matrix estimator, adjusted for age, urbanization levels, and tertiles of insured amount.

Results from the subgroup analysis of eye disorders-related ambulatory medical services utilization two years prior to index date are summarized in Table 3. The utilization of ambulatory medical care service for disorders of lacrimal system and keratitis were significantly higher in the cases compared to controls (rate ratio = 4.59, 95% CI = 3.23-6.36 and rate ratio = 4.16, 95% CI = 2.61-6.61, respectively). The medical utilization for disorder of conjunctive and eyelids were also significantly higher in the cases but with slightly lower rate ratios. No significant differences were observed in the rate ratios between the two groups for cataract.

Table 3

Number of utilization and incidence rate ratio of five subgroups of eye disorder-related ambulatory medical services in female patients with primary Sjögren syndrome and frequency matched controls two years prior to index date

Diagnosis (ICD-9-CM code)	Total number of visits Mean ± SD (median, minimum - maximum)		Incidence rate ratio (95% CI)	p value
	Case	Control		

Disorders of lacrimal system (375)	2.09 ± 4.63 (1, 0 – 42)	0.46 ± 2.19 (0, 0 – 26)	4.59 (3.32 – 6.36)	<0.001
Keratitis (370)	1.19 ± 5.23 (0, 0 – 38)	0.29 ± 1.86 (0, 0 – 43)	4.16 (2.61 – 6.61)	<0.001
Inflammation of eyelids (373) and other disorders of eyelids (374)	0.72 ± 3.01 (0, 0 – 38)	0.31 ± 1.48 (0, 0 – 32)	2.33 (1.42 – 3.82)	0.001
Disorder of conjunctive (372)	3.37 ± 5.06 (1, 0 – 31)	2.20 ± 4.68 (0, 0 – 53)	1.53 (1.27 – 1.85)	<0.001
Cataract (366)	1.09 ± 3.66 (0, 0 – 45)	0.91 ± 3.45 (0, 0 – 53)	1.20 (0.81 – 1.79)	0.363

ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

CI: confidence interval

Generalized linear models estimation with negative binomial distribution, log link function, and Huber/White/sandwich correlation matrix estimator.

DISCUSSION

To the best of our knowledge, this study is the first to use nationwide, population-based longitudinal administrative data to investigate the utilization of eye disorder-related ambulatory medical services prior to the diagnosis of primary SS. The main finding of this study was the significant increase in utilization of eye disorder-related ambulatory medical services in patients with primary SS compared with controls. This pattern was clearly reflected all the comparisons made in this study including the proportion of utilization of ambulatory medical services that were eye disorder-related over the 8-year interval prior to the index date, the proportions of patients who had used eye disorder-related ambulatory medical services in all of the annual intervals, and the numbers of annual eye disorder-related visits in all of the annual intervals except the 7-8 year interval prior to the index date.

Regarding the trend of annual frequency of eye disorder-related ambulatory services use over the 8-year intervals, both the cases and controls had higher rate ratios in the intervals closer to the index date. The increase in rate ratios in the controls could partly be explained by low copayment of medical services or aging in Taiwan. It often costs less to visit a doctor and obtain a prescription than to purchase over-the-counter medicine. Nonetheless, the rate ratio of the cases at 0-1 year interval was 3.05 compared to the reference intervals whereas that of the controls was only

1.90, suggesting a greater upward trend of eye disorder-related ambulatory services use in patients with primary SS over time. In fact, the incidence rate ratios of frequency of eye disorder-related ambulatory services use between the cases and controls in each of the time interval showed an increase in magnitude from 1.22 in the 7-8 year interval to 1.92 in the 0-1 year interval.

Results from the subgroup analysis of ambulatory medical services use over a two-year prior to the index date for common eye disorders revealed significant increase in four of the five eye disorders. The increase in the number of visits in disorders of lacrimal system and keratitis in the cases compared with controls two years prior to diagnosis of primary SS was associated with a rate ratio of 4.59 and 4.16, respectively. The risks of disorders of the eyelids (rate ratio = 2.33) and conjunctiva (rate ratio = 1.53) were also significantly increased in the cases compared with controls. These disorders were as expected because of the strong association between lacrimal dysfunction and the physiopathology of primary SS. A prospective cohort study on patients with clinically significant aqueous-deficient dry eye, increased staining in the corneal inferior zone was found in patients with primary SS. The authors hypothesized that it could be the result of constant direct contact between the inferior cornea and the tear meniscus, which contains inflammatory mediators.[10] In addition, results from the Sjögren's Syndrome International Registry revealed that

the most common lid and conjunctival diseases were the presence of a pingueculum (28%) followed by meibomitis (15%) and blepharitis (11%).[23] Conversely, the lack of significant difference in the number of visits related to cataract between the cases and controls was also as expected since there is no evidence suggesting an association between cataract and primary SS.

Furthermore, previous studies have shown that other rheumatologic diseases are often associated with ophthalmic manifestations.[24] In a medical record review study of 220 patients with a primary diagnosis of dry eye syndrome from a tertiary care ophthalmology clinic, 25 (11.4%) had rheumatoid arthritis and 24 (10.9%) had primary SS. The authors concluded that primary SS appeared to be underdiagnosed in patients with dry eye syndrome and therefore, primary SS should be included in the diagnostic evaluation of these patients.[25] In a cross-sectional study on 61 Thai patients with rheumatoid arthritis, the prevalence of dry eyes measured by Ocular Surface Disease Index scores were significantly higher in patients with secondary SS.[26] In addition, patients with systemic lupus erythematosus, another common and complex systemic autoimmune disease, also have high incidence of dry eye. A hospital based cross-sectional study on 91 Nepalese patients reported that dry eye were present in 39.5% of the patients.[27] Therefore, ophthalmologists can play an important role in the care of patients with various underlying rheumatoid disorders

including SS.

Several potential limitations of the present study should be noted. First, the identification of patients with primary SS was based on the registry for catastrophic illness and therefore, patients with minor manifestations of the disease and those who did not require exemption from copayment of medications might not have applied for a catastrophic illness certificate. However, this is not a common situation based on our clinical experience. Second, the diagnosis of eye disorders was based solely on ICD-9-CM codes. Nevertheless, the National Health Insurance Bureau of Taiwan routinely audits the validity of diagnosis. Third, the Classification criteria for SS proposed by the American-European Consensus Group in 2002 [19] was used for the diagnosis of primary SS in our study. The adoption of the 2012 American College of Rheumatology classification criteria [28] might affect the duration between the onset of eye disorders to the diagnosis of primary SS.

Despite these limitations, the findings of this study are compelling. An increase in the utilization of eye disorder-related ambulatory medical services was observed in patients with SS several years prior to the diagnosis of the disease. Thus, early diagnosis of SS may be possible in those afflicted with the disease through the recognition by ophthalmologists that the ocular manifestations are secondary to SS. Not only further ocular complications can be reduced by proper management of eye

symptoms. Patients can also be referred to specialist care for a more comprehensive approach to treatment of SS.

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Title: Increased utilization of eye disorder-related ambulatory medical services prior to the diagnosis of Sjögren syndrome in female patients: a longitudinal population-based study in Taiwan

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ABSTRACT

Objectives: To investigate the utilization of eye disorder-related ambulatory medical services prior to the diagnosis of primary Sjögren syndrome in female Taiwanese patients

Design: A nationwide, population-based case-control study

Setting: Taiwan's National Health Insurance Research Database.

Participants: A total of 347 patients with a diagnosis of primary Sjögren syndrome from 2005 to 2010 and 1735 controls frequency-matched on 10-year age interval and index year were identified from the Taiwan's National Health Insurance Research Database. Diagnoses of eye disorder (ICD-9-CM codes from 360 to 370) were retrospectively screened to 1997.

Main outcome measure: The utilization of eye disorder-related medical service use over different intervals prior to diagnosis of Sjögren syndrome between the cases and controls were compared using generalized linear models with negative binomial distribution.

Results: A significantly higher proportion of patients with Sjögren syndrome (7.5%) utilized eye disorder-related ambulatory medical services over an eight-year interval prior to the diagnosis of the disease compared with controls (4.8%). Utilization of services related to disorders of lacrimal

system, keratitis, disorders of eyelids, and disorders of conjunctiva were significantly greater in the cases compared with controls two years prior to the diagnosis of Sjögren syndrome.

Conclusions: An increase in the utilization of eye disorder-related ambulatory medical services was observed in patients with Sjögren syndrome several years prior to the diagnosis of the disease. General practitioners and ophthalmologists can play an important role by including Sjögren's syndrome in the diagnostic evaluation of their patients afflicted with relevant symptoms.

Article summary:

Article focus:

- Dry eyes is a common manifestation of Sjögren's syndrome.
- To examine the utilization of eye disorder-related ambulatory medical services prior to the diagnosis of primary Sjögren syndrome in females in a nationwide setting.

Key messages:

- An increase in the utilization of eye disorder-related ambulatory medical services was observed in patients with Sjögren's syndrome several years predating the diagnosis of the disease.
- Delays in diagnosis of Sjögren's syndrome may be minimized through recognizing the early manifestations of the disease.

Strengths and limitations:

- Major strengths of the study are the population-based design, based on a nationwide claim database, which could minimize recall and selection bias.
- Limitations include the possibility of misclassification because the diagnosis of eye disorders was based solely on ICD-9-CM codes and the identification of patients was based on the registry for catastrophic illness.

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INTRODUCTION

Dry eye, or xerophthalmia, is a common ophthalmological condition. However, persistent dry eye not only is associated with symptoms of discomfort and visual disturbance, it can ~~lead to~~ damage ~~to~~ the ocular surface with serious consequences such as cornea inflammation.[1] ~~Dry eye symptoms can be caused by increased tear evaporation, insufficient tear production, or tear film instability and these conditions are, in turn, can be attributed to a numbers~~A number of factors could contribute to dry eye such as aging, environment of low humidity, hormonal changes in women, pollution, video display terminal use, contact lens wear, ~~and~~ adverse effect of medications.~~[2-4] Aqueous tear deficient dry eye syndrome can be classified into two major subclasses, namely,~~ , meibomium gland dysfunction, and Sjögren's syndrome (SS~~) dry eye and non~~).[2-5]

SS ~~dry eye syndrome.[5] Sjögren's syndrome (SS),~~is a progressive systemic autoimmune disorder characterized by secretory gland dysfunction including dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia).[6, 7] In patients with SS, lymphocytic infiltration of the lacrimal gland can lead to a destruction of the acinar structures and impair glandular function.[~~7~~8] Meibomian gland dysfunction had also been suggested to partly contribute to the increased evaporation of tears in patients with SS.[~~8~~9]

Since patients may seek medical care because of their visual disturbance and ocular discomfort caused by dry eye, medical professionals can play an important role in identifying that the visual and ocular symptoms may be secondary to the underlying SS in some of the cases. In a prospective cohort of 327 patients with aqueous-deficient dry eye, 11.6% of the patients were found to have SS. The authors concluded that ophthalmologists should consider the likelihood of underlying SS in patients with clinically significant dry eye. [~~9~~10] Although there is no known cure for SS,[~~10~~11] early ~~management~~diagnosis of the ~~sicca manifestations may~~disease should help to reduce ~~further ocular complications and their~~ the negative impact on the quality of life~~.[11,~~ and the development of other associated complications such as intersitial lung diseases, neuropathy, renal tubular acidosis, autoimmune hepatitis, and primary bililary cirrhosis. [12~~]~~,13]

A population-based study using the National Health Insurance Research Database in Taiwan revealed that patients with dry eye disease had significantly higher prevalences in 25 of the 34 comorbidities examined. Among the comorbidities, systemic lupus erythematosus (odds ratio, OR = 4.0, 95% confidence interval, 95%CI = 2.9-5.4) and rheumatoid arthritis (OR = 2.9, 95%CI = 2.6-3.1) showed the strongest associations in patients with dry eye disease compared with the controls.[~~13~~14] However, SS was not included in the list of comorbidites in the study and other eye

disorders were not investigated. Therefore, the aim of the present study was to evaluate the utilization of eye disorder-related ambulatory care services by female patients prior to the diagnosis of primary SS through the use of a longitudinal population-based health claims database in Taiwan.

MATERIALS AND METHODS

Study design and data source

This case-control study is a secondary data analysis using claims data from the National Health Insurance Research Database (NHIRD) maintained by the National Health Research Institute, Taiwan. The NHIRD contains comprehensive administrative and claim data from the National Health Insurance (NHI) program, which is a mandatory single-payer social health insurance system implemented in 1995. [15] As of the end of 2011, 23.20 million out of 23.22 million (99.9%) residents were enrolled in the system.[~~14,15~~16,17]

The ambulatory care expenditures by visits files (CD) from the Longitudinal Health Insurance Database (LHID2000), the catastrophic illness files (HV), and the beneficiaries files (ID) were used in the present study to identify cases, controls, and their use of ambulatory medical care services. Details of the structure of the claims

data sets are described on the NHIRD website.[~~16~~18] Since the NHIRD files contain only de-identified secondary data, the need for informed consent from individual subjects was waived. The study protocol was reviewed and approved by the Institutional Review Board of the Buddhist Dalin Tzu Chi Hospital, Taiwan (No. A10104020).

Study samples

Cases were defined as female patients newly diagnosed with primary SS (International Classification of Diseases, Ninth Revision, clinical modification [ICD-9-CM] code 710.2) who had applied for a certificate of catastrophic illness between January 1, 2005 and December 31, 2010. In Taiwan, SS is one of the 30 major categories of conditions that are recognized as catastrophic illness or injury covered under the National Health Insurance scheme. These are conditions that require long term medical treatment and therefore, could put heavy economic burden on afflicted individuals. Holders of the catastrophic illness certificates are exempted from co-payment of medical cost related to the catastrophic illness. The application of catastrophic illness certificates are formally reviewed by the Bureau of NHI according to the criteria of the American-European Consensus Group for SS published in 2002.[~~17~~19] Therefore, the presence of certificate of catastrophic illness of SS is a

reliable indicator of its definitive diagnosis. Patients with catastrophic illness certificates of other autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, other connective tissue diseases, were excluded. Since SS occurs less commonly in children and adolescents, patients younger than 20 years of age were excluded from the study. The date of application of the catastrophic illness certificate was used as the index date for cases.

Controls were ~~randomly~~ selected from the LHID2000 at a ratio of 1:5 ~~on~~ frequency ~~of~~ matched on 10-year age interval and year of index date (index year). The index date ~~of a~~for the controls was assigned by randomly selected an ambulatory visit ~~during~~within the matched index year (2005 to 2010~~) was selected as the index date for the controls.~~). Both the cases and controls were linked to the LHID2000 to obtain data for their utilization of ambulatory care services from 1997 to 2010.

Eye disorders

To evaluate the utilization of eye disorders-related ambulatory medical care use prior to index date, both the cases and controls were retrospectively screened to 1997. Eye disorders were defined as any diagnosis of ICD-9-CM codes from 360 to 379. Additional subgroup analyses were conducted on disorder of conjunctive (ICD-9-CM: 372), inflammation of eyelids (ICD-9-CM: 373) or other disorders of eyelids

(ICD-9-CM: 374), disorders of lacrimal system (ICD-9-CM: 375), cataract (ICD-9-CM: 366), and keratitis (ICD-9-CM: 370).

Statistical analysis

Summary statistics are expressed as frequency and percentage for categorical data and mean ± standard deviation (SD) or median with minimum and maximum for continuous variables, as appropriate. Pearson Chi-square tests or Fisher's exact test were used to compare categorical data between cases and controls. Mann-Whitney U-test were used to compare continuous data between cases and controls.

Urbanization of levels of the residence of cases and controls were constructed according to a published categorization scheme, which is based on a combination of population density, percentage of residents with college level or higher education, percentage of residents 65 years and older, percentage of residents who were agriculture workers, and the number of physicians per 100000 people.[20] In addition, we also calculated payroll-related insured amount as a proxy measure to represent socioeconomic status. The variable was categories into tertiles with the lower and upper cut-points at 18300 and 24000 New Taiwan dollar, respectively.

To account for the substantial positive skewness and excess zeros present in the count data, generalized linear models with a negative binomial distribution and a log

link function were used compared the differences in eye disorder-related medical services use between the cases and controls. The positively-skewed frequency distribution of medical services utilization was consistent with a previous study on ambulatory care utilization patterns in Taiwan.[21]

Generalized estimating equations (GEEs) with negative binomial distribution and log link function ~~was~~were used to estimate the incidence rate ratios and ~~to~~ assess the linear trend of eye disorder-related medical services use across the eight annual intervals, taking into account ~~the~~of within-subject correlation over time.[22] In addition, incidence rate ratios of frequency of utilization of eye disorder-related medical services were calculated for each time interval. A two-sided p-value < 0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics software package, version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total 347 cases with primary SS and 1735 controls frequency-matched on 10-year age interval and index year of the cases were included in the analysis of the study. The mean age of both groups was 53.8 years (median = 54.0, range = 20-89). Table 1 shows the utilization of eye disorder-related ambulatory medical care services in ~~the~~ cases and controls. The proportion of eye disorder-related visits over all

medical visits was significantly higher in the cases (7.5%) compared with the controls (4.8%). In terms of the number of patients who had eye disorder-related visits, they were all significantly greater in the cases compared with controls, both over the 8-year interval ~~and~~or for each of the eight annual intervals. Furthermore, the counts of eye disorder-related visits between ~~the~~ cases and controls for each of the eight time intervals were compared using generalized linear models. Except for the 7-8 year interval, the numbers of eye disorder-related visits were significantly higher ~~in the cases over all the intervals.~~ for the cases in all the intervals. No significant differences were observed in levels of urbanization between the cases and controls (p = 208) but the distribution of tertiles of insured amount were significantly different (p = 0.016) with a higher proportion of cases in the upper tertile compared with controls.

Table 1

Utilization of eye disorder-related ambulatory medical services and urbanization levels, and income levels in female patients with primary Sjögren syndrome and frequency matched controls

Variable	Frequency (%) or Mean ± SD (median, minimum - maximum)	p value

	Case (n= 347)	Control (n = 1735)	
Eye disorder-related visits/all visits over the 8-year period	5609 / 74583 (7.5)	18914 / 393105 (4.8)	<0.001
Number of patients with eye disorder-related visits prior to index date by time interval (year)			
~~0 – 1~~	~~254 (73.2~~325 (93.7)	~~754 (43.5)~~	<0.001
~~1 – 2~~	135 (38.9)	~~745 (43.0)~~	0.018
~~2 – 3~~	157 (45.3)	~~744 (42.9)~~	0.005
~~3 – 4~~	163 (47.0)	~~676 (39.0)~~	0.020
~~4 – 5~~	171 (49.3)	~~680 (39.2)~~	<0.001
~~5 – 6~~	177 (51.0)	~~695 (40.1)~~	<0.001
~~6 – 7~~	193 (55.6)	~~643 (37.1)~~	<0.001
~~7 – 8~~	190 (54.8)	~~559 (32.2)~~	<0.001
Overall 0 – 8	~~193 (55.6)~~	1414 (81.5)	~~0.020~~
7 – 8	~~177 (51.0)~~	559 (32.2)	~~0.005~~
6 – 7	~~171 (49.3)~~	643 (37.1)	~~0.018~~
5 – 6	~~163 (47.0)~~	695 (40.1)	<0.001
4 – 5	~~157 (45.3)~~	680 (39.2)	
3 – 4	~~135 (38.9)~~	676 (39.0)	
2 – 3	~~325 (93.7)~~	744 (42.9)	
1 – 2	254 (73.2)	745 (43.0)	

0 – 1		754 (43.5)	
Number of eye disorder-related visits / patient prior to index date by time interval (year)			
7 – 8	1.11 ± 2.60 (0, 0 – 26)	0.92 ± 2.36 (0, 0 – 24)	0.177
6 – 7	1.70 ± 3.81 (0, 0 – 42)	1.14 ± 2.84 (0, 0 – 38)	0.004
5 – 6	1.73 ± 3.21 (0, 0 – 23)	1.30 ± 2.86 (0, 0 – 28)	0.013
4 – 5	2.08 ± 4.32 (0, 0 – 32)	1.32 ± 2.88 (0, 0 – 33)	<0.001
3 – 4	2.15 ± 4.05 (1, 0 – 32)	1.44 ± 3.34 (0, 0 – 42)	0.001
2 – 3	2.08 ± 3.72 (1, 0 – 25)	1.56 ± 3.36 (0, 0 – 37)	0.009
1 – 2	2.38 ± 4.01 (1, 0 – 29)	1.68 ± 3.64 (0, 0 – 33)	0.001
0 – 1	3.23 ± 4.55 (2, 0 – 33)	1.71 ± 3.39 (0, 0 – 26)	<0.001
~~1 – 2~~			~~0.013~~
~~2 – 3~~	~~2.38 ± 4.01 (1, 0 – 29)~~	~~1.68 ± 3.64 (0, 0 – 33)~~	~~0.004~~
~~3 – 4~~	~~2.08 ± 3.72 (1, 0 – 25)~~	~~1.56 ± 3.36 (0, 0 – 37)~~	~~0.177~~
~~4 – 5~~	~~2.15 ± 4.05 (1, 0 – 32)~~	~~1.44 ± 3.34 (0, 0 – 42)~~	
~~5 – 6~~	~~2.08 ± 4.32 (0, 0 – 32)~~	~~1.32 ± 2.88 (0, 0 – 33)~~	
~~6 – 7~~	~~1.73 ± 3.21 (0, 0 – 23)~~	~~1.30 ± 2.86 (0, 0 – 28)~~	
~~7 – 8~~	~~1.70 ± 3.81 (0, 0 – 42)~~	~~1.14 ± 2.84 (0, 0 – 38)~~	
	~~1.11 ± 2.60 (0, 0 – 26)~~	~~0.92 ± 2.36 (0, 0 – 24)~~	
Urbanization level of patient's residence*			0.208
1 (most urbanized)	109 (32.4)	553 (32.8)	

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2	117 (34.8)	527 (31.3)	
3	33 (9.8)	240 (14.2)	
4	42 (12.5)	215 (12.8)	
5 (least urbanized)	35 (10.4)	150 (8.9)	
Tertile of insured amount*			0.016
1 (lowest)	100 (29.1)	614 (35.8)	
2	112 (32.6)	568 (33.1)	
3 (highest)	132 (38.4)	535 (31.2)	

*11 cases and 50 controls had missing information on urbanization levels and 3 cases and 18 controls had missing information on insured amount.

Table 2 presents the incidence rate ratios of annual frequency of eye disorder-related visits using the 7-8 year interval as the reference category. The incidence rate ratios, for both cases and controls, were all significantly higher in intervals closer to the index date that the reference category. A significant linear trend of increasing incident rate ratios over time was also observed in both groups. In addition, the incidence rate ratios of annual frequency of eye disorder-related visits for each of the eight time interval between the cases and controls are shown in Table 2. The incidence rate ratios of eye disorder-related visits were significant for all time intervals except for that in the 7-8 year interval. The group effect comparing cases

with controls over the whole 8-year period was also significant (incidence rate ratio = 1.58, 95% CI = 1.36-1.84), $p < 0.001$).

Table 2

~~Trends~~Trend of incidence rate ratio of the annual frequency of utilization of eye disorder-related ambulatory medical services over different time intervals prior to index date and incidence rate ratio comparing cases and controls for each time interval.

Time interval between eye disorder-related visits and index date (year)	Case			Control			Case vs control		
	IRR	95% CI	p value*	IRR	95% CI	p value*	IRR	95% CI	p value†
7 – 8	1.00	-	-	1.00	-	-	1.22	0.95-1.57	0.116
6 – 7	1.~~51~~49	1.~~24~~22-1.~~8~~4~~82~~	<0.001	1.~~23~~22	1.10-1.~~37~~36	<0.001	1.49	1.18-1.90	0.001
5 – 6	1.~~59~~58	1.~~27 2.00~~2-1.99	<0.001	1.~~39~~36	1.~~24~~20-1.~~57~~53	<0.001	1.46	1.18-1.82	0.001
4 – 5	1.~~91~~88	1.~~46~~42-2.~~5~~	<0.001	1.~~43~~39	1.23-1.57	<0.001	1.63	1.26-~~1.61~~2.	<0.001

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		149						09	
3 – 4	2.001.96	1.5451-2.6	<0.001	1.5247	1.3429-1.	<0.001	1.65	1.31-2.08	<0.001
		156			7367				
2 – 3	1.9088	1.47-2.454	<0.001	1.6662	1.4743-1.	<0.001	1.43	1.17-1.76	0.001
		1			8984				
1 – 2	2.1822	1.6972-2.8	<0.001	1.8076	1.5754-2.	<0.001	1.51	1.23-1.86	<0.001
		188			0502				
0 – 1	3.0205	2.3739-3.8	<0.001	1.90	1.67-2.17	<0.001	1.92	1.6862-2.19	<0.001
		489						28	
Trend test	-	<0.001	<0.001	<0.001	-	<0.001	-	-	

* p values for comparisons between IRR within each column using the 7-8 year IRR as the reference category

† p values for comparisons between IRR within each row using the IRR of the control as the reference category

Group effect (case versus control overall the whole 8-year interval), IRR = 1.58 (95% CI = 1.36-1.84), p < 0.001.

IRR: incidence rate ratio

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CI: confidence interval

Generalized estimating equations with negative binomial distribution, log link function, and Huber/White/sandwich correlation matrix estimator, adjusted for age, urbanization levels, and tertiles of insured amount.

Results from the subgroup analysis of eye disorders-related ambulatory medical services utilization two years prior to index date are summarized in Table 3. The utilization of ambulatory medical care service for disorders of lacrimal system and keratitis were significantly higher in the cases compared ~~with~~to controls (rate ratio = 4.59, 95% CI = 3.23-6.36 and rate ratio = 4.16, 95% CI = 2.61-6.61, respectively). The medical utilization for disorder of conjunctive and eyelids were also significantly higher in the cases but with slightly lower rate ratios. No significant differences were observed in the rate ratios between the two groups for cataract.

Table 3

Number of utilization and incidence rate ratio of five subgroups of eye disorder-related ambulatory medical services in female patients with primary Sjögren syndrome and frequency matched controls two years prior to index date

Diagnosis (ICD-9-CM code)	Total number of visits Mean ± SD (median, minimum - maximum)		Incidence rate ratio (95% CI)	p value
	Case	Control		

Disorders of lacrimal system (375)	2.09 ± 4.63 (1, 0 – 42)	0.46 ± 2.19 (0, 0 – 26)	4.59 (3.32 – 6.36)	<0.001
Keratitis (370)	1.19 ± 5.23 (0, 0 – 38)	0.29 ± 1.86 (0, 0 – 43)	4.16 (2.61 – 6.61)	<0.001
Inflammation of eyelids (373) and other disorders of eyelids (374)	0.72 ± 3.01 (0, 0 – 38)	0.31 ± 1.48 (0, 0 – 32)	2.33 (1.42 – 3.82)	0.001
Disorder of conjunctive (372)	3.37 ± 5.06 (1, 0 – 31)	2.20 ± 4.68 (0, 0 – 53)	1.53 (1.27 – 1.85)	<0.001
Cataract (366)	1.09 ± 3.66 (0, 0 – 45)	0.91 ± 3.45 (0, 0 – 53)	1.20 (0.81 – 1.79)	0.363

ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

CI: confidence interval

Generalized linear models estimation with negative binomial distribution, log link function, and Huber/White/sandwich correlation matrix estimator.

DISCUSSION

To the best of our knowledge, this study is the first to use nationwide, population-based longitudinal administrative data to investigate the utilization of eye disorder-related ambulatory medical services prior to the diagnosis of primary SS. The main finding of this study was the significant increase in utilization of eye disorder-related ambulatory medical services in patients with primary SS compared with controls. This pattern was clearly reflected all the comparisons made in this study including the proportion of utilization of ambulatory medical services that were eye disorder-related over the 8-year interval prior to the index date, the proportions of patients who had used eye disorder-related ambulatory medical services in all of the annual intervals, and the numbers of annual eye disorder-related visits in all of the annual intervals except the 7-8 year interval prior to the index date.

Regarding the trend~~s~~ of annual frequency of eye disorder-related ambulatory services use over the 8-year intervals, both the cases and controls had higher rate ratios in the intervals closer to the index date. The increase in rate ratios in the controls could partly be explained by ~~aging and~~ low copayment of medical services or aging in Taiwan. It often costs less ~~for a patient~~ to visit a ~~physician~~doctor and obtain a prescription than to purchase over-the-counter medicine. Nonetheless, the rate ratio of the cases at 0-1 year interval was 3.~~02~~05 compared to the reference intervals whereas

that of the controls was only 1.~~92~~90, suggesting a greater upward trend of eye disorder-related ambulatory services use in patients with primary SS over time. In fact, the incidence rate ratios of frequency of eye disorder-related ambulatory services use between the cases and controls in each of the time interval showed an increase in magnitude from 1.22 in the 7-8 year interval to 1.92 in the 0-1 year interval.

Results from the subgroup analysis of ambulatory medical services use over a two-year ~~period~~ prior to the index date for common eye disorders revealed ~~a~~ significant increase in four of the five eye disorders. The increase in the number of visits in disorders of lacrimal system and keratitis in the cases compared with controls two years prior to diagnosis of primary SS was associated with a rate ratio of 4.59 and 4.16, respectively. The risks of disorders of the eyelids (rate ratio = 2.33) and conjunctiva (rate ratio = 1.53) were also significantly ~~higher~~increased in the cases compared with controls. ~~The increase in~~ These disorders ~~was~~were as expected because of the strong association between lacrimal dysfunction and the physiopathology of primary SS. A prospective cohort study on patients with clinically significant aqueous-deficient dry eye, increased staining in the corneal inferior zone was found in patients with primary SS. The authors hypothesized that it could be the result of constant direct contact between the inferior cornea and the tear meniscus, which contains inflammatory mediators.[~~9~~10] In addition, results from the Sjögren's

Syndrome International Registry revealed that the most common lid and conjunctival diseases were the presence of a pingueculum (28%) followed by meibomitis (15%) and blepharitis (11%).[~~18~~23] Conversely, the lack of significant difference in the number of visits related to cataract between the cases and controls was also as expected since there is no evidence suggesting an association between cataract and primary SS.

Furthermore, previous studies have shown that other rheumatologic diseases are often associated with ophthalmic manifestations.[~~19~~24] In a medical record review study of 220 patients with a primary diagnosis of dry eye syndrome from a tertiary care ophthalmology clinic, 25 (11.4%) had rheumatoid arthritis and 24 (10.9%) had primary SS. The authors concluded that primary SS appeared to be underdiagnosed in patients with dry eye syndrome and therefore, primary SS should be included in the diagnostic evaluation of these patients.[2~~0~~5] In a cross-sectional study on 61 Thai patients with rheumatoid arthritis, the prevalence of dry eyes measured by Ocular Surface Disease Index scores ~~was~~were significantly higher in patients with secondary SS.[~~21~~26] In addition, patients with systemic lupus erythematosus, another common and complex systemic autoimmune disease, also have ~~a~~ high incidence of dry eye. A hospital based cross-sectional study on 91 Nepalese patients reported that dry eye were present in 39.5% of the patients.[2~~2~~7] Therefore, ophthalmologists can play an

important role in the care of patients with various underlying rheumatoid disorders including SS.

Several potential limitations of the present study should be noted. First, the identification of patients with primary SS was based on the registry for catastrophic illness and therefore, patients with minor manifestations of the disease and those who did not require exemption from copayment of medications might not have applied for a catastrophic illness certificate. However, this is not a common situation based on our clinical experience. Second, the diagnosis of eye disorders was based solely on ICD-9-CM codes. Nevertheless, the National Health Insurance Bureau of Taiwan routinely audits the validity of diagnosis. Third, the Classification criteria for SS proposed by the American-European Consensus Group in 2002 [~~17~~19] was used for the diagnosis of primary SS in our study. The adoption of the 2012 American College of Rheumatology classification criteria [~~23~~28] might affect the duration between the onset of eye disorders to the diagnosis of primary SS.

Despite these limitations, the findings of this study are compelling. An increase in the utilization of eye disorder-related ambulatory medical services was observed in patients with SS several years prior to the diagnosis of the disease. Thus, early diagnosis of SS may be possible in those afflicted with the disease through the recognition by ophthalmologists that the ocular manifestations are ~~manifestations~~

~~of~~secondary to SS. Not only further ocular complications can be reduced by proper management of eye symptoms. Patients can also be referred to specialist care for a more comprehensive approach to treatment of SS.

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STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation
Title and abstract	1✓	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2✓	Explain the scientific background and rationale for the investigation being reported
Objectives	3✓	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4✓	Present key elements of study design early in the paper
Setting	5✓	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6✓	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls
		(*b*) For matched studies, give matching criteria and the number of controls per case
Variables	7✓	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*✓	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9✓	Describe any efforts to address potential sources of bias
Study size	10✓	Explain how the study size was arrived at
Quantitative variables	11✓	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12✓	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how matching of cases and controls was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*✓	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*✓	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*✓	Report numbers in each exposure category, or summary measures of exposure
Main results	16✓	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17✓	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18✓	Summarise key results with reference to study objectives
Limitations	19✓	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20✓	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21✓	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22✓	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Increased utilization of eye disorder-related ambulatory medical services prior to the diagnosis of Sjögren syndrome in female patients: a longitudinal population-based study in Taiwan

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Title: Increased utilization of eye disorder-related ambulatory medical services prior to the diagnosis of Sjögren syndrome in female patients: a longitudinal population-based study in Taiwan

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Word count: Abstract: 288; main text: 2738

ABSTRACT

Objectives: To investigate the utilization of eye disorder-related ambulatory medical services prior to the diagnosis of primary Sjögren syndrome in female Taiwanese patients

Design: A nationwide, population-based case-control study

Setting: Taiwan's National Health Insurance Research Database.

Participants: A total of 347 patients with a diagnosis of primary Sjögren syndrome from 2005 to 2010 and 1735 controls frequency-matched on 10-year age interval and index year were identified from the Taiwan's National Health Insurance Research Database. Diagnoses of eye disorder (ICD-9-CM codes from 360 to 370) were retrospectively screened to 1997.

Main outcome measure: The utilization of eye disorder-related medical service use over different intervals prior to diagnosis of Sjögren syndrome between the cases and controls were compared using generalized estimating equations with negative binomial distribution and log link function.

Results: A significantly higher proportion of patients with Sjögren syndrome (7.5%) utilized eye disorder-related ambulatory medical services over an eight-year interval prior to the diagnosis of the disease compared with controls (4.8%). The annual frequency of utilization of eye

disorder-related ambulatory medical services increased significantly faster when closer to the index date in patients with Sjögren syndrome compared with controls (interaction effect, p = 0.010). Subgroup analyses indicated that the changes over time in the utilization of services related to disorders of lacrimal system (interaction effect, p = 0.019) and conjunctiva (interaction effect, p = 0.066) were significantly greater in the patients with Sjögren syndrome compared with controls.

Conclusions: An increase in the utilization of eye disorder-related ambulatory medical services was observed in patients with Sjögren syndrome several years prior to the diagnosis of the disease. General practitioners and ophthalmologists can play an important role by including Sjögren's syndrome in the diagnostic evaluation of their patients afflicted with relevant symptoms.

Article summary:

Article focus:

- Dry eyes is a common manifestation of Sjögren's syndrome.

- To examine the utilization of eye disorder-related ambulatory medical services prior to the diagnosis of primary Sjögren syndrome in females in a nationwide setting.

Key messages:

- An increase in the utilization of eye disorder-related ambulatory medical services was observed in patients with Sjögren's syndrome several years predating the diagnosis of the disease.
- Delays in diagnosis of Sjögren's syndrome may be minimized through recognizing the early manifestations of the disease.

Strengths and limitations:

- Major strengths of the study are the population-based design, based on a nationwide claim database, which could minimize recall and selection bias.
- Limitations include the possibility of misclassification because the diagnosis of eye disorders was based solely on ICD-9-CM codes and the identification of patients was based on the registry for catastrophic illness.

INTRODUCTION

Dry eye, or xerophthalmia, is a common ophthalmological condition. However, persistent dry eye not only is associated with symptoms of discomfort and visual disturbance, it can damage the ocular surface with serious consequences such as cornea inflammation.[1] A number of factors could contribute to dry eye such as aging, environment of low humidity, hormonal changes in women, pollution, video display terminal use, contact lens wear, adverse effect of medications, meibomium gland dysfunction, and Sjögren's syndrome (SS).[2-5]

SS is a progressive systemic autoimmune disorder characterized by secretory gland dysfunction including dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia).[6, 7] In patients with SS, lymphocytic infiltration of the lacrimal gland can lead to a destruction of the acinar structures and impair glandular function.[8] Meibomian gland dysfunction had also been suggested to partly contribute to the increased evaporation of tears in patients with SS.[9]

Since patients may seek medical care because of their visual disturbance and ocular discomfort caused by dry eye, medical professionals can play an important role in identifying that the visual and ocular symptoms may be secondary to the underlying SS in some of the cases. In a prospective cohort of 327 patients with aqueous-deficient dry eye, 11.6% of the patients were found to have SS. The authors

concluded that ophthalmologists should consider the likelihood of underlying SS in patients with clinically significant dry eye. [10] Although there is no known cure for SS,[11] early diagnosis of the disease should help to reduce the negative impact on the quality of life and the development of other associated complications such as intersitial lung diseases, neuropathy, renal tubular acidosis, autoimmune hepatitis, and primary bililary cirrhosis. [12,13]

A population-based study using the National Health Insurance Research Database in Taiwan revealed that patients with dry eye disease had significantly higher prevalences in 25 of the 34 comorbidities examined. Among the comorbidities, systemic lupus erythematosus (odds ratio, OR = 4.0, 95% confidence interval, 95%CI = 2.9-5.4) and rheumatoid arthritis (OR = 2.9, 95%CI = 2.6-3.1) showed the strongest associations in patients with dry eye disease compared with the controls.[14] However, SS was not included in the list of comorbidites in the study and other eye disorders were not investigated. Therefore, the aim of the present study was to evaluate the utilization of eye disorder-related ambulatory care services by female patients prior to the diagnosis of primary SS through the use of a longitudinal population-based health claims database in Taiwan.

MATERIALS AND METHODS

Study design and data source

This case-control study is a secondary data analysis using claims data from the National Health Insurance Research Database (NHIRD) maintained by the National Health Research Institute, Taiwan. The NHIRD contains comprehensive administrative and claim data from the National Health Insurance (NHI) program, which is a mandatory single-payer social health insurance system implemented in 1995. [15] As of the end of 2011, 23.20 million out of 23.22 million (99.9%) residents were enrolled in the system.[16,17]

The ambulatory care expenditures by visits files (CD) from the Longitudinal Health Insurance Database (LHID2000), the catastrophic illness files (HV), and the beneficiaries files (ID) were used in the present study to identify cases, controls, and their use of ambulatory medical care services. Details of the structure of the claims data sets are described on the NHIRD website.[18] Since the NHIRD files contain only de-identified secondary data, the need for informed consent from individual subjects was waived. The study protocol was reviewed and approved by the Institutional Review Board of the Buddhist Dalin Tzu Chi Hospital, Taiwan (No. A10104020).

Study samples

Cases were defined as female patients newly diagnosed with primary SS (International Classification of Diseases, Ninth Revision, clinical modification [ICD-9-CM] code 710.2) who had applied for a certificate of catastrophic illness between January 1, 2005 and December 31, 2010. In Taiwan, SS is one of the 30 major categories of conditions that are recognized as catastrophic illness or injury covered under the National Health Insurance scheme. These are conditions that require long term medical treatment and therefore, could put heavy economic burden on afflicted individuals. Holders of the catastrophic illness certificates are exempted from co-payment of medical cost related to the catastrophic illness. The application of catastrophic illness certificates are formally reviewed by the Bureau of NHI according to the criteria of the American-European Consensus Group for SS published in 2002.[19] Therefore, the presence of a certificate of catastrophic illness of SS is a reliable indicator of its definitive diagnosis. Patients with catastrophic illness certificates of other autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, other connective tissue diseases, were excluded. Since SS occurs less commonly in children and adolescents, patients younger than 20 years of age were excluded from the study. The date of application of the catastrophic illness certificate was used as the index date for cases.

Controls were selected from the LHID2000 at a ratio of 1:5 frequency-matched on 10-year age interval and year of index date (index year). The index date for the controls was assigned by randomly selected an ambulatory visit within the matched index year (2005 to 2010). Both the cases and controls were linked to the LHID2000 to obtain data for their utilization of ambulatory care services from 1997 to 2010.

Eye disorders

To evaluate the utilization of eye disorders-related ambulatory medical care use prior to index date, both the cases and controls were retrospectively screened to 1997. Eye disorders were defined as any diagnosis of ICD-9-CM codes from 360 to 379, including their subcodes. Additional subgroup analyses were conducted on disorder of conjunctive (ICD-9-CM: 372.x), inflammation of eyelids (ICD-9-CM: 373.x) or other disorders of eyelids (ICD-9-CM: 374.x), disorders of lacrimal system (ICD-9-CM: 375.x), cataract (ICD-9-CM: 366), and keratitis (ICD-9-CM: 370.x).

Statistical analysis

Summary statistics are expressed as frequency and percentage for categorical data and mean ± standard deviation (SD) or median with minimum and maximum for continuous variables, as appropriate. Pearson Chi-square tests or Fisher's exact test

were used to compare categorical data between cases and controls. Mann-Whitney U-test were used to compare continuous data between cases and controls.

Urbanization of levels of the residence of cases and controls were constructed according to a published categorization scheme, which is based on a combination of population density, percentage of residents with college level or higher education, percentage of residents 65 years and older, percentage of residents who were agriculture workers, and the number of physicians per 100000 people.[20] In addition, we also calculated payroll-related insured amount as a proxy measure to represent socioeconomic status. The variable was categories into tertiles with the lower and upper cut-points at 18300 and 24000 New Taiwan dollar, respectively.

To account for the substantial positive skewness and excess zeros present in the count data, generalized linear models with a negative binomial distribution and a log link function were used compared the differences in eye disorder-related medical services use between the cases and controls. The positively-skewed frequency distribution of medical services utilization was consistent with a previous study on ambulatory care utilization patterns in Taiwan.[21]

Generalized estimating equations (GEEs) with negative binomial distribution and log link function were used to estimate the incidence rate ratios and assess the linear trend of eye disorder-related medical services use across the eight annual intervals,

taking into account of within-subject correlation over time.[22] In addition, incidence rate ratios of frequency of utilization of eye disorder-related medical services were calculated for each time interval. The interaction between group × time interval between eye disorder-related visits and index date was also assessed. A two-sided p-value < 0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics software package, version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total 347 cases with primary SS and 1735 controls frequency-matched on 10-year age interval and index year of the cases were included in the analysis of the study. The mean age of both groups was 53.8 years (median = 54.0, range = 20-89). Table 1 shows the utilization of eye disorder-related ambulatory medical care services in cases and controls. The proportion of eye disorder-related visits over all medical visits was significantly higher in the cases (7.5%) compared with the controls (4.8%). In terms of the number of patients who had eye disorder-related visits, they were all significantly greater in the cases compared with controls, both over the 8-year interval or for each of the eight annual intervals. Furthermore, the counts of eye disorder-related visits between cases and controls for each of the eight time intervals

were compared using generalized linear models. Except for the 7-8 year interval, the numbers of eye disorder-related visits were significantly higher for the cases in all the intervals. No significant differences were observed in levels of urbanization between the cases and controls (p = 0.208) but the distribution of tertiles of insured amount were significantly different (p = 0.016) with a higher proportion of cases in the upper tertile compared with controls.

Table 1

Utilization of eye disorder-related ambulatory medical services and urbanization levels, and income levels in female patients with primary Sjögren syndrome and frequency matched controls

Variable	Frequency (%) or Mean ± SD (median, minimum - maximum)		p value
	Case (n= 347)	Control (n = 1735)	
Eye disorder-related visits / all visits over the 8-year period	5609 / 74583 (7.5)	18914 / 393105 (4.8)	<0.001
Number of patients with eye			

disorder-related visits prior to index date by time interval (year)			
Overall 0 – 8	325 (93.7)	1414 (81.5)	<0.001
7 – 8	135 (38.9)	559 (32.2)	0.018
6 – 7	157 (45.3)	643 (37.1)	0.005
5 – 6	163 (47.0)	695 (40.1)	0.020
4 – 5	171 (49.3)	680 (39.2)	<0.001
3 – 4	177 (51.0)	676 (39.0)	<0.001
2 – 3	193 (55.6)	744 (42.9)	<0.001
1 – 2	190 (54.8)	745 (43.0)	<0.001
0 – 1	254 (73.2)	754 (43.5)	<0.001

Number of eye disorder-related visits / patient prior to index date by time interval (year)					
7 – 8	1.11 ± 2.60	(0, 0 – 26)	0.92 ± 2.36	(0, 0 – 24)	0.177
6 – 7	1.70 ± 3.81	(0, 0 – 42)	1.14 ± 2.84	(0, 0 – 38)	0.004
5 – 6	1.73 ± 3.21	(0, 0 – 23)	1.30 ± 2.86	(0, 0 – 28)	0.013
4 – 5	2.08 ± 4.32	(0, 0 – 32)	1.32 ± 2.88	(0, 0 – 33)	<0.001
3 – 4	2.15 ± 4.05	(1, 0 – 32)	1.44 ± 3.34	(0, 0 – 42)	0.001
2 – 3	2.08 ± 3.72	(1, 0 – 25)	1.56 ± 3.36	(0, 0 – 37)	0.009
1 – 2	2.38 ± 4.01	(1, 0 – 29)	1.68 ± 3.64	(0, 0 – 33)	0.001
0 – 1	3.23 ± 4.55	(2, 0 – 33)	1.71 ± 3.39	(0, 0 – 26)	<0.001

Urbanization level of patient's residence*			0.208
1 (most urbanized)	109 (32.4)	553 (32.8)	
2	117 (34.8)	527 (31.3)	
3	33 (9.8)	240 (14.2)	
4	42 (12.5)	215 (12.8)	
5 (least urbanized)	35 (10.4)	150 (8.9)	
Tertile of insured amount*			0.016
1 (lowest)	100 (29.1)	614 (35.8)	
2	112 (32.6)	568 (33.1)	
3 (highest)	132 (38.4)	535 (31.2)	

*11 cases and 50 controls had missing information on urbanization levels and 3 cases and 18 controls had missing information on insured amount.

Table 2 presents the incidence rate ratios of annual frequency of eye disorder-related visits using the 7-8 year interval as the reference category. The incidence rate ratios, for both cases and controls, were all significantly higher in intervals closer to the index date that the reference category. A significant linear trend of increasing incident rate ratios over time was also observed in the cases (β = 0.122,

$p < 0.001$) and controls ($\beta = 0.008$, $p < 0.001$). In addition, the incidence rate ratios of annual frequency of eye disorder-related visits for each of the eight time interval between the cases and controls are shown in Table 2. The incidence rate ratios of eye disorder-related visits were significant for all time intervals except for that in the 7-8 year interval.

Table 2

Trend of incidence rate ratio of the annual frequency of utilization of eye disorder-related ambulatory medical services over different time intervals prior to index date and incidence rate ratio comparing cases and controls for each time interval.

Time interval between eye disorder-related visits and index date (year)	Case			Control			Case vs. control for each time interval		
	IRR	95% CI	p value*	IRR	95% CI	p value*	IRR	95% CI	p value†
7 – 8	1.00	-	-	1.00	-	-	1.22	0.95-1.57	0.116
6 – 7	1.49	1.22-1.82	<0.001	1.22	1.10-1.36	<0.001	1.49	1.18-1.90	0.001
5 – 6	1.58	1.25-1.99	<0.001	1.36	1.20-1.53	<0.001	1.46	1.18-1.82	0.001
4 – 5	1.88	1.42-2.49	<0.001	1.39	1.23-1.57	<0.001	1.63	1.26-2.09	<0.001
3 – 4	1.96	1.51-2.56	<0.001	1.47	1.29-1.67	<0.001	1.65	1.31-2.08	<0.001
2 – 3	1.88	1.47-2.41	<0.001	1.62	1.43-1.84	<0.001	1.43	1.17-1.76	0.001

1 – 2	2.22	1.72-2.88	<0.001	1.76	1.54-2.02	<0.001	1.51	1.23-1.86	<0.001
0 – 1	3.05	2.39-3.89	<0.001	1.90	1.67-2.17	<0.001	1.92	1.62-2.28	<0.001
Trend test	β = 0.122, p < 0.001			β = 0.08, p < 0.001			-	-	-

* p values for comparisons between IRR within each column using the 7-8 year IRR as the reference category

† p values for comparisons between IRR within each row using the IRR of the control as the reference category

IRR: incidence rate ratio

CI: confidence interval

Generalized estimating equations with negative binomial distribution, log link function, and Huber/White/sandwich correlation matrix estimator, adjusted for age, urbanization levels, and tertiles of insured amount.

Table 3 shows the results of the GEEs analyses for assessing the interaction effect of group (case versus control) and time (the eight time intervals between eye disorder-related visits and index date). The presence of a significant interaction means that the changes in annual frequency of utilization of eye disorder-related ambulatory medical services over time are significantly different between the cases and control. For the overall eye disorder-related visits, there was a significant interaction effect between group by time (p= 0.010). Results from the subgroup analyses indicated that the group by time interaction was significant for the disorders of lacrimal system (p = 0.019), indicating that the increase in the annual frequency of medical visits related to disorders of lacrimal system over time was faster in the cases compared with controls. Disorders of conjunctive also showed a statistical trend of group by time interaction (p = 0.066). Although the group by time interaction terms for keratitis (ICD-9 CM: 370.x) and inflammation of eyelids or other disorders of eyelids were not significant, the group effects for these two disorders were significant. Over the entire 8-year period, the annual frequencies of medical visits related to keratitis were significantly higher in the cases compared with controls (incidence rate ratio of cases versus controls = 5.46, 95% CI = 3.13-9.53). Similarly, over the entire 8-year period, the annual frequencies of medical visits related to inflammation of eyelids or other disorders of eyelids were significantly higher in the cases compared with controls

(incidence rate ratio of cases versus controls = 2.24, 95% CI = 1.38-3.65). Conversely, no significant interaction effect or group differences were observed in the rate ratio of cataract.

Table 3

Incidence rate ratios of overall and five subgroups of eye disorder-related ambulatory medical services in female patients with primary Sjögren syndrome and frequency matched controls

Diagnosis (ICD-9-CM code)	Group effect (case vs. control)		Time effect (time interval between eye disorder-related visits and index date)		Group × time interaction	
	IRR (95% CI)	p value	IRR (95% CI)	p value	IRR (95% CI)	p value
All eye disorders (360.x to 379.x)	1.77 (1.50-2.10)	<0.001	0.92 (0.90-0.94)	<0.001	0.96 (0.92-0.99)	0.010
Disorders of lacrimal system (375.x)	5.47 (3.86-7.74)	<0.001	0.83 (0.79-0.87)	<0.001	0.90 (0.82-0.98)	0.019
Keratitis (370.x)	5.46 (3.13-9.53)	<0.001	0.84 (0.70-1.00)	0.044	1.03 (0.83-1.28)	0.789

Inflammation of eyelids (373.x) or other disorders of eyelids (374.x)	2.24 (1.38-3.65)	0.001	0.91 (0.88-0.96)	<0.001	0.96 (0.88-1.05)	0.394
Disorders of conjunctive (372.x)	1.54 (1.28-1.83)	<0.001	0.92 (0.91-0.94)	<0.001	0.97 (0.93-1.00)	0.066
Cataract (366)	1.10 (0.80-1.52)	0.564	0.86 (0.83-0.90)	<0.001	1.05 (0.97-1.15)	0.244

ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

Generalized estimating equations with negative binomial distribution, log link function, and Huber/White/sandwich correlation matrix estimator, adjusted for age, urbanization levels, and tertiles of insured amount.

DISCUSSION

To the best of our knowledge, this study is the first to use nationwide, population-based longitudinal administrative data to investigate the utilization of eye disorder-related ambulatory medical services prior to the diagnosis of primary SS. The main finding of this study was the significant increase in utilization of eye disorder-related ambulatory medical services in patients with primary SS compared with controls. This pattern was clearly reflected all the comparisons made in this study including the proportion of utilization of ambulatory medical services that were eye disorder-related over the 8-year interval prior to the index date, the proportions of patients who had used eye disorder-related ambulatory medical services in all of the annual intervals, and the numbers of annual eye disorder-related visits in all of the annual intervals except the 7-8 year interval prior to the index date.

Regarding the trend of annual frequency of eye disorder-related ambulatory services use over the 8-year intervals, both the cases and controls had higher rate ratios in the intervals closer to the index date. The increase in rate ratios in the controls could partly be explained by low copayment of medical services or aging in Taiwan. It often costs less to visit a doctor and obtain a prescription than to purchase over-the-counter medicine. Nonetheless, the presence of a significant interaction

effect between group by time interval between eye disorder-related visits and index date (p = 0.010) indicated that the rate of increase in the annual frequency of utilization of eye disorder-related visits over time was higher in patients with primary SS compared with controls.

Results from the subgroup analysis of common eye disorders revealed that the rate of the annual frequency of medical visits related to disorders of lacrimal system increased significantly faster in the cases compared with controls. Disorders of conjunctive also showed a statistical trend of faster increase over time in the cases compared with controls. These disorders were as expected because of the strong association between lacrimal dysfunction and the physiopathology of primary SS. A prospective cohort study on patients with clinically significant aqueous-deficient dry eye, increased staining in the corneal inferior zone was found in patients with primary SS. The authors hypothesized that it could be the result of constant direct contact between the inferior cornea and the tear meniscus, which contains inflammatory mediators.[10] In addition, results from the Sjögren's Syndrome International Registry revealed that the most common lid and conjunctival diseases were the presence of a pingueculum (28%).[23] Conversely, the lack of a significant difference in the number of visits related to cataract between the cases and controls was also as expected since there is no evidence suggesting an association between cataract and primary SS.

Previous studies have shown that other rheumatologic diseases are often associated with ophthalmic manifestations.[24] In a medical record review study of 220 patients with a primary diagnosis of dry eye syndrome from a tertiary care ophthalmology clinic, 25 (11.4%) had rheumatoid arthritis and 24 (10.9%) had primary SS. The authors concluded that primary SS appeared to be underdiagnosed in patients with dry eye syndrome and therefore, primary SS should be included in the diagnostic evaluation of these patients.[25] In a cross-sectional study on 61 Thai patients with rheumatoid arthritis, the prevalence of dry eyes measured by Ocular Surface Disease Index scores were significantly higher in patients with secondary SS.[26] In addition, patients with systemic lupus erythematosus, another common and complex systemic autoimmune disease, also have high incidence of dry eye. A hospital based cross-sectional study on 91 Nepalese patients reported that dry eye were present in 39.5% of the patients.[27] Therefore, ophthalmologists can play an important role in the care of patients with various underlying rheumatoid disorders including SS.

Several potential limitations of the present study should be noted. First, the identification of patients with primary SS was based on the registry for catastrophic illness and therefore, patients with minor manifestations of the disease and those who

did not require exemption from copayment of medications might not have applied for a catastrophic illness certificate. However, this is not a common situation based on our clinical experience. Second, the diagnosis of eye disorders was based solely on ICD-9-CM codes. Nevertheless, the National Health Insurance Bureau of Taiwan routinely audits the validity of diagnosis. Third, the Classification criteria for SS proposed by the American-European Consensus Group in 2002 [19] was used for the diagnosis of primary SS in our study. The adoption of the 2012 American College of Rheumatology classification criteria [28] might affect the duration between the onset of eye disorders to the diagnosis of primary SS.

Despite these limitations, the findings of this study are compelling. An increase in the utilization of eye disorder-related ambulatory medical services was observed in patients with SS several years prior to the diagnosis of the disease. Thus, early diagnosis of SS may be possible in those afflicted with the disease through the recognition by ophthalmologists that the ocular manifestations are secondary to SS. Not only further ocular complications can be reduced by proper management of eye symptoms. Patients can also be referred to specialist care for a more comprehensive approach to treatment of SS.

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Title: Increased utilization of eye disorder-related ambulatory medical services prior to the diagnosis of Sjögren syndrome in female patients: a longitudinal population-based study in Taiwan

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ABSTRACT

Objectives: To investigate the utilization of eye disorder-related ambulatory medical services prior to the diagnosis of primary Sjögren syndrome in female Taiwanese patients

Design: A nationwide, population-based case-control study

Setting: Taiwan's National Health Insurance Research Database.

Participants: A total of 347 patients with a diagnosis of primary Sjögren syndrome from 2005 to 2010 and 1735 controls frequency-matched on 10-year age interval and index year were identified from the Taiwan's National Health Insurance Research Database. Diagnoses of eye disorder (ICD-9-CM codes from 360 to 370) were retrospectively screened to 1997.

Main outcome measure: The utilization of eye disorder-related medical service use over different intervals prior to diagnosis of Sjögren syndrome between the cases and controls were compared using generalized estimating equations with negative binomial distribution and log link function.

Results: A significantly higher proportion of patients with Sjögren syndrome (7.5%) utilized eye disorder-related ambulatory medical services over an eight-year interval prior to the diagnosis of the disease compared with controls (4.8%). The annual frequency of utilization of eye

disorder-related ambulatory medical services increased significantly faster when closer to the index date in patients with Sjögren syndrome compared with controls (interaction effect, p = 0.010). Subgroup analyses indicated that the changes over time in the utilization of services related to disorders of lacrimal system (interaction effect, p = 0.019) and conjunctiva (interaction effect, p = 0.066) were significantly greater in the patients with Sjögren syndrome compared with controls.

Conclusions: An increase in the utilization of eye disorder-related ambulatory medical services was observed in patients with Sjögren syndrome several years prior to the diagnosis of the disease. General practitioners and ophthalmologists can play an important role by including Sjögren's syndrome in the diagnostic evaluation of their patients afflicted with relevant symptoms.

Article summary:

Article focus:

- Dry eyes is a common manifestation of Sjögren's syndrome.

- To examine the utilization of eye disorder-related ambulatory medical services prior to the diagnosis of primary Sjögren syndrome in females in a nationwide setting.

Key messages:

- An increase in the utilization of eye disorder-related ambulatory medical services was observed in patients with Sjögren's syndrome several years predating the diagnosis of the disease.
- Delays in diagnosis of Sjögren's syndrome may be minimized through recognizing the early manifestations of the disease.

Strengths and limitations:

- Major strengths of the study are the population-based design, based on a nationwide claim database, which could minimize recall and selection bias.
- Limitations include the possibility of misclassification because the diagnosis of eye disorders was based solely on ICD-9-CM codes and the identification of patients was based on the registry for catastrophic illness.

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INTRODUCTION

Dry eye, or xerophthalmia, is a common ophthalmological condition. However, persistent dry eye not only is associated with symptoms of discomfort and visual disturbance, it can damage the ocular surface with serious consequences such as cornea inflammation.[1] A number of factors could contribute to dry eye such as aging, environment of low humidity, hormonal changes in women, pollution, video display terminal use, contact lens wear, adverse effect of medications, meibomium gland dysfunction, and Sjögren's syndrome (SS).[2-5]

SS is a progressive systemic autoimmune disorder characterized by secretory gland dysfunction including dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia).[6, 7] In patients with SS, lymphocytic infiltration of the lacrimal gland can lead to a destruction of the acinar structures and impair glandular function.[8] Meibomian gland dysfunction had also been suggested to partly contribute to the increased evaporation of tears in patients with SS.[9]

Since patients may seek medical care because of their visual disturbance and ocular discomfort caused by dry eye, medical professionals can play an important role in identifying that the visual and ocular symptoms may be secondary to the underlying SS in some of the cases. In a prospective cohort of 327 patients with aqueous-deficient dry eye, 11.6% of the patients were found to have SS. The authors

concluded that ophthalmologists should consider the likelihood of underlying SS in patients with clinically significant dry eye. [10] Although there is no known cure for SS,[11] early diagnosis of the disease should help to reduce the negative impact on the quality of life and the development of other associated complications such as intersitial lung diseases, neuropathy, renal tubular acidosis, autoimmune hepatitis, and primary bililary cirrhosis. [12,13]

A population-based study using the National Health Insurance Research Database in Taiwan revealed that patients with dry eye disease had significantly higher prevalences in 25 of the 34 comorbidities examined. Among the comorbidities, systemic lupus erythematosus (odds ratio, OR = 4.0, 95% confidence interval, 95%CI = 2.9-5.4) and rheumatoid arthritis (OR = 2.9, 95%CI = 2.6-3.1) showed the strongest associations in patients with dry eye disease compared with the controls.[14] However, SS was not included in the list of comorbidites in the study and other eye disorders were not investigated. Therefore, the aim of the present study was to evaluate the utilization of eye disorder-related ambulatory care services by female patients prior to the diagnosis of primary SS through the use of a longitudinal population-based health claims database in Taiwan.

MATERIALS AND METHODS

Study design and data source

This case-control study is a secondary data analysis using claims data from the National Health Insurance Research Database (NHIRD) maintained by the National Health Research Institute, Taiwan. The NHIRD contains comprehensive administrative and claim data from the National Health Insurance (NHI) program, which is a mandatory single-payer social health insurance system implemented in 1995. [15] As of the end of 2011, 23.20 million out of 23.22 million (99.9%) residents were enrolled in the system.[16,17]

The ambulatory care expenditures by visits files (CD) from the Longitudinal Health Insurance Database (LHID2000), the catastrophic illness files (HV), and the beneficiaries files (ID) were used in the present study to identify cases, controls, and their use of ambulatory medical care services. Details of the structure of the claims data sets are described on the NHIRD website.[18] Since the NHIRD files contain only de-identified secondary data, the need for informed consent from individual subjects was waived. The study protocol was reviewed and approved by the Institutional Review Board of the Buddhist Dalin Tzu Chi Hospital, Taiwan (No. A10104020).

Study samples

Cases were defined as female patients newly diagnosed with primary SS (International Classification of Diseases, Ninth Revision, clinical modification [ICD-9-CM] code 710.2) who had applied for a certificate of catastrophic illness between January 1, 2005 and December 31, 2010. In Taiwan, SS is one of the 30 major categories of conditions that are recognized as catastrophic illness or injury covered under the National Health Insurance scheme. These are conditions that require long term medical treatment and therefore, could put heavy economic burden on afflicted individuals. Holders of the catastrophic illness certificates are exempted from co-payment of medical cost related to the catastrophic illness. The application of catastrophic illness certificates are formally reviewed by the Bureau of NHI according to the criteria of the American-European Consensus Group for SS published in 2002.[19] Therefore, the presence of a certificate of catastrophic illness of SS is a reliable indicator of its definitive diagnosis. Patients with catastrophic illness certificates of other autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, other connective tissue diseases, were excluded. Since SS occurs less commonly in children and adolescents, patients younger than 20 years of age were excluded from the study. The date of application of the catastrophic illness certificate was used as the index date for cases.

Controls were selected from the LHID2000 at a ratio of 1:5 frequency-matched on 10-year age interval and year of index date (index year). The index date for the controls was assigned by randomly selected an ambulatory visit within the matched index year (2005 to 2010). Both the cases and controls were linked to the LHID2000 to obtain data for their utilization of ambulatory care services from 1997 to 2010.

Eye disorders

To evaluate the utilization of eye disorders-related ambulatory medical care use prior to index date, both the cases and controls were retrospectively screened to 1997. Eye disorders were defined as any diagnosis of ICD-9-CM codes from 360 to 379, including their subcodes. Additional subgroup analyses were conducted on disorder of conjunctive (ICD-9-CM: 372.x), inflammation of eyelids (ICD-9-CM: 373.x) or other disorders of eyelids (ICD-9-CM: 374.x), disorders of lacrimal system (ICD-9-CM: 375.x), cataract (ICD-9-CM: 366), and keratitis (ICD-9-CM: 370.x).

Statistical analysis

Summary statistics are expressed as frequency and percentage for categorical data and mean ± standard deviation (SD) or median with minimum and maximum for continuous variables, as appropriate. Pearson Chi-square tests or Fisher's exact test

were used to compare categorical data between cases and controls. Mann-Whitney U-test were used to compare continuous data between cases and controls.

Urbanization of levels of the residence of cases and controls were constructed according to a published categorization scheme, which is based on a combination of population density, percentage of residents with college level or higher education, percentage of residents 65 years and older, percentage of residents who were agriculture workers, and the number of physicians per 100000 people.[20] In addition, we also calculated payroll-related insured amount as a proxy measure to represent socioeconomic status. The variable was categories into tertiles with the lower and upper cut-points at 18300 and 24000 New Taiwan dollar, respectively.

To account for the substantial positive skewness and excess zeros present in the count data, generalized linear models with a negative binomial distribution and a log link function were used compared the differences in eye disorder-related medical services use between the cases and controls. The positively-skewed frequency distribution of medical services utilization was consistent with a previous study on ambulatory care utilization patterns in Taiwan.[21]

Generalized estimating equations (GEEs) with negative binomial distribution and log link function were used to estimate the incidence rate ratios and assess the linear trend of eye disorder-related medical services use across the eight annual intervals,

taking into account of within-subject correlation over time.[22] In addition, incidence rate ratios of frequency of utilization of eye disorder-related medical services were calculated for each time interval. The interaction between group × time interval between eye disorder-related visits and index date was also assessed. A two-sided p-value < 0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics software package, version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total 347 cases with primary SS and 1735 controls frequency-matched on 10-year age interval and index year of the cases were included in the analysis of the study. The mean age of both groups was 53.8 years (median = 54.0, range = 20-89). Table 1 shows the utilization of eye disorder-related ambulatory medical care services in cases and controls. The proportion of eye disorder-related visits over all medical visits was significantly higher in the cases (7.5%) compared with the controls (4.8%). In terms of the number of patients who had eye disorder-related visits, they were all significantly greater in the cases compared with controls, both over the 8-year interval or for each of the eight annual intervals. Furthermore, the counts of eye disorder-related visits between cases and controls for each of the eight time intervals

were compared using generalized linear models. Except for the 7-8 year interval, the numbers of eye disorder-related visits were significantly higher for the cases in all the intervals. No significant differences were observed in levels of urbanization between the cases and controls (p = 0.208) but the distribution of tertiles of insured amount were significantly different (p = 0.016) with a higher proportion of cases in the upper tertile compared with controls.

Table 1

Utilization of eye disorder-related ambulatory medical services and urbanization levels, and income levels in female patients with primary Sjögren syndrome and frequency matched controls

Variable	Frequency (%) or Mean ± SD (median, minimum - maximum)		p value
	Case (n= 347)	Control (n = 1735)	
Eye disorder-related visits / all visits over the 8-year period	5609 / 74583 (7.5)	18914 / 393105 (4.8)	<0.001
Number of patients with eye			

disorder-related visits prior to index date by time interval (year)			
Overall 0 – 8	325 (93.7)	1414 (81.5)	<0.001
7 – 8	135 (38.9)	559 (32.2)	0.018
6 – 7	157 (45.3)	643 (37.1)	0.005
5 – 6	163 (47.0)	695 (40.1)	0.020
4 – 5	171 (49.3)	680 (39.2)	<0.001
3 – 4	177 (51.0)	676 (39.0)	<0.001
2 – 3	193 (55.6)	744 (42.9)	<0.001
1 – 2	190 (54.8)	745 (43.0)	<0.001
0 – 1	254 (73.2)	754 (43.5)	<0.001

Number of eye disorder-related visits / patient prior to index date by time interval (year)					
7 – 8	1.11 ± 2.60	(0, 0 – 26)	0.92 ± 2.36	(0, 0 – 24)	0.177
6 – 7	1.70 ± 3.81	(0, 0 – 42)	1.14 ± 2.84	(0, 0 – 38)	0.004
5 – 6	1.73 ± 3.21	(0, 0 – 23)	1.30 ± 2.86	(0, 0 – 28)	0.013
4 – 5	2.08 ± 4.32	(0, 0 – 32)	1.32 ± 2.88	(0, 0 – 33)	<0.001
3 – 4	2.15 ± 4.05	(1, 0 – 32)	1.44 ± 3.34	(0, 0 – 42)	0.001
2 – 3	2.08 ± 3.72	(1, 0 – 25)	1.56 ± 3.36	(0, 0 – 37)	0.009
1 – 2	2.38 ± 4.01	(1, 0 – 29)	1.68 ± 3.64	(0, 0 – 33)	0.001
0 – 1	3.23 ± 4.55	(2, 0 – 33)	1.71 ± 3.39	(0, 0 – 26)	<0.001

Urbanization level of patient's residence*			0.208
1 (most urbanized)	109 (32.4)	553 (32.8)	
2	117 (34.8)	527 (31.3)	
3	33 (9.8)	240 (14.2)	
4	42 (12.5)	215 (12.8)	
5 (least urbanized)	35 (10.4)	150 (8.9)	
Tertile of insured amount*			0.016
1 (lowest)	100 (29.1)	614 (35.8)	
2	112 (32.6)	568 (33.1)	
3 (highest)	132 (38.4)	535 (31.2)	

*11 cases and 50 controls had missing information on urbanization levels and 3 cases and 18 controls had missing information on insured amount.

Table 2 presents the incidence rate ratios of annual frequency of eye disorder-related visits using the 7-8 year interval as the reference category. The incidence rate ratios, for both cases and controls, were all significantly higher in intervals closer to the index date that the reference category. A significant linear trend of increasing incident rate ratios over time was also observed in the cases (β = 0.122,

$p < 0.001$) and controls ($\beta = 0.008$, $p < 0.001$). In addition, the incidence rate ratios of annual frequency of eye disorder-related visits for each of the eight time interval between the cases and controls are shown in Table 2. The incidence rate ratios of eye disorder-related visits were significant for all time intervals except for that in the 7-8 year interval.

Table 2

Trend of incidence rate ratio of the annual frequency of utilization of eye disorder-related ambulatory medical services over different time intervals prior to index date and incidence rate ratio comparing cases and controls for each time interval.

Time interval between eye disorder-related visits and index date (year)	Case			Control			Case vs. control for each time interval		
	IRR	95% CI	p value*	IRR	95% CI	p value*	IRR	95% CI	p value†
7 – 8	1.00	-	-	1.00	-	-	1.22	0.95-1.57	0.116
6 – 7	1.49	1.22-1.82	<0.001	1.22	1.10-1.36	<0.001	1.49	1.18-1.90	0.001
5 – 6	1.58	1.25-1.99	<0.001	1.36	1.20-1.53	<0.001	1.46	1.18-1.82	0.001
4 – 5	1.88	1.42-2.49	<0.001	1.39	1.23-1.57	<0.001	1.63	1.26-2.09	<0.001
3 – 4	1.96	1.51-2.56	<0.001	1.47	1.29-1.67	<0.001	1.65	1.31-2.08	<0.001
2 – 3	1.88	1.47-2.41	<0.001	1.62	1.43-1.84	<0.001	1.43	1.17-1.76	0.001

1 – 2	2.22	1.72-2.88	<0.001	1.76	1.54-2.02	<0.001	1.51	1.23-1.86	<0.001
0 – 1	3.05	2.39-3.89	<0.001	1.90	1.67-2.17	<0.001	1.92	1.62-2.28	<0.001
Trend test	β = 0.122, p < 0.001			β = 0.08, p < 0.001			-	-	-

* p values for comparisons between IRR within each column using the 7-8 year IRR as the reference category

† p values for comparisons between IRR within each row using the IRR of the control as the reference category

IRR: incidence rate ratio

CI: confidence interval

Generalized estimating equations with negative binomial distribution, log link function, and Huber/White/sandwich correlation matrix estimator, adjusted for age, urbanization levels, and tertiles of insured amount.

Table 3 shows the results of the GEEs analyses for assessing the interaction effect of group (case versus control) and time (the eight time intervals between eye disorder-related visits and index date). The presence of a significant interaction means that the changes in annual frequency of utilization of eye disorder-related ambulatory medical services over time are significantly different between the cases and control. For the overall eye disorder-related visits, there was a significant interaction effect between group by time (p= 0.010). Results from the subgroup analyses indicated that the group by time interaction was significant for the disorders of lacrimal system (p = 0.019), indicating that the increase in the annual frequency of medical visits related to disorders of lacrimal system over time was faster in the cases compared with controls. Disorders of conjunctive also showed a statistical trend of group by time interaction (p = 0.066). Although the group by time interaction terms for keratitis (ICD-9 CM: 370.x) and inflammation of eyelids or other disorders of eyelids were not significant, the group effects for these two disorders were significant. Over the entire 8-year period, the annual frequencies of medical visits related to keratitis were significantly higher in the cases compared with controls (incidence rate ratio of cases versus controls = 5.46, 95% CI = 3.13-9.53). Similarly, over the entire 8-year period, the annual frequencies of medical visits related to inflammation of eyelids or other disorders of eyelids were significantly higher in the cases compared with controls

(incidence rate ratio of cases versus controls = 2.24, 95% CI = 1.38-3.65). Conversely, no significant interaction effect or group differences were observed in the rate ratio of cataract.

Table 3

Incidence rate ratios of overall and five subgroups of eye disorder-related ambulatory medical services in female patients with primary Sjögren syndrome and frequency matched controls

Diagnosis (ICD-9-CM code)	Group effect (case vs. control)		Time effect (time interval between eye disorder-related visits and index date)		Group × time interaction	
	IRR (95% CI)	p value	IRR (95% CI)	p value	IRR (95% CI)	p value
All eye disorders (360.x to 379.x)	1.77 (1.50-2.10)	<0.001	0.92 (0.90-0.94)	<0.001	0.96 (0.92-0.99)	0.010
Disorders of lacrimal system (375.x)	5.47 (3.86-7.74)	<0.001	0.83 (0.79-0.87)	<0.001	0.90 (0.82-0.98)	0.019
Keratitis (370.x)	5.46 (3.13-9.53)	<0.001	0.84 (0.70-1.00)	0.044	1.03 (0.83-1.28)	0.789

Inflammation of eyelids (373.x) or other disorders of eyelids (374.x)	2.24 (1.38-3.65)	0.001	0.91 (0.88-0.96)	<0.001	0.96 (0.88-1.05)	0.394
Disorders of conjunctive (372.x)	1.54 (1.28-1.83)	<0.001	0.92 (0.91-0.94)	<0.001	0.97 (0.93-1.00)	0.066
Cataract (366)	1.10 (0.80-1.52)	0.564	0.86 (0.83-0.90)	<0.001	1.05 (0.97-1.15)	0.244

ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

Generalized estimating equations with negative binomial distribution, log link function, and Huber/White/sandwich correlation matrix estimator, adjusted for age, urbanization levels, and tertiles of insured amount.

DISCUSSION

To the best of our knowledge, this study is the first to use nationwide, population-based longitudinal administrative data to investigate the utilization of eye disorder-related ambulatory medical services prior to the diagnosis of primary SS. The main finding of this study was the significant increase in utilization of eye disorder-related ambulatory medical services in patients with primary SS compared with controls. This pattern was clearly reflected all the comparisons made in this study including the proportion of utilization of ambulatory medical services that were eye disorder-related over the 8-year interval prior to the index date, the proportions of patients who had used eye disorder-related ambulatory medical services in all of the annual intervals, and the numbers of annual eye disorder-related visits in all of the annual intervals except the 7-8 year interval prior to the index date.

Regarding the trend of annual frequency of eye disorder-related ambulatory services use over the 8-year intervals, both the cases and controls had higher rate ratios in the intervals closer to the index date. The increase in rate ratios in the controls could partly be explained by low copayment of medical services or aging in Taiwan. It often costs less to visit a doctor and obtain a prescription than to purchase over-the-counter medicine. Nonetheless, the presence of a significant interaction

effect between group by time interval between eye disorder-related visits and index date ($p = 0.010$) indicated that the rate of increase in the annual frequency of utilization of eye disorder-related visits over time was higher in patients with primary SS compared with controls.

Results from the subgroup analysis of common eye disorders revealed that the rate of the annual frequency of medical visits related to disorders of lacrimal system increased significantly faster in the cases compared with controls. Disorders of conjunctive also showed a statistical trend of faster increase over time in the cases compared with controls. These disorders were as expected because of the strong association between lacrimal dysfunction and the physiopathology of primary SS. A prospective cohort study on patients with clinically significant aqueous-deficient dry eye, increased staining in the corneal inferior zone was found in patients with primary SS. The authors hypothesized that it could be the result of constant direct contact between the inferior cornea and the tear meniscus, which contains inflammatory mediators.[10] In addition, results from the Sjögren's Syndrome International Registry revealed that the most common lid and conjunctival diseases were the presence of a pingueculum (28%).[23] Conversely, the lack of a significant difference in the number of visits related to cataract between the cases and controls was also as expected since there is no evidence suggesting an association between cataract and primary SS.

Previous studies have shown that other rheumatologic diseases are often associated with ophthalmic manifestations.[24] In a medical record review study of 220 patients with a primary diagnosis of dry eye syndrome from a tertiary care ophthalmology clinic, 25 (11.4%) had rheumatoid arthritis and 24 (10.9%) had primary SS. The authors concluded that primary SS appeared to be underdiagnosed in patients with dry eye syndrome and therefore, primary SS should be included in the diagnostic evaluation of these patients.[25] In a cross-sectional study on 61 Thai patients with rheumatoid arthritis, the prevalence of dry eyes measured by Ocular Surface Disease Index scores were significantly higher in patients with secondary SS.[26] In addition, patients with systemic lupus erythematosus, another common and complex systemic autoimmune disease, also have high incidence of dry eye. A hospital based cross-sectional study on 91 Nepalese patients reported that dry eye were present in 39.5% of the patients.[27] Therefore, ophthalmologists can play an important role in the care of patients with various underlying rheumatoid disorders including SS.

Several potential limitations of the present study should be noted. First, the identification of patients with primary SS was based on the registry for catastrophic illness and therefore, patients with minor manifestations of the disease and those who

did not require exemption from copayment of medications might not have applied for a catastrophic illness certificate. However, this is not a common situation based on our clinical experience. Second, the diagnosis of eye disorders was based solely on ICD-9-CM codes. Nevertheless, the National Health Insurance Bureau of Taiwan routinely audits the validity of diagnosis. Third, the Classification criteria for SS proposed by the American-European Consensus Group in 2002 [19] was used for the diagnosis of primary SS in our study. The adoption of the 2012 American College of Rheumatology classification criteria [28] might affect the duration between the onset of eye disorders to the diagnosis of primary SS.

Despite these limitations, the findings of this study are compelling. An increase in the utilization of eye disorder-related ambulatory medical services was observed in patients with SS several years prior to the diagnosis of the disease. Thus, early diagnosis of SS may be possible in those afflicted with the disease through the recognition by ophthalmologists that the ocular manifestations are secondary to SS. Not only further ocular complications can be reduced by proper management of eye symptoms. Patients can also be referred to specialist care for a more comprehensive approach to treatment of SS.

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STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation
Title and abstract	1✓	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2✓	Explain the scientific background and rationale for the investigation being reported
Objectives	3✓	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4✓	Present key elements of study design early in the paper
Setting	5✓	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6✓	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls
		(*b*) For matched studies, give matching criteria and the number of controls per case
Variables	7✓	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*✓	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9✓	Describe any efforts to address potential sources of bias
Study size	10✓	Explain how the study size was arrived at
Quantitative variables	11✓	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12✓	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how matching of cases and controls was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*✓	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*✓	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*✓	Report numbers in each exposure category, or summary measures of exposure
Main results	16✓	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17✓	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18✓	Summarise key results with reference to study objectives
Limitations	19✓	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20✓	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21✓	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22✓	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.