Sex- and Age-Specific Prevalence and Incidence Rates of Sight-Threatening Diabetic Retinopathy in Taiwan

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**IMPORTANCE** The prevalence of diabetic retinopathy (DR) is high in individuals with diabetes mellitus. Published estimates for sight-threatening DR (STDR) prevalence range widely. There is a need for precise contemporary estimates of the prevalence and incidence of STDR for providing optimal strategies of clinical management in Taiwan.

**OBJECTIVE** To determine the precise contemporary estimates of the prevalence and incidence of STDR in patients with type 2 diabetes mellitus in Taiwan.

**DESIGN, SETTING, AND PARTICIPANTS** Data were collected from a representative database, the Longitudinal Health Insurance Database 2005, from 2005 to 2011, on a total of 2926 incident cases of patients with STDR among 63,582 patients with type 2 diabetes. *Sight-threatening DR* was defined as clinically significant macular edema, severe nonproliferative DR, or proliferative DR according to the classification of the Early Treatment Diabetic Retinopathy Study research group. Sex-specific and age-adjusted incidence and prevalence rates of STDR were analyzed for patients with type 2 diabetes and STDR identified using *International Classification of Diseases, Ninth Revision, Clinical Modification* codes and procedure codes.

**MAIN OUTCOMES AND MEASURES** Procedure codes were used to determine the diagnosis of STDR.

**RESULTS** The number of incident cases of STDR increased in line with the increasing diabetic population during 2005-2011. Sex differences in the age-adjusted incidence rates were observed, showing a declining trend from 10.84 (95% CI, 10.69%-10.99%) to 6.00 (95% CI, 5.86%-6.14%) per 1000 person-years for women (*P* < .001) contrasting with an increasing trend in men, from 14.86 (95% CI, 14.71%-15.01%) to 21.89 (95% CI, 21.76%-22.02%) per 1000 person-years (*P* < .001). The age-adjusted prevalence rates of STDR were in decreasing trends for both sexes, with a mean of 2.75% for women and 2.87% for men. Apart from apparent sex differences in prevalence rates of STDR, increasing trends were observed among younger patients (aged <60 years).

**CONCLUSIONS AND RELEVANCE** We found considerable variation in the incidence trends between sexes. Our findings provide evidence that the incident cases of STDR have increased among patients with type 2 diabetes, but the overall prevalence of STDR is in a declining trend in Taiwan, suggesting that decreased mortality rate, better diabetes management, and early detection of treatable DR might contribute to the prevalence patterns.
According to a report from the World Health Organization, in 2002, approximately 161 million people worldwide were visually impaired, and approximately 23% of these individuals were blind. The World Health Organization also predicted that the global prevalence of diabetes mellitus in adults will reach 6.4% by 2030, representing a 39% rise from 2000 to 2030. This increase in diabetes has been attributed mainly to a rise in new cases of type 2 diabetes mellitus, the population aging, and improved survival. However, these projections were based on the assumption that obesity rates would remain constant; therefore, the prevalence is likely to be underestimated.

The incidence of diabetic retinopathy (DR) has declined in reports from many countries during the past 30 years. However, there are considerable variations in DR prevalence estimates, with rates of 17.6% in India, 33.2% in the United States, and 43% in rural China, owing to the differing study populations, periods, and methodology. Worldwide reports have shown that sight-threatening DR (STDR), including proliferative DR and diabetic macular edema, is prevalent in both type 1 and type 2 diabetes. Reported estimates for STDR prevalence also range widely, from 1.2% to 32.2%.

Differences in the prevalence of DR may be attributed to differing levels of susceptibility and risk factors among ethnic groups. Socioeconomic factors including the level and access to diabetes care, as well as genetic susceptibility, are likely to affect the differences in rate and severity of DR among ethnic groups.

In Taiwan, the prevalence of DR was 35%, with 2.2% of proliferative DR in the early 1990s. Results of a cross-sectional study using the Taiwan National Health Insurance (NHI) database in 2008 indicated that 25% of patients with diabetes also had DR, with rates of 24.4% for nonproliferative and 0.7% for proliferative DR. Furthermore, the prevalence of type 2 diabetes has been increasing for both men and women in Taiwan, particularly among those younger than 40 years and 80 years or older. Although the incidence was decreasing in people aged 40 years or older, there was a higher incidence of type 2 diabetes in younger men (aged 20-40 years).

Given the significance of the rising and changing prevalence of diabetes and associated DR, as well as the fact that visual loss due to DR may be preventable either through photocoagulation treatment or better control of glycemia, blood pressure, and serum lipid levels, there is a need for precise up-to-date estimates of the prevalence and incidence of STDR to provide optimal strategies for clinical management. The present study was conducted using the claims data derived from the NHI database. We aimed to determine the prevalence and incidence of STDR from January 1, 2005, to December 31, 2011, in Taiwan; describe the contribution of changes to the trends during these years; and examine whether sex differences existed.

**Methods**

**Data Source**
A universal compulsory NHI program was launched by the Taiwanese government in 1995. By the end of 2007, it provided reimbursement coverage for approximately 99% of the total population of 23 million in Taiwan and has maintained that level since. The large computerized administrative and claims data sets derived from this program have been maintained as the National Health Research Institute Database and made available to investigators for research purposes after individual health information was de-identified.

The Longitudinal Health Insurance Database 2005, a representative subset of the National Health Research Institute Database, comprises the complete original claims data of 1,000,000 individuals randomly sampled from the Registry of the National Health Research Institute Database. The database reported no significant differences in age, sex, or health care costs between the sample groups and all enrollees. In the present study, inpatient and outpatient claims between 2005 and 2011 were used. This study was approved by the investigational review board of National Taiwan University Hospital and conducted in accordance with the tenants of the Declaration of Helsinki.

**Definition of STDR**

Sight-threatening DR included clinically significant macular edema and/or severe nonproliferative DR according to the classification in the Early Treatment Diabetic Retinopathy Study, or clinically significant macular edema and/or proliferative DR. The diagnostic criteria for diabetic macular edema included (1) central retinal thickness of 300 μm or more, (2) hemoglobin A1c of less than 10% (to convert to proportion of total hemoglobin, multiply by 0.01) in the most recent 3 months, and (3) clinical data of fluorescein angioplasty, optical coherence tomography, best-corrected visual acuity, and color fundus photography. All patients with STDR received photocoagulation according to the guidelines from the Early Treatment Diabetic Retinopathy Study and the Diabetic Retinopathy Study.

**Case Selection**

Patients with type 2 diabetes were identified if they had at least 1 hospital admission with the diagnostic code of diabetes mellitus (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 250) or 3 or more outpatient visits associated with diabetes. Patients with STDR were selected according to the first encounter of any of the following NHI procedure codes: panretinal photocoagulation (60003C and 60004C), macular photocoagulation (60001C and 60002C), and pars plana vitrectomy (86206B and 86207B) among patients with diabetes having at least 3 outpatient visits each year between 2005 and 2011. The first day of STDR identification was considered the index date. We excluded individuals with the same procedure codes during 2002-2004, younger than 20 or older than 100 years, with type 1 diabetes (ICD-9-CM codes 250.1, 250.x1, and 250.x3), with sex unidentified, and with a gestational diabetes diagnostic code (ICD-9-CM code 648.8) 270 days before delivery or during 2005-2011. To reduce confounding, patients with diagnoses of retinal detachments and defects (ICD-9-CM code 361), other proliferative retinopathy (ICD-9-CM code 362.2), and vascular occlusion (ICD-9-CM code 362.3) during 2005-2011 were excluded.
Ascertainment of Incident and Prevalent Cases

An incident case was ascertained after confirming that the patient had no previous claim for STDR in the database for a minimum of 3 years before their diagnosis was first noted. The hospital admission date or the first date of an outpatient visit that met the definition for STDR, whichever came first, was used as the date of the incident event. Patients remained prevalent cases regardless of whether they had diagnosis claims relating to STDR in subsequent follow-up as long as they remained in the data set.

Prevalence and Incidence

Sex- and age-stratified analyses were performed for the prevalence and incidence rates of STDR. The rates were age-adjusted to the Taiwanese diabetes population using the age strata 20 to 39 years, 40 to 59 years, 60 to 79 years, and ≥80 years.

Statistical Analysis

Statistical analysis was undertaken using SAS, version 9.3 (SAS Institute Inc). The crude prevalence of STDR was estimated by age and sex. Annual incidence and prevalence rates of STDR were calculated by dividing the number of patients with confirmed incident STDR and adjusted to the midyear Taiwanese population for each year. The 95% CIs were calculated assuming a Poisson distribution of cases. The reported age- and sex-specific annual rates were stratified into 4 age groups (20-39 years, 40-59 years, 60-79 years, and ≥80 years). The equation \( \frac{[\text{number of new cases during study period}] \times 1000 \text{ for each of these specific age groups was used to calculate for 1000 person-years}}{\text{time each person is observed, totaled for all persons}} \) was used to calculate age-adjusted rates:

\[
aR = \sum w_i \cdot r_i,
\]

where \( aR \) is the age-adjusted rate, \( w_i \) is the age weight provided by the study population, and \( r_i \) is the age-specific rate in the study population. Temporal trends in age-adjusted rates were examined using Poisson regression analysis, with calendar year as an independent variable. Significance levels were tested using Wald \( \chi^2 \) tests. The temporal trends were analyzed by contrasting rates in earlier vs later years, with the magnitude of the change expressed using rate ratios (RRs) and 95% CIs. An RR less than 1 indicated a decreasing trend, RR equaling 1 indicated no change, and RR greater than 1 represented an increasing trend. If the 95% CIs of rate did not overlap, the difference between the trends was considered statistically significant. Graphs stratified by sex and age were presented to illustrate the yearly trends.

Results

Data on 63,582 patients with diabetes fulfilling the inclusion criteria during 2005-2011 were analyzed. A significant increasing trend of the diabetic population was observed (Supplement [eTable 1]) by a mean of 10.1% annually. Our findings indicated that the population with type 2 diabetes mellitus grew by 72% for women and 82% for men. However, the year-on-year increasing rates have been slowing from 2006 to 2011: 17.5%, 12.4%, 9.7%, 8.7%, 7.3%, and 4.9% (data not shown).

The 29,26 patients with type 2 diabetes (1,501 women and 14,25 men) had further diagnostic claims confirming STDR, giving an annual mean of 418 new cases (Supplement [eTable 1]). The age-specific incidence rates of STDR revealed that the greatest rise in patients with newly diagnosed diabetes occurred in those aged 40 to 59 years for both sexes. The increases in incident cases of STDR were in line with the increased number of patients with diabetes during the study period. However, sex differences were observed in the temporal trends in the total annual age-adjusted incidence rates per 1000 person-years (Figure 1). During the study span, the incidence rate significantly declined by 44.6%, from 10.84 (95% CI, 10.69%–10.99%) in 2005 to 6.00 (95% CI, 5.86%–6.14%) per 1000 person-years in 2011, for women (\( P < .001 \)), but significantly increased by 47.3%, from 14.86 in 2005 to 21.89 in 2011, for men (\( P < .001 \)).

Figure 2 illustrates the trends in annual incidence rates per 1000 person-years of STDR among different age groups (20-39 years, 40-59 years, 60-79 years, and ≥80 years). For women, the trend in the group aged 20 to 39 years remained stable; however, the incidence rates of all other age groups decreased, and greater reduction occurred in the group aged 60 to 79 years. In contrast, we observed significant upward trends in men aged 20 to 39 years, 40 to 59 years, and 80 years or older; those aged 60 to 79 years had a relatively slow increasing trend. The most significant differences in the annual incidence rates of STDR between sexes were in the groups aged 40 to 59 and 80 years or older. A substantial decreasing trend was observed for women aged 40 to 59 years, from 14.77 in 2005 to 10.81 in 2011 (Figure 2B); however, a dramatic increasing trend was found for men in the same age range, with incidence rates increasing from 15.33 in 2005 to 26.16 in 2011. Despite a few incident cases in the groups aged 80 years or older, similar patterns but greater differences appeared between the sexes (Figure 2D).

The numbers of patients with STDR increased steadily during 2005-2011 (Supplement [eTable 2]), by 98% for women (from 575 to 1142) and by 72% (from 668 to 1149) for men. The age-adjusted prevalence rates of STDR fluctuated between 2.34% in 2005 and 2.53% in 2011 for women and between 2.87% in 2005 and 2.53% in 2011 for men (Figure 1B). Overall, changes in trend slightly but significantly decreased for both sexes (both \( P < .001 \)). To explore further, the data were stratified by age. For women, upward trends in the prevalence rates were observed in the younger age groups. The prevalence of STDR increased from 3.17 to 5.38 in the group aged 20 to 39 years and from 4.17 to 6.03 in those aged 40 to 59 years. However, the increases were largely offset by the downward prevalence in
those aged 60 to 79 years (Figure 3A), which has undergone significant reduction from 4.55 in 2007 to 2.25 in 2011.

The prevalence rates of STDR in men were persistently greater in younger age groups (20-39 and 40-59 years) during the study years (Figure 3B); the fluctuation pattern and magnitudes were different from those in women. The prevalence of STDR increased from 3.70 in 2005 to 4.16 in 2011 for the group of men aged 20 to 39 years and decreased from 5.01 to 4.84 in 2011 for the group aged 40 to 59 years. The decreasing trend in the group aged 60 to 79 years was significant, from 3.85 in 2006 to 2.36 in 2011, which contributed to an overall slightly decreasing trend in the prevalence rate.

Discussion

This study provides evidence that the number of incident cases of STDR increased in line with the growing diabetic population. The age-adjusted incidence rates of men were in an increasing trend in contrast with women showing a declining trend. Overall, the decreasing trends in age-adjusted prevalence of STDR for both sexes may also imply a decreased mortality rate of people in Taiwan. The increasing patterns of incidence rates suggested that men generally had a shorter duration of diagnosed STDR.

Our findings also support previous studies demonstrating that the age-standardized prevalence of type 2 diabetes mellitus increased more for men. A recent study reported the global estimates of age-standardized prevalence of DR and severe stages of DR on the basis of data from 35 studies (1980-2008) including more than 20,000 individuals aged 20 to 79 years across different ethnic groups. The results indicated that the overall prevalence of STDR in patients with diabetes (types 1 and 2) was 10.2% and the age-standardized prevalence was 11.7%; no significant sex difference was observed. The age-standardized prevalence of STDR was 6.15% in Chinese and 5.25% in Asians (combined). Compared with these data, our findings from the present study revealed that the prevalence of STDR was lower in the population with type 2 diabetes in Taiwan, with rates of 2.75% for women and 2.87% for men. Even after adding the 7.5% of patients (n = 5449) with type 1 diabetes excluded in the present study, the overall rate would be expected to remain lower.

This decrease, in line with declining rates of diabetes in the Western world observed during the past 3 decades, is probably attributable to earlier detection of diabetes and improved control of DR risk factors (hyperglycemia, hypertension, and dyslipidemia) as well as earlier identification and treatment of DR. Another possible factor is the increasing use of more aggressive approaches for DR, such as intraocular corticosteroids, photocoagulation, and antivascular endothelial growth factor therapy. Although the practice guideline for diabetic care has been established to assess and accredit the institutional implementation of diabetes care and set up shared care networks in Taiwan, the percentage of patients with diabetes who ever received eye care services for examinations was the lowest (only 16.8%) compared with the use of other health care services.

Our findings of increasing incidence rates of STDR in men aged 40 to 59 years and 80 years or older are of concern. Men aged 40 to 59 years are in a critical stage of career development and are not likely to seek eye care until visual impairment worsens. Sex-based differences in disease perception and eye care access can be affected by factors that lie beyond the scope of the present study. However, previous observations have shown that less-educated individuals, younger vs older adults, and men vs women have lower rates of eye care, and among patients with diabetes, men have a lower rate of health care use than women. Factors that may contribute to the low prevalence rates (in line with few incident cases) in the oldest (≥80 years) age group include limited access to ophthalmic facilities as a result of comorbidities or impaired mobility, absence of family support, negligence or inattention by care providers, and a less aggressive treatment-seeking attitude for eye care. These disparities should be addressed by promoting awareness of the
problem to provide appropriate diagnostic eye care. Furthermore, our findings indicate that incidence rates of STDR grew most rapidly in the population younger than 60 years. Considering the fact that lifetime health burden and cost will be greater for these people and screening for STDR is cost-effective, the importance of prevention strategies among patients with diabetes should be highlighted to adequately allocate health care resources to reduce the burden of diabetes and consequent STDR.

The strengths of our study relate to the use of a large, comprehensive, population-based data source. The results of our 7-year analysis of new cases of STDR were ascertained by using a national data set with high accuracy. The comprehension of health care needs for patients and resource allocation planning for policy makers may be enabled by the reliable estimates of STDR rates in the present study. Limitations of this study might cause inaccuracy in estimation. First, although type 2 diabetes accounted for only 3% of identified cases of diabetes, the algorithm identified only patients with type 2 diabetes, which underestimated the true prevalence of diabetes and associated STDR. Second, several off-label treatment modalities, such as antivascular endothelial growth factor therapy, are currently in clinical use for various aspects of DR. Information on patients who received such treatment and benefitted from slowed development and progression of DR was not available because records of procedures and treatments not covered by NHI are not included in the database. Third, data on the prevalence of and reasons for refusal of conventional surgical treatments (eg, fear of adverse effects or choice of alternative therapies) were unavailable, although these approaches are included in the NHI program. Fourth, because clinical data relating to patients with clinically significant macular edema (eg, fluorescein angiography, optical coherence tomography, or best-corrected visual acuity or fundus photograph) were unavailable in the database, we were unable to identify the effect of misclassification on the estimates of prevalence and incidence rates.

The rates are presented as per 1000 person-years and stratified by sex and the age groups 20 to 39 years (A), 40 to 59 years (B), 60 to 79 years (C), and 80 years or older (D) for patients included in Longitudinal Health Insurance Database 2005 data during 2005-2011 in Taiwan.
### Conclusions

The declining trends in overall age-adjusted prevalence rates of STDR might be attributable to better diabetes management, early detection of treatable DR, and decreased mortality rates of the diabetic population. Significantly distinct differences in the incidence rates between sexes might indicate different eye care behaviors. Preventive strategies for modifiable risk factors are important for reducing the prevalence of diabetes and consequent STDR.

### References


