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

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ABSTRACT

Objectives: To investigate the utilisation of eye disorder-related ambulatory medical services prior to the diagnosis of primary Sjögren's 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's syndrome from 2005 to 2010 and 1735 controls frequency matched on 10-year age interval and index year were identified from Taiwan's National Health Insurance Research Database. Diagnoses of eye disorder (International Classification of Diseases, Ninth Revision, clinical modification (ICD-9-CM) codes from 360 to 370) were retrospectively screened to 1997.

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

Results: A significantly higher proportion of patients with Sjögren's syndrome (7.5%) utilised eye disorder-related ambulatory medical services over an 8-year interval prior to the diagnosis of the disease compared with controls (4.8%). The annual frequency of utilisation of eye disorder-related ambulatory medical services increased significantly faster when closer to the index date in patients with Sjögren's syndrome compared with controls (interaction effect, p=0.010). Subgroup analyses indicated that the changes over time in the utilisation of services related to disorders of lacrimal system (interaction effect, p=0.019) and conjunctiva (interaction effect, p=0.066) were significantly greater in patients with Sjögren's syndrome compared with controls.

Conclusions: An increase in the utilisation of eye disorder-related ambulatory medical services was observed in patients with Sjögren's 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.

Strengths and limitations of this study

- The major strengths of the study are the population-based design, based on a nationwide claim database, which could minimise recall and selection bias.
- The major limitation of the study was the possibility of misclassification because the diagnosis of eye disorders was based solely on ICD-9-CM codes.
- Other study limitations included the identification of patients was based on the registry for catastrophic illness and the classification criteria for Sjögren's syndrome proposed by the American-European Consensus Group in 2002 were used.

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 but also can damage the ocular surface with serious consequences such as cornea inflammation.[1] A number of factors could contribute to dry eye such as ageing, environment of low humidity, hormonal changes in women, pollution, video display terminal use, contact lens wear, adverse effect of medications,

meibomiam gland dysfunction and Sjögren's syndrome (SS).[2–5]

SS is a progressive systemic autoimmune disorder characterised 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 has 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 cases. In a prospective cohort of 327 patients with aqueous-deficient dry eye, 11.6% of 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 interstitial lung diseases, neuropathy, renal tubular acidosis, autoimmune hepatitis and primary biliary cirrhosis.[12 13]

A population-based study using the National Health Insurance Research Database (NHIRD) 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 (OR=4.0, 95% CI 2.9 to 5.4) and rheumatoid arthritis (OR=2.9, 95% CI 2.6 to 3.1) showed the strongest associations in patients with dry eye disease compared with 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 utilisation 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 NHIRD maintained by the National Health Research Institute, Taiwan. The NHIRD contains comprehensive administrative and claim data from the National Health Insurance (NHI) programme, 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 participants was waived.

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 1 January 2005 and 31 December 2010. In Taiwan, SS is 1 of the 30 major categories of conditions that are recognised as catastrophic illness or injury covered under the NHI 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 copayment 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 and 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 controls was assigned by a randomly selected ambulatory visit within the matched index year (2005–2010). Cases and controls were linked to the LHID2000 to obtain data for their utilisation of ambulatory care services from 1997 to 2010.

Eye disorders

To evaluate the utilisation of eye disorder-related ambulatory medical care prior to the index date, cases and controls were retrospectively screened up 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 the conjunctiva (ICD-9-CM: 372.x), inflammation of the eyelids (ICD-9-CM: 373.x) or other disorders of the eyelids (ICD-9-CM: 374.x), disorders of the 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±SD or median with minimum and maximum for continuous variables, as appropriate. Pearson χ^2 test or Fisher's exact test were used to compare categorical data between cases and controls. The Mann-Whitney U test was used to compare continuous data between cases and controls.

The urbanisation level of patients' residence was derived according to a published categorisation scheme. The scheme 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/100 000 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 New Taiwan $18 300 and $24 000 , respectively.

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

Generalised 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 the within-subject correlation over time.[22] In addition, incidence rate ratios of the frequency of utilisation 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, V.21.0 (IBM Corp, Armonk, New York, USA).

RESULTS

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

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 cases and controls were all significantly higher in intervals closer to the index date than the reference category. A significant linear trend of increasing incidence rate ratios over time was also observed in cases (β=0.122, p<0.001) and controls (β=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 intervals between 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 3 shows the results of the GEEs analyses for assessing the interaction effect of group (case vs 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 utilisation of eye disorder-related ambulatory medical services over time are significantly different between cases and controls. 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 the lacrimal system (p=0.019), indicating that the increase in the annual frequency of medical visits related to the disorders of the lacrimal system over time was faster in cases compared with controls. Disorders of the conjunctiva 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 the eyelids or other disorders of the 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 cases compared with controls (incidence rate ratio of cases vs controls=5.46, 95% CI 3.13 to 9.53). Similarly, over the entire 8-year period, the annual frequencies of medical visits related to inflammation of the eyelids or other disorders of the eyelids were significantly higher in cases compared with controls (incidence rate ratio of cases vs controls=2.24, 95% CI 1.38 to 3.65). Conversely, no significant interaction effects or group differences were observed in the rate ratio of cataract.

Table 1 Utilisation of eye disorder-related ambulatory medical services and urbanisation levels, and income levels in female patients with primary Sjögren's 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	5609/74 583 (7.5)	18 914/393 105 (4.8)	<0.001
Number of patients with eye disorder-related visits prior to the 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 the 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
Urbanisation level of patient's residence*			
1 (most urbanised)	109 (32.4)	553 (32.8)	0.208
2	117 (34.8)	527 (31.3)	
3	33 (9.8)	240 (14.2)	
4	42 (12.5)	215 (12.8)	
5 (least urbanised)	35 (10.4)	150 (8.9)	
Tertile of insured amount*			
1 (lowest)	100 (29.1)	614 (35.8)	0.016
2	112 (32.6)	568 (33.1)	
3 (highest)	132 (38.4)	535 (31.2)	

*Eleven cases and 50 controls had missing information on urbanisation levels and 3 cases and 18 controls had missing information on 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 utilisation 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 utilisation of eye disorder-related ambulatory medical services in patients with primary SS compared with controls. This pattern clearly reflected all the comparisons made in this study, including the proportion of utilisation of ambulatory medical services that were eye disorder-related over the 8-year interval prior to the index date, the proportion 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, cases and controls had higher rate ratios in the intervals closer to the index date. The increase in rate ratios in controls could partly be explained by the low copayment of medical services or ageing 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 groups by the time interval between eye disorder-related visits and the index date (p=0.010) indicated that the rate of increase in the annual frequency of utilisation 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 the lacrimal system increased significantly faster in cases compared with controls. Disorders of the conjunctiva also showed a statistical trend of faster increase over time in cases compared with controls. These disorders were as

Table 2 Trend of incidence rate ratio (IRR) of the annual frequency of utilisation of eye disorder-related ambulatory medical services over different time intervals prior to the index date and IRR 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 to 1.57	0.116
6–7	1.49	1.22 to 1.82	<0.001	1.22	1.10 to 1.36	<0.001	1.49	1.18 to 1.90	0.001
5–6	1.58	1.25 to 1.99	<0.001	1.36	1.20 to 1.53	<0.001	1.46	1.18 to 1.82	0.001
4–5	1.88	1.42 to 2.49	<0.001	1.39	1.23 to 1.57	<0.001	1.63	1.26 to 2.09	<0.001
3–4	1.96	1.51 to 2.56	<0.001	1.47	1.29 to 1.67	<0.001	1.65	1.31 to 2.08	<0.001
2–3	1.88	1.47 to 2.41	<0.001	1.62	1.43 to 1.84	<0.001	1.43	1.17 to 1.76	0.001
1–2	2.22	1.72 to 2.88	<0.001	1.76	1.54 to 2.02	<0.001	1.51	1.23 to 1.86	<0.001
0–1	3.05	2.39 to 3.89	<0.001	1.90	1.67 to 2.17	<0.001	1.92	1.62 to 2.28	<0.001
Trend test	β=0.122, p<0.001			β=0.08, p<0.001			–	–	–

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

expected because of the strong association between lacrimal dysfunction and the physiopathology of primary SS. In 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 hypothesised 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 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 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 rheumatological 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 the

Table 3 Incidence rate ratios (IRRs) of the overall and five subgroups of eye disorder-related ambulatory medical services in female patients with primary Sjögren's 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–379.x)	1.77 (1.50 to 2.10)	<0.001	0.92 (0.90 to 0.94)	<0.001	0.96 (0.92 to 0.99)	0.010
Disorders of the lacrimal system (375.x)	5.47 (3.86 to 7.74)	<0.001	0.83 (0.79 to 0.87)	<0.001	0.90 (0.82 to 0.98)	0.019
Keratitis (370.x)	5.46 (3.13 to 9.53)	<0.001	0.84 (0.70 to 1.00)	0.044	1.03 (0.83 to 1.28)	0.789
Inflammation of the eyelids (373.x) or other disorders of the eyelids (374.x)	2.24 (1.38 to 3.65)	0.001	0.91 (0.88 to 0.96)	<0.001	0.96 (0.88 to 1.05)	0.394
Disorders of the conjunctiva (372.x)	1.54 (1.28 to 1.83)	<0.001	0.92 (0.91 to 0.94)	<0.001	0.97 (0.93 to 1.00)	0.066
Cataract (366)	1.10 (0.80 to 1.52)	0.564	0.86 (0.83 to 0.90)	<0.001	1.05 (0.97 to 1.15)	0.244

Generalised estimating equations with negative binomial distribution, log link function, and Huber/White/sandwich correlation matrix estimator, adjusted for age, urbanisation levels, and tertiles of insured amount.
ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

Ocular Surface Disease Index scores was significantly higher in patients with secondary SS.[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 was 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 NHI 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] were 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 and the diagnosis of primary SS.

Despite these limitations, the findings of this study are compelling. An increase in the utilisation 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 recognition by ophthalmologists that ocular manifestations are secondary to SS. Not only can further ocular complications be reduced by proper management of eye symptoms but also patients can be referred to specialist care for a more comprehensive approach to treatment of SS.

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REFERENCES

1. Lemp MA. Advances in understanding and managing dry eye disease. *Am J Ophthalmol* 2008;146:350–6.
2. Yao W, Davidson RS, Durairaj VD, *et al*. Dry eye syndrome: an update in office management. *Am J Med* 2011;124:1016–18.
3. Uchino M, Nishiwaki Y, Michikawa T, *et al*. Prevalence and risk factors of dry eye disease in Japan: Koumi study. *Ophthalmology* 2011;118:2361–7.
4. Fraunfelder FT, Sciubba JJ, Mathers WD. The role of medications in causing dry eye. *J Ophthalmol* 2012;2012:285851.
5. The definition and classification of dry eye disease: report of the definition and classification subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf* 2007;5:75–92.
6. Mohsenin A, Huang JJ. Ocular manifestations of systemic inflammatory diseases. *Conn Med* 2012;76:533–44.
7. Ramos-Casals M, Brito-Zerón P, Sisó-Almirall A, *et al*. Primary Sjogren syndrome. *BMJ* 2012;344:e3821.
8. Bayetto K, Logan RM. Sjögren's syndrome: a review of aetiology, pathogenesis, diagnosis and management. *Aust Dent J* 2010;55 (Suppl 1):39–47.
9. Shimazaki J, Goto E, Ono M, *et al*. Meibomian gland dysfunction in patients with Sjögren syndrome. *Ophthalmology* 1998;105:1485–8.
10. Liew MS, Zhang M, Kim E, *et al*. Prevalence and predictors of Sjogren's syndrome in a prospective cohort of patients with aqueous-deficient dry eye. *Br J Ophthalmol* 2012;96:1498–503.
11. Mavragani CP, Moutsopoulos HM. Conventional therapy of Sjogren's syndrome. *Clin Rev Allergy Immunol* 2007;32:284–91.
12. Akpek EK, Lindsley KB, Adyanthaya RS, *et al*. Treatment of Sjögren's syndrome-associated dry eye an evidence-based review. *Ophthalmology* 2011;118:1242–52.
13. Friedman NJ. Impact of dry eye disease and treatment on quality of life. *Curr Opin Ophthalmol* 2010;21:310–16.
14. Wang TJ, Wang IJ, Hu CC, *et al*. Comorbidities of dry eye disease: a nationwide population-based study. *Acta Ophthalmol* 2012;90: 663–8.
15. Bureau of National Health Insurance. National Health Insurance in Taiwan. 2012–2013 Annual Report. http://www.nhi.gov.tw/resource/Webdata/22955_1_NHI_2012–2013%20ANNUAL%20REPORT.pdf (accessed 25 Feb 2014).
16. Directorate General of Budget, Accounting and Statistics, Executive Yuan, Republic of China. Statistical Yearbook of Republic of China 2011. Insured persons of social insurance. http://eng.stat.gov.tw/public/data/dgbas03/bs2/yearbook_eng/y087.pdf (accessed 25 Feb 2014).
17. Directorate General of Budget, Accounting and Statistics, Executive Yuan, Republic of China. Statistical Yearbook of Republic of China 2011. Population by sex, rate of population increase, average persons per household, density and natural increase rate. http://eng.stat.gov.tw/public/data/dgbas03/bs2/yearbook_eng/y008.pdf (accessed 25 Feb 2014).
18. National Health Insurance Research Database, Taiwan. http://nhird.nhri.org.tw/en/index.htm (accessed 25 Feb 2014).
19. Vitali C, Bombardieri S, Jonsson R, *et al*. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002;61:554–8.

20. Liu CY, Hung YT, Chuang YL, *et al*. Incorporating development stratification of Taiwan townships into sampling design of large scale health interview survey. *J Health Manag* 2006;4:1–22.
21. Chen TJ, Chou LF, Hwang SJ. Patterns of ambulatory care utilization in Taiwan. *BMC Health Serv Res* 2006;6:54.
22. Hardin JW, Hilbe JM. *Generalized estimating equations*. 2nd edn. Boca Raton, FL: Chapman and Hall/CRC, 2012.
23. Whitcher JP, Shiboski CH, Shiboski SC, *et al*. A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjögren's Syndrome International Registry. *Am J Ophthalmol* 2010;149:405–15.
24. Petris CK, Almony A. Ophthalmic manifestations of rheumatologic disease: diagnosis and management. *Mo Med* 2012;109: 53–8.
25. Akpek EK, Klimava A, Thorne JE, *et al*. Evaluation of patients with dry eye for presence of underlying Sjögren syndrome. *Cornea* 2009;28:493–7.
26. Kosrirukvongs P, Ngowyutagon P, Pusuwan P, *et al*. Prevalence of dry eye syndrome and Sjogren's syndrome in patients with rheumatoid arthritis. *J Med Assoc Thai* 2012;95(Suppl 4):S61–9.
27. Sitaula R, Shah DN, Singh D. The spectrum of ocular involvement in systemic lupus erythematosus in a tertiary eye care center in Nepal. *Ocul Immunol Inflamm* 2011;19:422–5.
28. Shiboski SC, Shiboski CH, Criswell L, *et al*. American College of Rheumatology classification criteria for Sjögren's syndrome: a data-driven, expert consensus approach in the Sjögren's International Collaborative Clinical Alliance cohort. *Arthritis Care Res (Hoboken)* 2012;64:475–87.