Int Ophthalmol (2019) 39:2731–2739
https://doi.org/10.1007/s10792-019-01117-5

ORIGINAL PAPER

Population-based study on the epidemiology of dry eye disease and its association with presbyopia and other risk factors

Elsa L. C. Mai · Chih-cheng Lin · Iebin Lian · Renhao Liao · Meiling Chen · Chaokai Chang

Received: 6 May 2018 / Accepted: 22 May 2019 / Published online: 29 July 2019

Abstract

Background To investigate the incidence and prevalence of dry eye disease (DED) in Taiwan and to explore its potential risk factors.

Methods Population-based longitudinal data from 2000 to 2013 based on Taiwan National Health Insurance Research Database were used in this study. To explore potential risks factor of interest, patients who had DED diagnosis before the exposure were excluded. Each patient from the exposure and his/her matched non-exposure controls were followed until either the diagnosis of DED or censorship. Kaplan–Meier method was used to compare the hazard of DED between cohorts. Stratified Cox proportional hazard models were applied to estimate the adjusted effect.

Results The age-adjusted prevalence for men and women were 6.81% and 16.16%, respectively. The age–gender rate of the same period was 549 per 10^5 person-years. The propensity-adjusted hazard ratio of DED is 1.816 for the presbyopia versus non-presbyopia (with 95% CI = [1.737, 1.897] with p value < 0.0001).

Conclusions The DED incidence for women peaked at age 50–74, while that for men peaked at age $\geqq 75$. The incidence in young people seems stable both for women and for men. While exploring the factors of DED, there is a significant association between presbyopia and DED even after matching age/gender and comorbidity conditions. Further clinical studies are needed to justify whether the corrective refractive

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10792-019-01117-5) contains supplementary material, which is available to authorized users.

E. L. C. Mai
Far Eastern Memorial Hospital, Taipei, Taiwan, ROC
e-mail: elsamark@yahoo.com

C. Lin · M. Chen
Yuanpei University of Medical Technology, Hsinchu, Taiwan, ROC
e-mail: icc@mail.ypu.edu.tw

M. Chen
e-mail: cmloph@yahoo.com

I. Lian · R. Liao
National Changhua University of Education, Changhua, Taiwan, ROC
e-mail: maiblian@cc.ncue.edu.tw

R. Liao
e-mail: hgl290512@hotmail.com.tw

C. Chang (✉)
Taipei Nobel Eye Clinic, Taipei, Taiwan, ROC
e-mail: chaokai@nobelgroup.com.tw

treatment such as presbyopic glasses to treat the frequently hyperopic status of these patients could be beneficial to both dry eye and presbyopic condition.

Keywords Presbyopia · Dry eye disease · Cox regression · Propensity score

Abbreviations

DED	Dry eye disease
DM	Diabetes mellitus
LASIK	Laser-assisted in situ keratomileusis
MGD	Meibomian gland dysfunction
NHIRD	National Health Insurance Research Database
OSDI	Ocular Surface Disease Index
PK	Penetrating keratoplasty
PS	Propensity score
SLE	Systemic lupus erythematosus
VDT	Video display terminal

Background

Dry eye disease (DED) is a multifactorial disease of the ocular surface caused by an inadequate quantity or quality of the tears [1]. The estimates of DED prevalence ranged widely among the past literature [2], which depends on the locations and the ascertained criterion used. A study in USA found the age-adjusted prevalence of DED among women was 7.8% [3] and that for men was 4.34% [4]. A community-based study during 1999 and 2000 on the elderly in Taiwan estimated it as 5.4% (25/459) among those who visit eye clinics [5], and a population-based study estimates the prevalence before 2008 to be 4.87% [6].

Aside from age and gender, numerous risk factors for DED had been reported [7–11], including acne/seborrheic dermatitis, allergic eye, allergic rhinitis, ankylosis spondylosis, anxiety/depression, arrhythmia, asthma, autoimmune disease, cataract, contraceptive pills, cornea edema due to wearing of CL, diabetes mellitus (DM), fibromyalgia, follow-up post-operation on ocular surface (LASIK), glaucoma medication, hyper-/hypothyroidism, insomnia, keratoconjunctivitis sicca, menopausal, meibomian gland dysfunction (MGD), ovarian failure, post-chemotherapy, postmenopausal status, post-cataract operation, post-PK (corneal transplant), post-radiotherapy, rheumatoid arthritis, secondary hypertension, systemic lupus erythematosus (SLE), subconjunctival hemorrhage, urticarial and presbyopia. These risk factors may be associated with each other; therefore, the confounding effects have to be carefully controlled or adjusted while analyzing the data.

The most stringent way to adjust the confounding effects is by matching. However, when the confounders are numerous, matching them all is not plausible even with large data set. An efficient alternative in epidemiological study is by matching a propensity score (PS) [12]. Ideally, PS summarizes the necessary information of the confounders for balancing their distribution between exposure and non-exposure, and matching on PS alone is expected to have similar effect as matching on all the confounders [13]. The purposes of this 14-year longitudinal study were aimed to investigate the incidence and prevalence of DED and to explore its potential risk factors by propensity adjustment.

Methods

Population-based longitudinal data from Taiwan National Health Insurance Research Database (NHIRD) of 1 million citizens were used for the two separate analyses in this study. (1) epidemiology of DED: We calculated the yearly prevalence and incidence rate of DED based on the 1 million samples (see Figs. 1, 2) and (2) risk factor association exploration. Taking presbyopia as example, we selected the presbyopia and non-presbyopia cohorts (Tables 1, 2) from the 1 million samples and compare their DED status as the end point via survival analysis.

In (1), the inclusion criteria for DED are the patients who aged above 20 with diagnosis of DED for at least three times during period 2000–2013. By dividing into three age-groups: 21–49, 50–74 and $\geqq$ 75, the corresponding prevalence rate with respect to gender and year was calculated as the ratio of the DED case number to the age–gender-specific population at risk (Fig. 1). On the other hand, the yearly incidence rate is the ratio of the number of new DED cases to that of each specific age–gender population at risk (Fig. 2). The exact rates are provided in Supplementary Table. In (2), the inclusion criteria for presbyopia cohort are (a) patients aged above 20 with diagnosis of presbyopia during period 2000–2013 and (b) without DED

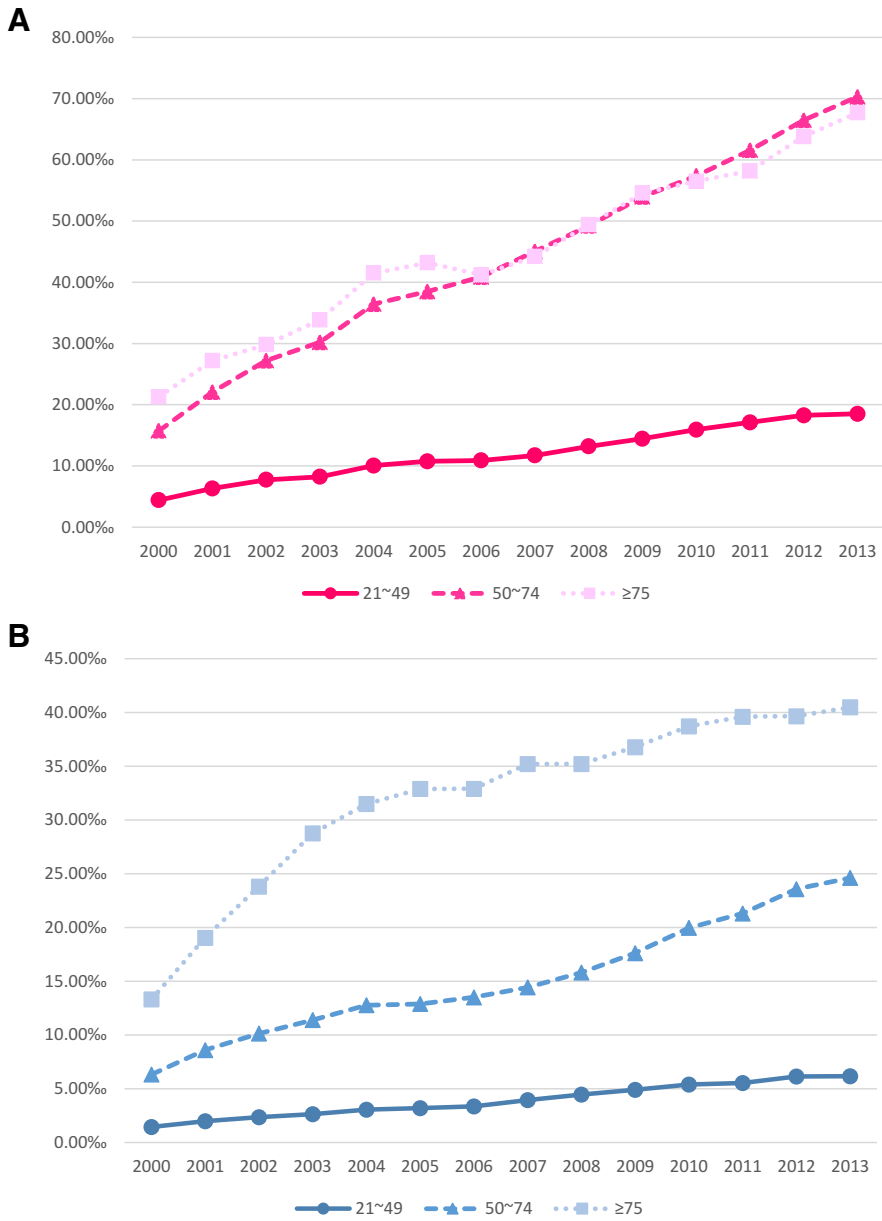


Fig. 1 Trend of age-specific DED prevalence for women (**a**) and men (**b**)

diagnosis before presbyopia in NHIRD. The corresponding non-presbyopia cohort was selected using double-stage matching scheme which was described below. Beside presbyopia, age and gender, 37 potential risk factors for DED mentioned in "Appendix" were taken into account. Other risk factors were not considered due to ambiguous ascertained criteria in NHIRD.

To controlling these potential confounders, we applied a double-stage matching scheme to minimize the confounding effect: (1) For each patient, we used a 1-to-4 age–gender matching to randomly select the non-presbyopia cohort from the same data bank. (2) Propensity score (PS) was estimated from the potential confounders, and the presbyopia and non-presbyopia cohorts were further matched by using PS. Each presbyopia patient and his/her controls were followed from the first presbyopia diagnosis until either the diagnosis of DED or censorship. Due to the matching scheme, stratified Cox proportional hazard models

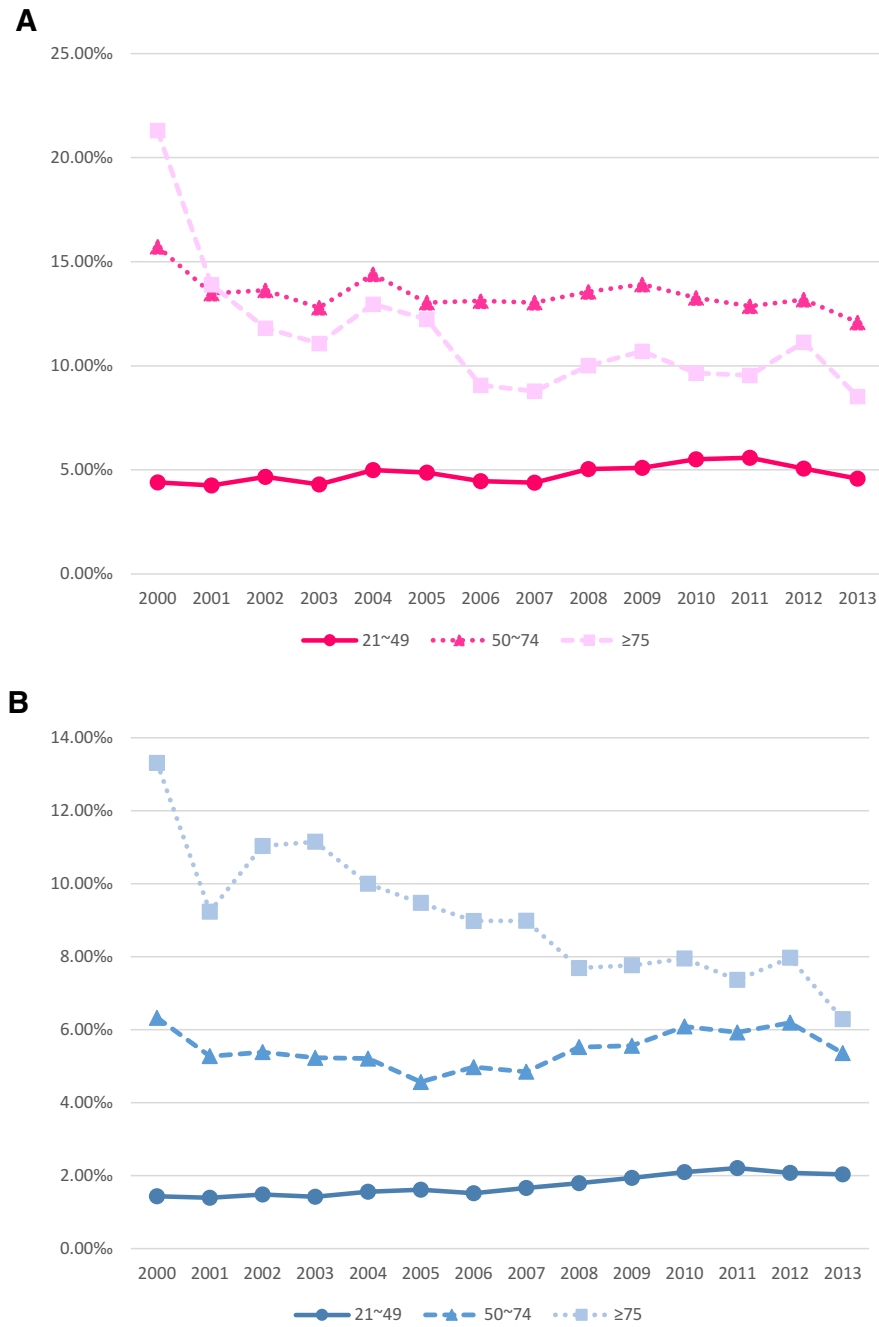


Fig. 2 Trend of age-specific DED incidence rate for woman (**a**) and man (**b**)

instead of conventional Cox model were applied to estimate the adjusted effect of presbyopia on DED. Kaplan–Meier method was used to compare the hazard of DED between cohorts.

In this study, the ascertained criteria of DED are (1) one DED diagnosis (ICD-9 code 375.15) with Schirmer test or (2) at least three times of DED diagnoses from eye clinic. For other risk factors, such as diabetes, three clinical visits with DM diagnosis code within 1 year are needed.

The statistical analysis and matching scheme were conducted by using the of SAS 9.3 macros. P-values

Table 1 Comparison of clinical characteristic distributions between cohorts before propensity matching: 31,542 presbyopia cases versus 181,832 non-presbyopia

	Presbyopia		Non-presbyopia		T^*
Age	52.32	(52.26, 52.37)	52.42	(52.29, 52.56)	0.009
	n	Proportion	*n*	Proportion	
Gender	12,892	40.87%	75,727	41.65%	0.016
Acne/seborrheic dermatitis	7325	23.22%	28,239	15.53%	0.195
Allergic rhinitis	15,481	49.08%	64,101	35.26%	0.283
Allergic eye Dx	12,155	38.53%	36,854	20.27%	0.409
Ankylosis spondylosis	681	2.16%	2475	1.36%	0.061
Anxiety/depression	13,788	43.71%	54,710	30.09%	0.285
Arrhythmia	7240	22.95%	30,421	16.73%	0.156
Asthma	7100	22.51%	32,342	17.79%	0.118
Autoimmune	334	1.06%	1102	0.61%	0.050
Cataract	13,397	42.47%	48,209	26.52%	0.340
Contraceptive pills	3	0.01%	7	0.00%	0.007
Cornea edema due to wearing of CL	27	0.09%	194	0.11%	0.007
DM	9881	31.32%	45,902	25.25%	0.135
Fibromyalgia	1473	4.67%	4793	2.64%	0.109
Follow-up post-op	3128	9.92%	13,653	7.51%	0.085
Glaucoma medication	3894	12.34%	11,546	6.35%	0.207
Hives	13,088	41.49%	64,152	35.29%	0.128
HRT	9	0.03%	27	0.01%	0.009
Hyper-/hypothyroidism	1545	4.90%	6293	3.46%	0.072
Hyperlipidemia	15,378	48.75%	67,263	37.00%	0.239
Hypertension	16,249	51.51%	86,530	47.59%	0.078
Insomnia	16,957	53.76%	75,450	41.50%	0.247
Keratoconjunctivitis sicca	1378	4.37%	2490	1.37%	0.180
Menopausal	9951	31.55%	41,976	23.09%	0.191
MGD	5064	16.05%	14,248	7.84%	0.255
Hyperlipidemia	15,370	48.73%	67,223	36.98%	0.239
Ovarian failure	868	2.75%	3271	1.80%	0.064
Paresis of accommodation	360	1.14%	637	0.35%	0.092
Post-chemotherapy	189	0.60%	1153	0.63%	0.004
Postmenopausal	17	0.05%	52	0.03%	0.012
Post-cataract operation	3381	10.72%	12,770	7.02%	0.130
Post-PK	11	0.03%	67	0.04%	0.001
Post-radiotherapy	6021	19.09%	23,396	12.87%	0.008
Rheumatoid arthritis	121	0.38%	786	0.43%	0.095
Secondary hypertension	2674	8.48%	10,939	6.02%	0.004
Sicca syndrome/sjogren syndrome	329	1.04%	1814	1.00%	0.158
Systemic lupus erythematosus	1832	5.81%	4813	2.65%	0.043
Subconjunctival hemorrhage	267	0.85%	901	0.50%	0.170

T^*: standardized difference scores, computed as the standardized difference between presbyopia and non-presbyopia cohort in means or proportion. Being greater than 0.1 is considered to be unbalance between cohorts as rule of thumb

from regressions were considered significant compared with level 0.05, and means or proportion between two cohorts is considered to be unbalance if the standardized difference scores T^* is greater than 0.1. The research was approved by the Institutional Review Board of National Changhua University of

Table 2 After further propensity matching, 23,354 presbyopia cases were matched with 93,403 non-presbyopia, with similar distributions of clinical characteristic

	Presbyopia		Non-presbyopia		*T**
Age	51.83	Year old	52.06	Year old	0.019
	n	Proportion	*n*	Proportion	
Gender	9670	41.40%	38,871	41.61%	0.004
Acne/seborrheic dermatitis	4455	19.08%	18,187	19.47%	0.010
Allergic rhinitis	9888	42.34%	40,315	43.15%	0.017
Allergic eye Dx	6432	27.54%	25,269	27.05%	0.011
Ankylosis spondylosis	390	1.67%	1539	1.65%	0.002
Anxiety/depression	8459	36.22%	34,775	37.22%	0.021
Arrhythmia	4555	19.50%	18,158	19.44%	0.002
Asthma	4610	19.74%	18,759	20.08%	0.009
Autoimmune	182	0.78%	678	0.73%	0.006
Cataract	8027	34.37%	31,745	33.98%	0.008
Contraceptive pills	0	0.00%	3	0.00%	0.008
Cornea edema due to wearing of CL	18	0.08%	91	0.10%	0.007
DM	6635	28.41%	26,685	28.56%	0.003
Fibromyalgia	781	3.34%	3112	3.33%	0.001
Follow-up post-op	1976	8.46%	7996	8.56%	0.004
Glaucoma medication	2066	8.85%	7495	8.02%	0.030
Hives	8966	38.39%	36,970	39.57%	0.024
HRT	2	0.01%	17	0.02%	0.008
Hyper-/hypothyroidism	927	3.97%	3824	4.09%	0.006
Hyperlipidemia	10,029	42.94%	40,640	43.50%	0.011
Hypertension	11,552	49.46%	45,947	49.18%	0.006
Insomnia	11,183	47.88%	45,546	48.75%	0.017
Keratoconjunctivitis sicca, not specified as Sjogren	465	1.99%	1490	1.59%	0.030
Menopausal	6414	27.46%	25,409	27.20%	0.006
MGD	2487	10.65%	9285	9.94%	0.023
Obesity, hyperlipidemia	10,023	42.92%	40,622	43.48%	0.011
Ovarian failure	512	2.19%	2100	2.25%	0.004
Paresis of accommodation	117	0.50%	406	0.43%	0.010
Post-chemotherapy	144	0.62%	559	0.60%	0.002
Postmenopausal status	7	0.03%	39	0.04%	0.006
Post-cataract operation	2118	9.07%	8098	8.67%	0.014
Post-PK	10	0.04%	38	0.04%	0.001
Post-radiotherapy	3701	15.85%	14,603	15.63%	0.006
Rheumatoid arthritis	95	0.41%	345	0.37%	0.006
Secondary hypertension	1600	6.85%	6377	6.83%	0.001
Sicca syndrome/sjogren syndrome	233	1.00%	938	1.00%	0.001
Systemic lupus erythematosus	870	3.73%	3072	3.29%	0.024
Subconjunctival hemorrhage	149	0.64%	555	0.59%	0.006

*After propensity matching, most of the *T* are mostly reduced under 0.1

Education (No. NCUEREC-103-211) and carried out in compliance with the Declaration of Helsinki.

Results

Figure 1 shows the secular trend of age-specific DED prevalence for women (a) and men (b). It is noted that women at age-group 50–74 and ≧ 75 have similar prevalence, while that in men strictly increases with age. Prevalence of all age-groups increased along with time. The average age-adjusted prevalence rate for men and women is 6.81% and 16.16%, respectively, during 2000–2013.

Figure 2a, b shows the secular trend of age-specific DED incidence rate for women and men, respectively. The incidence rate peaked at age 50–74 and was twice more common in women than in men for all three age strata. For female, the trend of incidences remains steady for all age; however, for male, the middle age-group remains steady, while the elderly (≧ 70) decrease gradually. The incidence in young people seems stable both for women and for men.

Tables 1 and 2 compare the distributions of age, gender and 37 potential risk factors between the presbyopia cohort and the non-presbyopia cohort. Table 1 is for the sample before propensity matching. We used standardized difference scores (T) to manifest the unbalance between cohorts. It can be seen that matching the age and gender only could not really balance the distributions of 37 potential confounders with $T > 0.1$. However, after further propensity matching (Table 2), the distributions of confounders between presbyopia and non-presbyopia cohort are much more balanced.

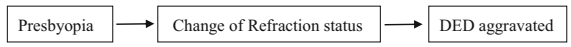
Discussion

Both the DED prevalence and incidence in women are twice higher than those in men. For women, the trend of incidences remains steady for all age; however, for male, the younger group (20–44) had increasing incidence. Although elderly people (≧ 50 years) have higher prevalence than younger people, women of 50–74 age-group bypass the 75-or-more age-group to have higher incidence rate in 2001.

While examining the risk factors for DED, we found a strong association between presbyopia and DED, which coincides with our clinical experience. After carefully controlling the confounders including age, gender and 37 comorbidities by propensity score matching, the PS-adjusted hazard rate ratio for DED obtained from stratified Cox proportional hazard models is 1.816 with 95% CI = [1.737, 1.897] and p value < 0.0001, which indicating that presbyopia patients have 1.8-fold higher risk of DED than the non-presbyopia.

The Kaplan–Meier plots in Fig. 3 graphically demonstrate the difference of free-to-DED rates between the presbyopia and non-presbyopia cohorts. Five years after the clinical visit, the presbyopia cohort has 8.8% diagnosed as new DED cases, while that for the matched non-presbyopia is only 4.8%. And 10 years after the clinical visit, the rates of new DED cases are 15.4% and 10.3% for the respective cohorts.

According to clinical experience of the authors, many DED patients show great improvement of signs and symptoms of DED after full corrective hyperopic glasses. Glasses may have some protective effect and might be a “shield” and avoid brief vaporization of the lacrimal film. Another explanation is that presbyopic refractive error may aggravate DED, inducing symptoms such as eye pain, grittiness, asthenopia, cornea staining. A recent study in Japan by Kaido et al. [14] found that tear film instability dry eye is associated with accommodative microfluctuation, through an observational study in human patient subjects in their clinic. This raises the following hypothesis:



In neuropathic pain terminology, hyperalgesia is an increased response to a stressful/noxious stimulus, whereas allodynia is a painful response to a normally innocuous stimulus. Dry eye with up-regulated inflammatory cytokine in the eye has pre-sensitized the nociceptor nerve fiber in the cornea and orbit; therefore, the normally innocuous effort of accommodation and ciliary muscle contraction produce intolerable retro-orbital eye pain, driving the patients to seek medical attention. Therefore, treating the condition that leads to the pre-sensitization would be helpful to the DED condition, such as in VDT users, computer glass or fully corrected hyperopia glasses. These should be an option of treatment recommendation to

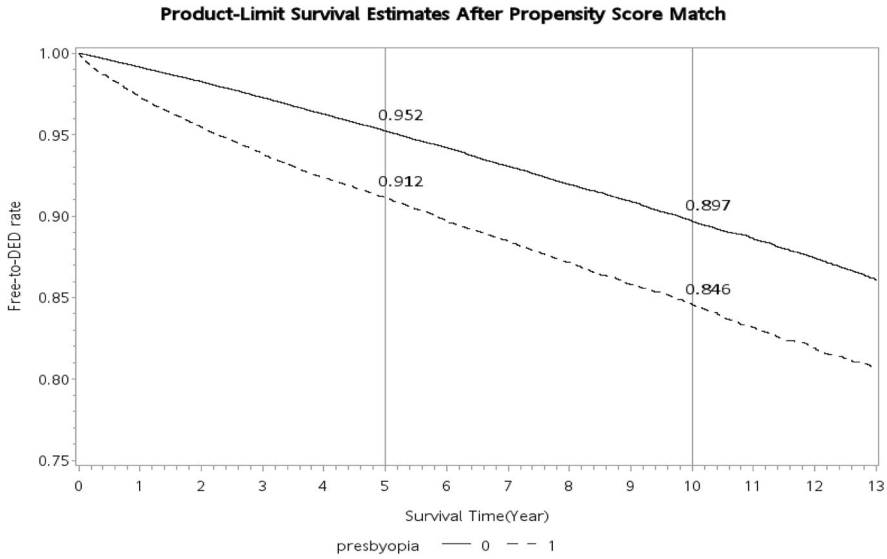


Fig. 3 Kaplan–Meier plots: comparing the free-to-DED rates between the presbyopia and non-presbyopia cohorts. Five years after the clinical visit, the presbyopia cohort has 8.8% diagnosed as new DED cases, while that for the matched non-presbyopia is only 4.8%

dry eye patient. Further clinical studies are needed to justify whether the corrective refractive treatment such as presbyopic glasses to treat the frequently hyperopic status of these patients could be beneficial to both dry eye and presbyopic condition.

Conclusions

The DED incidence for women peaked at age 50–74, while that for men peaked at age $\geqq$ 75. Both the DED prevalence and incidence in women are twice higher than those in men. There is strong association between presbyopia and DED after controlling age, gender and comorbidity conditions. To understand more about the above hypothesis of the causal relationship of eye pain in dry eye patients with presbyopic refractive error, we suggest further clinical follow-up study to be conduct on dry eye patients with aggressive treatment of refractive error such as use of full corrective glasses.

In this study, we also found that the two-stage propensity score matching scheme we adopted is an efficient approach to control the confounding effect in ophthalmological studies, especially when the potential confounders are numerous.

Acknowledgements The authors would like to thank Taiwan National Health Research Institute for the approval of using the National Health Insurance Research Data.

Authors' contribution EM conceived the study and drafted the manuscript, CL participated in the design of the study and coordination, IL coordinated the statistical analysis and interpreted the results, RL and CM carried out the data management and analysis, and CC carried out the epidemiological studies and revised the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Availability of data and materials Data used in analysis are available upon request to corresponding author.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All personal identification numbers in NHIRD used in this study were encrypted by conversion into scrambled numbers before data processing. Because the database used consists of de-identified secondary data released for research purposes, this study was exempt from full review by the Institutional Review Board National Changhua University of Education (No. NCUEREC-103-211).

Appendix

See Table 3.

Table 3 ICD-9 codes for potential confounders (in alphabetic order)

Acne/seborrheic dermatitis: 706.1–706.9	Insomnia: 307.4, 780.5, 780.59, 780.52
Allergic eye: 372.14	Keratoconjunctivitis sicca, not specified as Sjogren: 370.33
Allergic rhinitis: 477.8, 477.9	LASIK, cataract: V67.00/V67.09
Ankylosis spondylosis: 720	Menopausal: 627.0–627.9
Anxiety/depression: 300, 300.02, 300.09	MGD: 373
Arrhythmia: 427.0–427.9	Ovarian failure: 256.1–256.9
Asthma: 493.00–493.92	Paresis of accommodation: 367.51
Autoimmune: 279.4	Post-chemotherapy: V58.1/v67.2
Cataract: 366.00–366.9	Postmenopausal status: V49.81
Contraceptive pills: V25.41	Post-cataract op (lens replaces by other means): V43.1
Cornea edema due to wearing of contact lenses: 371.24	Post-PK (corneal transplant): V42.5
diabetes mellitus (DM): 250.00–250.02	Post-radiotherapy: V58.0
Fibromyalgia: 729	Presbyopia: 367.4
Follow-up post-op: V67.00/V67.09	Rheumatoid arthritis (RA): 714.0–714.9
Glaucoma medication: 365.00–365.9	Secondary hypertension: 405.99
Hormone replacement therapy (HRT): V07.4	Sicca syndrome: 710.2
Hyper-/hypothyroidism: 242.9	Systemic lupus erythematosus (SLE): 710.0
Hyperlipidemia: 272.2–272.4	Subconjunctival hemorrhage: 372.72
Hypertension: 401–405	Urticaria: 708.0–708.9

References

1. Solomon JD (2010) Outcomes of corneal spherical aberration-guided cataract surgery measured by the OPD-scan. J Refract Surg 26(11):863–869
2. Courtin R, Pereira B, Naughton G et al (2016) Prevalence of dry eye disease in visual display terminal workers: a systematic review and meta-analysis. BMJ Open 6:e009675. https://doi.org/10.1136/bmjopen-2015-009675
3. Schaumberg DA, Sullivan DA, Buring JE, Dana MR (2003) Prevalence of dry eye syndrome among US women. Am J Ophthalmol 136(2):318–326
4. Schaumberg DA, Dana R, Buring JE, Sullivan DA (2009) Prevalence of dry eye disease among US men: estimates from the Physicians' Health Studies. Arch Ophthalmol 127(6):763–768. https://doi.org/10.1001/archophthalmol.2009.103
5. Lin PU, Tsai SY, Cheng CY, Liu JH, Chou P, Hsu WM (2003) Prevalence of dry eye among an elderly Chinese population in Taiwan: The Shihpai Eye Study. Ophthalmology 110:1096–1101
6. Yen JC, Hsu CA, Li YC et al (2015) The prevalence of dry eye syndrome's and the likelihood to develop Sjögren's syndrome in Taiwan: a population-based study. Int J Environ Res Public Health 12:7647–7655. https://doi.org/10.3390/ijerph120707647
7. Lee AJ, Lee J, Saw SM et al (2002) Prevalence and risk factors associated with dry eye symptoms: a population based study in Indonesia. Br J Ophthalmol 86:1347–1351
8. Ţuru L, Alexandrescu C, Stana D, Tudosescu R (2012) Dry eye disease after LASIK. J Med Life 5(1):82–84
9. Yilmaz U, Gokler ME, Unsal A (2015) Dry eye disease and depression-anxiety-stress: a hospital-based case control study in Turkey. Pak J Med Sci 31(3):626–631. https://doi.org/10.12669/pjms.313.7091
10. Chen CH, Yang TY, Lin CL et al (2016) Dry eye syndrome risks in patients with fibromyalgia: A National Retrospective Cohort Study. Medicine 95(4):e2607
11. Galor A, Feuer W, Lee JD et al (2011) Prevalence and risk factors of dry eye syndrome in a United States veterans affairs population. Am J Ophthalmol 152(3):377–384. https://doi.org/10.1016/j.ajo.2011.02.026
12. Denoyer A et al (2015) Dry eye disease after refractive surgery: comparative outcomes of small incision lenticule extraction versus LASIK. Ophthalmology 122:669–676
13. Rosenbaum PR, Rubin DB (1984) Reducing bias in observational studies using subclassification on the propensity score. J Am Stat Assoc 79:516–524
14. Kaido M, Kawashima M, Ishida R, Tsubota K (2017) Severe symptoms of short tear break-up time dry eye are associated with accommodative microfluctuations. Clinic Ophthalmol 11:861–869