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# Long-term Natural History of Dry Eye Disease from the Patient's Perspective

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## Abstract

**Objective—**The goal of this study is to describe the natural history of Dry Eye Disease (DED), which chronically affects millions of people in the US alone.

**Design—**This study includes cohorts from the Women's Health Study (WHS) and Physicians' Health Studies (PHS), and utilizes a combination of cross-sectional surveys and review of existing medical records.

**Participants—**398 men from the PHS and 386 women from the WHS who reported they had DED and responded to a questionnaire about change in various aspects of the disease since initial diagnosis.

**Methods—**Three subscales were developed based on factor analysis of questionnaire responses: ocular surface symptoms, vision-related symptoms, and social impact. We examined correlates of patient-reported worsening on each subscale. We also obtained medical records from a subset of 261 study participants, and examined changes in clinical signs of DED over time.

**Main Outcome Measures—**Ocular surface symptoms, vision-related symptoms, and social impact plus presence/absence of various clinical signs in patients' medical charts.

**Results—**Participants reported an average duration of DED of 10.5 years (SD 9.5 years). Worsening was reported by 24% for ocular surface symptoms, 29% for vision-related symptoms,

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and 10% for social impact. Factors associated with worsening on at least 2 of 3 subscales included a previous report of severe DED symptoms (OR=2.17 for ocular surface symptoms; OR=2.35 for vision-related symptoms), spending >$20 a month on DED treatments (OR=1.80 for ocular surface symptoms; OR=1.99 for vision-related symptoms), history of blepharitis or meibomian gland dysfunction (MGD) (OR=1.57 for vision-related symptoms; OR=2.12 for social impact) and use of systemic beta-blockers (OR=1.62 for ocular surface symptoms; OR=1.84 for vision-related symptoms, and OR=1.86 for the social impact of DED). Presence of corneal staining based on review of medical records was associated with use of level 2 or higher DED treatments (OR=1.54, CI=1.01-2.36), a previous report of severe DED symptoms (OR=1.79, CI=1.07-3.00), having a tear break-up test performed (OR=2.73, CI=1.72-4.36), and with having either blepharitis or MGD (OR=0.59, CI=0.35-0.98).

**Conclusions—**The present study suggests that a proportion of DED patients experience worsening of their DED over time, tending to present with more severe symptoms earlier in the disease. Forthcoming data on the natural history of DED from prospective studies should help clarify some of the limitations of this retrospective study.

### Keywords

Dry-eye disease; natural history; longitudinal; retrospective; patient medical record; questionnaire

## Introduction

Dry eye disease (DED) is a pervasive disorder affecting an estimated 3.2 million women and 1.68 million men aged 50 and over in the U.S.[1,2] The disease is thought to progress via a series of events initiated by reduced tear production or increased tear evaporation, resulting in a destabilization of the cornea-tear interface, and often accompanied by characteristic ocular surface inflammation.[3]

The diagnosis is achieved primarily through patient-reported symptoms[4] supported by clinical findings, most commonly evaluation of ocular surface staining, and less commonly the Schirmer test and tear break-up time.[5] Clinical tests in DED tend to have poor reproducibility, and symptoms and signs may fluctuate. Newer techniques such as in-vivo confocal microscopy and tear osmolarity also have limitations.[6]

The most common treatment for DED is artificial tears, with beneficial short-term effects on symptomatology.[7] Other therapies include topical cyclosporine A (Restasis).[7] topical steroids, certain antibiotics, punctual occlusion, and dietary supplementation with omega-3 fatty acids. Even with therapy, DED tends to persist but despite data supporting the importance of DED as a public health problem,[1,2] the long-term course of the disease is not yet well-characterized. The present study, using data from the well-characterized Women's Health Study and Physicians' Health Study cohorts, aims to provide needed data on this issue.

## Methods

Study participants were recruited from two large longitudinal studies of healthcare professionals in the US: the Women's Health Study (WHS) and the Physicians' Health Studies (PHS) I and II in which we previously assessed diagnoses of DED and DED symptoms using a short questionnaire.[8,9] From these cohorts, we selected N=4000 participants (N=2500 women and N=1500 men) who previously reported a diagnosis of DED or severe dry eye symptoms. We sent this group an expanded DED questionnaire to obtain a more detailed ascertainment of DED symptoms using the Ocular Surface Disease Index (OSDI) and Symptom Assessment in Dry Eye (SANDE) questionnaires; co-morbid conditions; dry eye treatments; cost of dry eye treatments; other medication use; patient satisfaction with DED treatments; and the impact of DED on quality of life. We classified DED medications as Level 1 or Level 2 or higher according to the schema of the International Dry Eye Workshop (2007).[3]

About 1 year later, we distributed a second questionnaire to a selected subgroup of N=1000 DED study participants (N=500 women and N=500 men) who completed the expanded DED questionnaire and had reconfirmed a diagnosis of DED. The second questionnaire (DED-Change questionnaire) ascertained patient-reported data changes in DED relative to when it was first diagnosed. Participants were oriented by asking them to think about how they feel now, and then to indicate how much change they experienced (better or worse) compared to when they were first diagnosed. Responses ranged from “much worse” to “much better” and were scored on a 7-point Likert scale centered on “no change.” Due to concerns about overall participant burden in these very active and comprehensive cohorts, we sent only a single request for response to the DED-change questionnaire.

To compare and supplement the patient-reported data, we reviewed the medical records of a subset of participants who completed the DED-Change questionnaire and provided consent. The a priori goal was to review records of N=250 participants. To achieve this goal, we sent out a single request for permission to review medical records to all participants who responded to the DED-Change questionnaire, and received informed consent from N=533. We contacted these participants' eye doctors and obtained medical record information on dry eye from N=261 participants. Medical records from the remainder were not pursued. For all clinical visits on record, we abstracted data on the presence of symptoms, treatments used, clinical exam findings (e.g. ocular surface evaluation, tear break-up time, Schirmer test), as well as diagnoses and treatment recommendations. The study was approved by the Institutional Review Board at Partners Health Care, is HIPAA-compliant and adheres to the tenets of the Declaration of Helsinki.

We performed statistical analyses using SAS v9.2 (Cary, NC). We performed factor analysis, resulting in the identification of three subscales: ocular surface symptoms, vision-related symptoms, and social impact of DED. The subscale for ocular surface symptoms was composed of the questions on frequency and severity of symptoms, satisfaction with treatment, and overall severity of condition. The questions pertaining to vision quality, visual fluctuation, ability to work, ability to read, ability to drive during the day and at night, overall eye health, and working with a computer or ATM comprised the vision-related

symptom subscale. The social impact subscale was formed from questions pertaining to work satisfaction, ability to socialize, satisfaction with socializing, overall mood, irritableness, quality of marriage, quality of friendships, and overall health. For each subscale, we summed the responses to each relevant question, and then divided by the number of questions answered for that subscale, rounding to the nearest integer value. Subscale scores formed outcomes for further analyses.

For our primary analysis, we dichotomized subscale scores to compare subjects who experienced any degree of worsening to those who experienced either no change or improvement. Multivariate logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CI) for associations of variables with the measures of patient perceptions of change. We also explored models comparing improvement versus no change and worsening, as well as ordinal logistic regression models using collapsed scores of worsening, no change, and improvement, and models preserving the 7-point Likert scale. The latter two methods were found to violate the proportional odds assumptions, and were therefore abandoned. The first two methods gave qualitatively similar results, so we report results based on any worsening versus no change or improvement.

We selected variables for consideration *a priori* based on the literature and our knowledge of DED. We adjusted for age and sex, then extended models initially using a stepwise procedure to consider inclusion of: use of level 2 or higher DED treatments[3], frequency of use of artificial tears, spending at least $20 a month on DED treatment, history of blepharitis or MGD, corneal ulcer, use of topical glaucoma medications, and ocular surgery (cataract, strabismus, glaucoma, refractive surgery), history of dry mouth, allergy, rosacea, autoimmune disease (Sjogren's, lupus, and rheumatoid arthritis), fibromyalgia, diabetes, hypertension, anxiety, treated and untreated depression, use of systemic beta-blockers and antihistamines, and an indicator of overall self-reported health. A history of past severe symptoms was ascertained from participant responses of experiencing *both* symptoms of dryness and irritation either constantly or often on the short dry eye symptom questionnaire we periodically administered since 1997. As we have previously done, we classified participants as having severe symptoms if they reported.[1] After fitting an initial set of stepwise models, we manually added and excluded variables based on clinical knowledge and past literature. Though statistical significance varied between one outcome and another, relationships between covariates and each outcome were qualitatively consistent so we consequently utilized a homogenous set of covariates for each outcome measure to enhance comparability.

For clinical record data, we used longitudinal generalized estimating equations (GEEs) to obtain estimates of the probability of an observed change in the frequency of corneal staining/superficial punctate keratopathy (SPK) over time. In these models, we used a logit link function and binomial distribution, and compared exchangeable and autoregressive covariance matrices, and observed little change in the empirical standard error estimates.

## Results

We received responses from 784/1000 (78%) men (N=398) and women (N=386) sent a single request to complete the DED-change questionnaire. There was no significant difference in OSDI scores among those who did versus did not return the DED-change questionnaire (P=0.53). Men were aged between 60.2 and 97.3 years, and had an average duration of DED of 10.5 years (SD 9.5 years). Women were aged between 61.2 and 89.9 years old, with an average duration of DED of 14.5 years (SD 7.7 years; Table 1). More women (68.1%) than men (34.7%) had past history of severe DED symptoms (P<0.0001).

### Patient-Reported Outcomes

Overall, the median scores were zero for responses to all DED-change questions, and only nighttime driving showed significant (P<0.05) worsening by single sample t-test (data not shown). The three DED-Change subscale scores were correlated with one another (correlation coefficients ranging from 0.50 to 0.76). Consistent with the median scores, the most common response of study participants was to report no change since the time of their initial DED diagnosis (Figure 1): 32.0% for ocular surface symptoms, 52.3% for vision-related symptoms, 71.1% for social impact. Some amount of improvement since diagnosis was reported by 44.0% for ocular surface symptoms, 19.0% for vision-related symptoms, and, 19.2% for social impact. Some amount of worsening was reported by 24.1% for ocular surface symptoms, 28.7% for vision-related symptoms, and 9.7% for social impact.

For ocular surface symptoms, 27.7% of women versus 20.4% of men reported at least some worsening, whereas 30.9% of women and 26.5% of men reported at least some worsening of vision-related symptoms. More men (11.3%) than women (8.0%) reported worsening of social impact of their DED (Figure 1). Thirty six percent of patients were using level 2 treatments[3], and the other 64% of patients were using level 1 or no treatment[3]. A total of 25.9% on category 2 treatments versus 35.4% of those on category 1 or 0 had no change in ocular surface symptoms. The distribution of change for vision-related symptoms and social impact was virtually identical between treatment categories (Figure 2). Among participants who reported severe OSDI scores around the time of completing the DED-Change questionnaire, 31.5% experienced worsening of ocular surface symptoms, versus 16.1% of participants with mild to moderate OSDI scores, with a similar pattern for vision-related and social impact subscales (Figure 3).

In multivariable logistic regression models for ocular surface symptoms, we observed that spending >$20 a month DED treatments (OR=1.80), a history of past severe DED symptoms (OR=2.17), and use of systemic beta blockers (OR=1.62) were each significantly associated with patient-reported worsening (Table 2). Other factors such as age, sex, blepharitis or MGD, history of ocular surgery, and treated and untreated depression did not reach the level of statistical significance.

The results of the model for vision-related symptoms were qualitatively similar; spending > $20 a month on DED treatments (OR=1.99), a history of past severe DED symptoms (OR=2.35), and using systemic beta blockers (OR=1.84) were significantly associated with worsening. In addition, a history of ocular surgery (OR=1.50), untreated depression

(OR=2.33), and blepharitis or MGD (OR=1.57) were also associated with patient-reported worsening (Table 2).

Worsening of the social impact of DED, was significant associated with a 5-year increase in age (OR=1.25), use of systemic beta-blockers (OR=1.86), and blepharitis or MGD (OR=2.12). Although not significant, factors associated with the other two subscales such as a previous report of severe DED symptoms, spending >$20 a month on DED treatment, and history of ocular surgery were associated in the same direction as in the other models.

A fourth model examined responses to the single question on how the severity of each participant's DED condition had changed overall. Results for this outcome, which also contributed to results of the model for ocular surface symptoms, showed many similarities with that model, as well as the models for the other DED-Change subscales (Table 2). Results of tests for interactions were non-significant and are consequently not reported. Additionally, although we did not include current OSDI categories in the final models, participants who reported worsening of their ocular surface symptoms, vision-related symptoms, or the social impact of DED had increased ORs of 3.17 (2.19,4.58), 3.57 (2.50-5.13), and 2.03 (1.20-3.44) respectively, for also currently being classified as severe on the OSDI questionnaire.

For the subset of 261 participants with review of clinical records, N=154 (59.0%) were women and N=107 (41.0%) were men, and the number of exams ranged from 1 to 23 with a mean of 6 exams over an average follow-up of 5.0 years (Table 3). Over three quarters had a medical record documentation of symptoms of discomfort on at least one visit. The presence of SPK or corneal staining was recorded in 45.2% of patients, and 34.9% of patients had a record of either blepharitis or MGD. Other clinical tests for dry eye were seldom performed, e.g. a record of a Schirmer test being performed was found in 9.6% of patients and tear break up time in 14.1% of patients with a diagnosis of DED (Table 3). General comments such as poor tear quality or reductions in tear quantity were documented in 12.5% of patients. Only 1.5% of patients had a subtype of DED indicated on their clinical records.

Because of our prior work on sex-differences in DED,[10,11] we examined whether variables obtained from clinical exams differed by sex. Women were more likely to have a record of artificial tear use (P=0.01), corneal staining/SPK (P=0.03) and punctal occlusion (P=0.006); and less likely to have blepharitis or MGD (P=0.001); Table 3. Women were also more likely to be prescribed topical gels or ointments (P=0.03), as well as topical antibiotic/steroid combinations (P=0.02). In contrast, topical antibiotics were prescribed more commonly among men (P=0.03).

Using GEE logistic regression models we found no evidence to support disease progression as indicated by an increased probability of corneal staining/SPK over time (Table 4), however use of level 2 or higher DED treatments (OR=1.54, CI=1.01-2.36), past report of severe symptoms (OR=1.79, CI=1.07-3.00), and having a tear break-up time test performed (OR=2.73, CI=1.74-4.36) were associated with this outcome. Although female sex (OR=1.52), and history of refractive surgery (OR=1.81) were not significantly associated with corneal staining/SPK, both had coefficients of relatively large magnitude. Patient-

reported worsening of symptoms was not significantly related to the probability of corneal staining/SPK.

## Discussion

DED is a chronic disease that increases in prevalence with older age and is more common among women.[1,2] In this study, we used a combination of self-reported patient information and review of medical records to shed light on the natural history of DED among a group of men and women with an average duration of DED of 10.5 and 14.5 years, respectively. The majority of men and women with DED recalled little or no change in ocular surface symptoms, vision-related symptoms, or the social impact of DED since diagnosis, and a similar number reported an improvement as reported worsening. These results, supported by review of clinical records, call into question the suggested tendency for DED to progress over time, but also point to possible inadequacies of current therapies.[5,7]

This study has a number of strengths including a large sample size, a long average duration of DED, and a combination of self-reported and clinical information, but there are also a number of limitations to consider. The participants were selected from two ongoing cohort studies of health care professionals, who may not be representative of the population of patients with DED in the US, although they are geographically dispersed and consequently may provide a more useful representation of the general clinical care of patients with DED than would be obtained from a study limited to a single geographical area. There is also a possibility of selection bias, since only a single request was made to complete the study questionnaires and to obtain consent for medical record review. However, concerns are minimized since >78% of contacted patients completed the survey, and there were no differences in OSDI scores among those who did versus did not respond.

The retrospective design increases the likelihood of, recall bias due to possible differences in recall between participants who, for example, were currently experiencing more severe dry eye symptoms versus those who were not. We also recognize that our findings could be the result of patients learning to cope with their disease. Some studies of quality of life have found that patient-reported quality of life is higher than that reported by the general population asked to imagine having the illness in question.[12] Additionally, dry eye is thought to wax and wane, and it is possible that patients are not able to accurately integrate such fluctuations in symptoms to estimate how much their condition changed. Although the recall bias could theoretically alter results in either direction, it is important to note that a large part of the impact of dry eye is based on patient perceptions, and here the most common perception was of no change in the condition over time.

The possibility of successful therapeutic management, and/or down-regulation of corneal pain sensation resulting in reduced symptoms over time could not be evaluated in the present study. However, the likelihood of corneal staining/SPK on clinical exams also failed to show any significant increase over time. The small number of patients with clinical tests such as the Schirmer test and tear break-up time documented in their medical record restricted our ability to analyze any changes in those factors. Frequency of performance of clinical tests appeared to be lower than in a previous review of DED patient charts from a

single center, as well as compared to recommended tests from a scientific roundtable panel of clinicians.[13,14] Although it is possible that tests were done but not recorded in the medical record, literature tends to support[13] that it is more likely that clinicians rely primarily on patient-reported symptoms and slit-lamp assessment of the ocular surface, and that abnormal findings would have been recorded. Arguably, since the participants were all healthcare providers themselves, one might expect the quality of their care to be higher than in the general population. Given the significance of DED as a public health concern, we hope that increasing knowledge of the disease will result in improvements of its clinical management. We would encourage clinicians to not only investigate potential causes of corneal epitheliopathy, but to also inquire routinely in a more standardized fashion about symptoms of DED. Simple short questionnaires, such as the SANDE questionnaire, have been developed and may be useful for this purpose.[15,16]

Although women were not significantly more likely to report worsening, female sex was highly correlated with past severe DED symptoms, which was associated with worsening. Women also had a record of more frequent corneal staining/SPK on exams, and more frequent application of clinical tests for DED. These observations are consistent with our prior work demonstrating a greater impact of DED on symptoms and quality of life among women.[11]

One of the most consistent correlates of worsening was a record of past severe symptoms. This finding is in line with the idea that patients who present with more severe symptoms early in the course of their disease are the ones who are most likely to experience a worsening, usually in spite of therapy. Patients with more severe symptoms may be more likely to see their doctor more often, or more likely to seek specialist care, and this could lead to a skewed perception of disease progression among clinicians. Indeed, patients with self-reported worsening on at least one DED-change subscale had a higher average number of exams per year (not statistically significant).

We also observed consistent associations between the use of systemic beta-blockers and patient-reported worsening on all three DED-Change subscales, supported by prior research linking use of systemic beta-blockers as well as hypertension to risk of DED,[17–19] and other work suggesting an association with topical beta-blockers.[20,21] Patients on such medications may benefit from DED symptom and ocular surface assessment and attention to DED management over time.

The present data also suggest the continued need for more effective treatments for DED. Similar percentages of people using level 2 or higher treatments for DED and people using level 1 or no treatment reported worsening of the 3 DED-change subscales. We previously observed that patients with more frequent symptoms are more likely to be treated with level 2 or higher therapies,[22] and these new data show that approximately 30% of such patients experience some level of long-term worsening, regardless of therapy. People who reported spending more than $20 a month on dry eye treatments were more likely to experience worsening, likely due to people with worsening symptoms seeking relief. The possibility that patients would have experienced an even higher degree of worsening in the absence of these therapies could not be evaluated.

Patient reported outcomes were supported by clinical data on the probability of corneal staining/SPK over time, showing no association with time since diagnosis. Those with severe DED symptoms in the past were more likely to have a record of corneal staining/SPK, providing additional support for the notion of more severe disease in this group of patients.

In summary, these results from a large group of men and women with an average of over 10 years of diagnosed DED, suggest that DED is not necessarily progressive over the long term, and most men and women report no change or some level of improvement. Patients who reported severe symptoms of DED in the past were more likely to report worsening and more likely to have corneal staining/SPK, suggesting one clinically relevant indicator of the probability of disease progression. Prospective data on the natural history of dry eye from a large ancillary study within the Vitamin D and Omega-3 Fatty Acid Trial (VITAL) are currently being collected and should provide additional informative data on the natural history of dry eye in the near future. Meanwhile, the current data are relevant to clinicians who manage patients with DED.

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Research to Prevent Blindness, New York, NY. Research to Prevent Blindness had no role in the design or conduct of this research.

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## Abbreviations

| | |
|---|---|
| **DED** | Dry eye disease |
| **WHS** | Women's Health Study |
| **PHS** | Physicians' Health Studies |
| **SANDE** | Symptom Assessment in Dry Eye |
| **OSDI** | Ocular Surface Disease Index |
| **OR** | Odds Ratio |
| **CI** | 95% Confidence Intervals |
| **GEE** | Generalized Estimating Equation |
| **SPK** | Superficial Punctate Keratopathy |
| **MGD** | meibomian gland dysfunction |

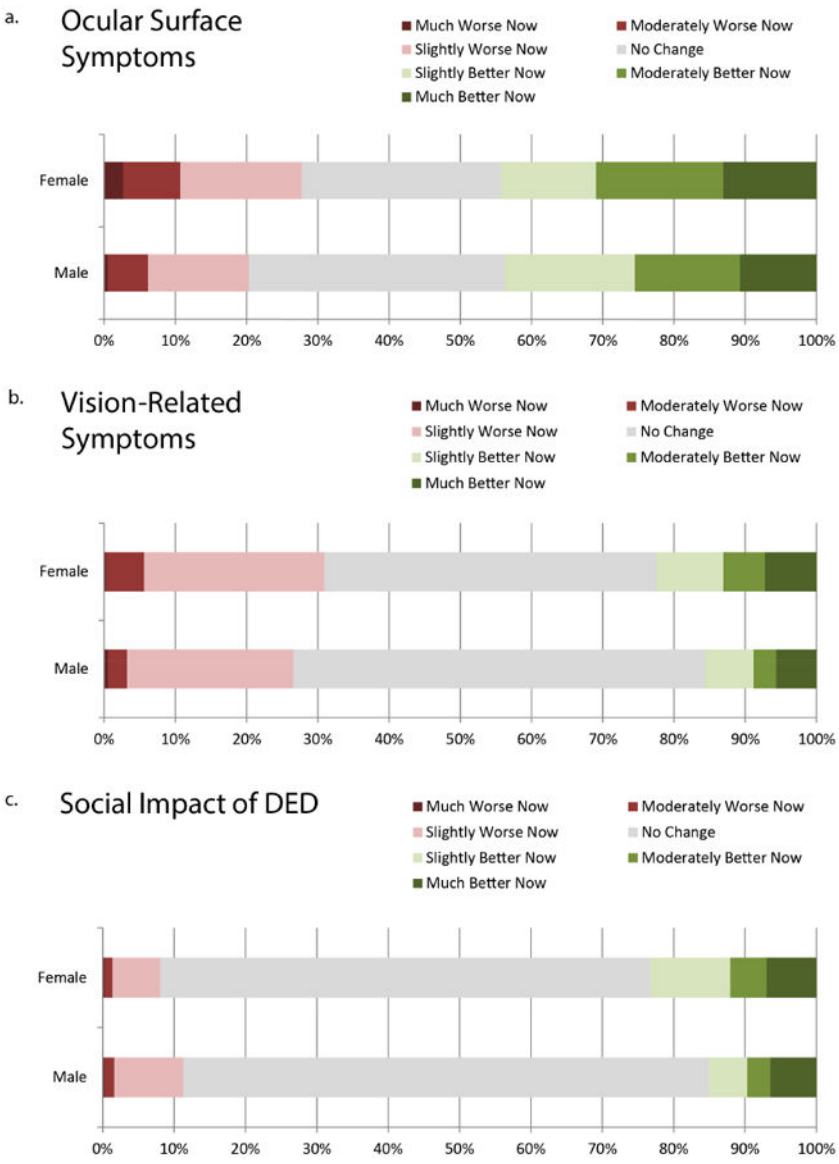


**Figure 1.**

Changes in DED symptoms over time, by sex. This figure depicts self-reported change in DED symptoms separately for men (n=398) and women (n=386) on the three subscales of a) Ocular Surface Symptoms, b) Vision-related Symptoms, and c) the Social Impact of DED.

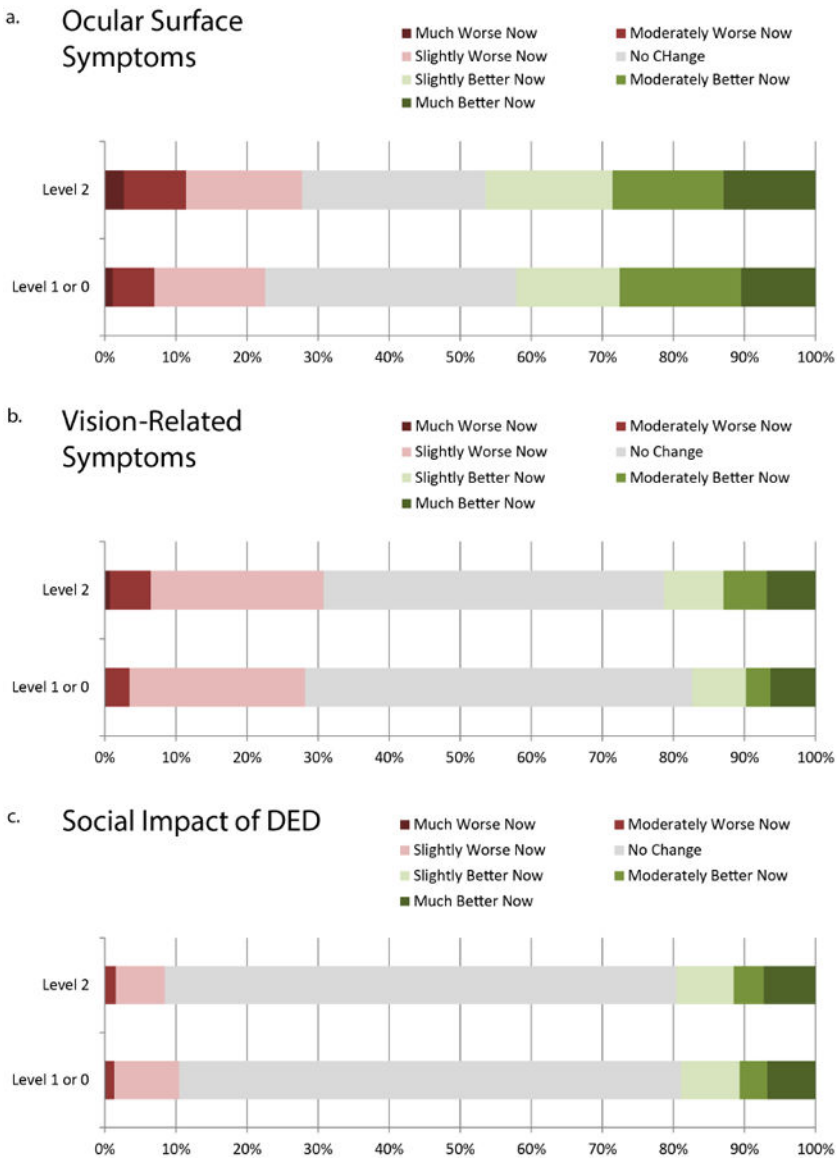


**Figure 2.**

Changes in DED symptoms over time, by treatment category. This figure depicts self-reported change in DED symptoms separately for those on level 0 or 1 treatments (n=484) and those on level 2 treatments (n=272) on the three subscales of a) Ocular Surface Symptoms, b) Vision-related Symptoms, and c) the Social Impact of DED.

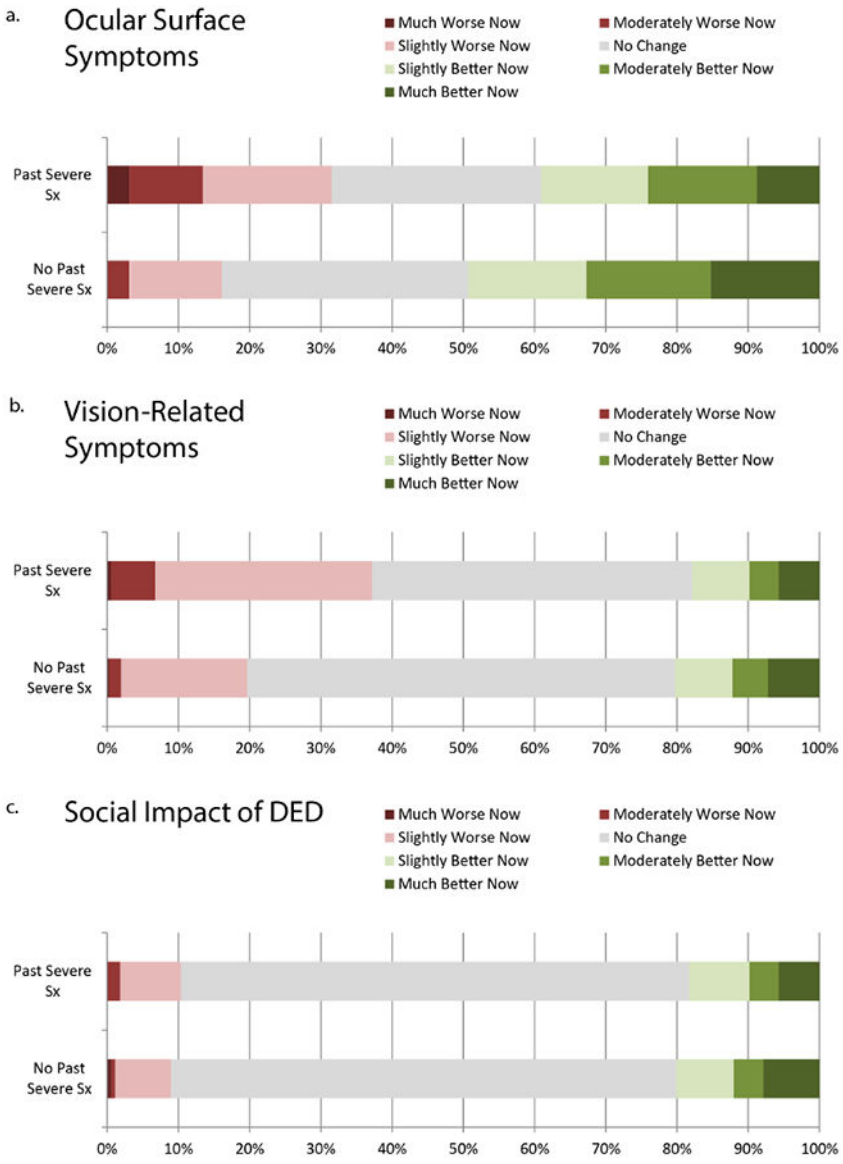


**Figure 3.**

Changes in DED symptoms over time, by self-reported past severe DED symptoms. This figure depicts self-reported change in DED symptoms separately for those who noted they previously had severe symptoms (n=370) and those who noted they did not (n=414) on the three subscales of a) Ocular Surface Symptoms, b) Vision-related Symptoms, and c) the Social Impact of DED.

## Table 1

Demographic characteristics of study participants who completed the DED-change questionnaire.

| | Men | Women |
|---|---|---|
| **Sample Size, n** | **398** | **386** |
| Race, n (%) | | |
| White | 373 (93.7) | 370 (97.1) |
| Hispanic | 5 (1.3) | 4 (1.1) |
| Black | 3 (0.8) | 1 (0.3) |
| Asian | 13 (3.3) | 5 (1.3) |
| Pacific Islander | 0 (0) | 1 (0.3) |
| Other/Unknown | 4 (1.0) | 0 (0) |
| Professional Qualification, n (%) | | |
| MD or equivalent | 398 (100) | 9 (2.3) |
| RN | 0 (0) | 299 (77.5) |
| LPN/LVN | 0 (0) | 48 (12.4) |
| Other | 0 (0) | 30 (7.8) |
| Highest Education Level, n (%) | | |
| Licensed/registered nurse training | 0 | 216 (56.4) |
| BS nursing | 0 | 85 (22.2) |
| Master's degree | 0 | 59 (15.4) |
| MD/doctoral degree | 398 (100) | 23 (6.0) |
| Current age, y mean (SD) | 76.7 (8.3) | 70.8 (6.3) |
| Age at diagnosis of DED, y mean (SD) | 65.9 (12.2) | 56.3 (9.9) |
| Duration of DED, y mean (SD) | 10.5 (9.5) | 14.5 (7.7) |

**Table 2**

Results of logistic regression models for three DED-Change questionnaire subscales (ocular surface symptoms, vision-related symptoms, and social impact), as well as patient-reported change in overall severity of DED since the time of DED diagnosis.

| | Model Outcome* | | | |
|---|---|---|---|---|
| | **Ocular Surface Symptoms** | **Vision-Related Symptoms** | **Social Impact of DED** | **Severity of DED Overall** |
| **Variable** | **OR (95% CI)†** | **OR (95% CI)†** | **OR (95% CI)†** | **OR (95% CI)†** |
| Female sex | 1.24 (0.83,1.83) | 0.93 (0.64,1.35) | 0.80 (0.50,1.44) | 1.25 (0.84,1.86) |
| 5-year increase in age | 1.06 (0.94,1.20) | 1.01 (0.90,1.14) | **1.25 (1.05,1.47)** | 1.10 (0.98,1.25) |
| Previous report of severe DED Symptoms‡ | **2.17 (1.49,3.18)** | **2.35 (1.63,3.37)** | 1.32 (0.77,2.27) | **2.85 (1.93,4.20)** |
| Spending of >$20/mo on DED treatments | **1.80 (1.07,3.01)** | **1.99 (1.20,3.31)** | 1.47 (0.70,3.11) | **2.02 (1.21,3.37)** |
| Any use of systemic beta blockers | **1.62 (1.10,2.39)** | **1.84 (1.27,2.66)** | **1.86 (1.10,3.17)** | **1.62 (1.10,2.39)** |
| Any ocular surgery | 1.23 (0.86,1.77) | **1.50 (1.06,2.11)** | 1.37 (0.82,2.29) | 1.09 (0.76,1.57) |
| Treated depression | 1.05 (0.63,1.75) | 0.91 (0.55,1.50) | 1.44 (0.72,2.90) | 1.02 (0.61,1.70) |
| Untreated depression | 1.22 (0.59,2.50) | **2.33 (1.21,4.49)** | 1.75 (0.69,4.49) | 1.41 (0.70,2.84) |
| Blepharitis or meibomian gland dysfunction | 1.32 (0.86,2.01) | **1.57 (1.05,2.40)** | **2.12 (1.22,3.68)** | **1.57 (1.04,2.38)** |

*Models were fit for dichotomous outcomes indicating any reported worsening versus no change or better.

†ORs greater than 1 indicate a greater likelihood of self-reported worsening of the outcome since time of DED diagnosis.

‡Symptoms reported with a frequency of either constantly or often.

**Table 3**

Clinical information on DED obtained from review of participant medical records (N= 261).

| | All Participants (N=261) | | Men (N=107) | | Women (N=154) | | |
|---|---|---|---|---|---|---|---|
| **Characteristic** | **N (percent) with characteristic on at least 1 exam** | **Average proportion n of visits per patient** | **N (percent) with characteristic on at least 1 exam** | **Average proportion of visits per patient** | **N (percent) with characteristic on at least 1 exam** | **Average proportion of visits per patient** | **P- value †** |
| Symptoms of discomfort | 197 (75.5%) | 43.0% | 79 (73.8%) | 39.6% | 118 (76.6%) | 45.5% | 0.19 |
| Symptoms of fluctuating/blurr ed vision | 120 (46.0%) | 16.4% | 44 (41.1%) | 14.6% | 76 (49.4%) | 17.6% | 0.35 |
| Indication of artificial tear use | 237 (90.8%) | 70.1% | 94 (87.9%) | 64.2% | 143 (92.9%) | 74.2% | 0.01 |
| Indication of Restasis use | 72 (27.6%) | 15.6% | 27 (25.2%) | 13.4% | 45 (29.2%) | 17.1% | 0.33 |
| Superficial punctuate keratopathy | 118 (45.2%) | 20.8% | 35 (32.7%) | 15.8% | 83 (53.9%) | 24.3% | 0.03 |
| Blepharitis or meibomian gland dysfunction | 91 (34.9%) | 17.1% | 45 (42.1%) | 25.2% | 46 (29.9%) | 11.5% | 0.001 |
| Tear break up time tested | 42 (14.1%) | 6.6% | 14 (13.1%) | 5.2% | 28 (18.2%) | 7.6% | 0.32 |
| Schirmer test performed | 26 (10.0%) | 2.1% | 9 (8.4%) | 1.1% | 17 (11.0%) | 2.8% | 0.08 |
| Abnormal tear film noted | 80 (30.7%) | 12.5% | 35 (32.7%) | 14.4% | 45 (29.2%) | 11.3% | 0.34 |
| Punctal occlusion noted | 53 (20.3%) | 8.5% | 13 (12.2%) | 4.4% | 40 (26.0%) | 11.3% | 0.006 |

*Number of visits ranged from 1 to 23 with an average of 6 visits per participant.

†For comparison by sex of average proportion of visits with each characteristic

## Table 4

Results of generalized estimating equations logistic regression models for outcomes of recorded symptoms of discomfort or corneal staining/SPK based on clinical information from N=261 study participants.

| Variable | Corneal SPK or staining OR (95% CI) |
|---|---|
| Female sex | 1.52 (0.93,2.50) |
| Time since diagnosis (per 5 years) | 1.00 (0.96,1.04) |
| Use of level 2 or higher DED treatments | **1.54 (1.01,2.36)** |
| Patient-reported worsening of symptoms since time of diagnosis* | 1.28 (0.80,2.06) |
| History of refractive surgery | 1.81 (0.98,3.33) |
| History of severe symptoms | **1.79 (1.07,3.00)** |
| Blepharitis or Meibomian Gland Dysfunction | **0.59 (0.35,0.98)** |
| Tear break up test performed | **2.73 (1.72,4.36)** |

Based on the question regarding dry eye disease symptoms overall (any worsening versus no change or better). Alternative models were also fit using an indicator of worsening versus no change or better on each of the three DED-change subscales, with no substantial differences in estimates (data not shown).