Patient-Reported Burden of Dry Eye Disease in the United States: Results of an Online Cross-Sectional Survey

REZA DANA, JULIETTE MEUNIER, JESSICA T. MARKOWITZ, COREY JOSEPH, AND CSABA SIFFEL

• PURPOSE: To evaluate functional vision, general health status, and work productivity in individuals with and without dry eye disease (DED).
• DESIGN: Cross-sectional study.
• METHODS: SETTING: General US population (2018). STUDY POPULATION: Adults ≥18 years with (n = 1003) or without (n = 1006) self-reported DED. Main Outcome Measures: All respondents completed the National Eye Institute Visual Function Questionnaire (VFQ) and the EuroQol 5-dimensions 5-levels (EQ-5D-5L). All respondents with DED completed the eye dryness score (EDS) visual analogue scale, Ocular Comfort Index (OCI), and Work Productivity and Activity Impairment (WPAI) questionnaire. Half of respondents with DED completed the Impact of Dry Eye on Everyday Life (IDEEL) questionnaire; the other half completed the Dry Eye Questionnaire 5 (DEQ-5) and Standardized Patient Evaluation of Eye Dryness (SPEED), McMonnies, and Symptom Assessment in Dry Eye (SANDE) questionnaires. All analyses were descriptive.
• RESULTS: Respondents with DED reported more comorbidities, greater exposure to adverse environmental conditions, and lower (worse) mean (standard deviation) scores on the modified Rasch-scored 28-item VFQ (VFQ-28R) total score (68.8 [11.9] vs 81.2 [12.7]) and EQ-5D-5L (0.82 [0.13] vs 0.88 [0.14]) than respondents without DED. Respondents with DED and EDS ≥60 (highest discomfort) fared worse on OCI, VFQ-28R, and WPAI than respondents with DED and EDS <40 (lowest discomfort). Similar findings were observed with IDEEL, DEQ-5, SPEED, McMonnies, and SANDE scores.
• CONCLUSIONS: There is a substantial burden of DED on functional vision, general health status, and productivity; and further, these parameters appear to worsen with increasing EDS. (Am J Ophthalmol 2020;216:7–17.

Accepted for publication Mar 31, 2020.

From Massachusetts Eye and Ear, Harvard Medical School, Boston, Massachusetts, USA (R.D.); Modus Outcomes, Lyon, France (J.M.); Modus Outcomes, Cambridge, Massachusetts, USA (J.T.M.); Takeda, Lexington, Massachusetts, USA (C.J., C.S.); and College of Allied Health Sciences, Augusta University, Augusta, Georgia, USA (C.S.).

Inquiries to Reza Dana, Massachusetts Eye and Ear, Harvard Medical School, 20 Staniford St, Boston, MA 02114, USA; e-mail: Reza_Dana@meei.harvard.edu

DRY EYE DISEASE (DED) IS A CHRONIC, PROGRESSIVE ocular surface disorder of multifactorial etiology characterized by disturbed homeostasis of the tear film.[1,2] DED prevalence in the United States ranges from 5% to 15%,[3–6] increases with age, and is higher in women than in men.[3–6] More than 1 in 5 individuals between the ages of 48 and 91 years developed DED over a 10-year period in the Beaver Dam Eye Study,[7] providing further epidemiologic evidence for DED as a commonly occurring medical condition.

A range of symptoms are experienced by patients with DED, including feeling of grittiness, stinging, or burning sensation in the eyes; painful or fatigued eyes; and having visual disturbance.[1,8] DED has a deleterious effect on visual, physical, and social functioning that can compromise an affected individual's ability to perform everyday tasks such as reading, watching television, using a computer, driving, and performing in the workplace.[9–13] Time trade-off analysis indicated that patients with less severe DED are willing to forego a greater amount of life expectancy in return for perfect health than patients with mild psoriasis, while patients with severe DED would trade a similar amount of time as patients with moderate-to-severe angina.[14] Productivity lost as a consequence of the impact of DED is substantial.[10,12,15]

In a US population-based study, DED was ranked as the sixth most common ocular disorder leading patients to seek medical attention and treatment.[8] Indeed, the annual $3.84 billion (2008 values) cost of DED to payers[15] is primarily driven by pharmacotherapy and surgical expenditures.[15,16]

In the US, a comprehensive assessment of the impact of DED on patients' health-related quality of life (QoL) and other patient-reported outcome measures (PROMs) is lacking. Nine publications describing the impact of DED on QoL and productivity in the United States are limited in scope with regard to scale and breadth of PROMs studied.[5,9,11,13,14,17–20] The sample sizes of most US studies were too small to accurately estimate the effects of DED on health-related QoL and work productivity and to quantify those differences between people with and without DED.[9,11,13,14,17–19] The findings of 2 large US

studies were limited by the finite number of PROMs used to assess health-related QoL and work productivity.[5,20] In addition, the findings reported in 6 publications were restricted to optometry/ophthalmology practices.[11,13,14,17–19]

In recognition that DED affects multiple aspects of daily life, a more comprehensive approach is needed to estimate its overall burden. Therefore, we conducted a cross-sectional survey to evaluate vision-related QoL, ocular symptoms, general health status, and work productivity in individuals with and without DED.

METHODS

• **STUDY DESIGN AND CONDUCT:** This was a cross-sectional study of adults with and without DED residing in the United States during 2018 using an online survey. A targeted literature review was performed to provide appropriate context for the study in consultation with a panel of clinicians. The review provided minimal evidence to justify the choice of using only 1 specific PROM to assess DED burden. Hence, the most frequently used PROMs were used.

The online web-based screener, consent form, and study questions were developed and approved by a central institutional review board (New England Independent Review Board). The study was conducted in accordance with market research ethical codes and data privacy regulations and reported according to best practice.[21] The convenience sample was recruited from panels of individuals who previously agreed to participate in online research regarding healthcare-related issues. The online study was advertised directly to potential respondents. The study invitation included a unique link to complete the online survey without including any information about the topics. Potential responders gave informed consent and were compensated nominally after survey completion for their participation. Data were anonymized before being sent for analysis.

To reduce participant completion burden, a main survey was developed with a unified set of questions, supplemented with 1 of 2 unique sets of additional symptom and impact instruments (survey A and survey B). The main survey was completed by respondents with and without DED and comprised a sociodemographic form (including racial designation, level of education, working status, description of daily living environment) and medical history, the National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) with 6 additional items,[22] and the EuroQol 5-dimensions 5-levels (EQ-5D-5L).[23] Respondents indicating a diagnosis of DED or with ≥2 of the symptoms were assigned on an alternating basis to also complete survey A or survey B. Time to complete the main survey was 20 minutes, and time to complete the main survey plus either survey A or survey B was approximately 45 minutes.

All patients with DED (survey A and B) were administered the following assessments: eye dryness score (EDS) visual analogue scale (VAS), symptom severity/frequency VAS, Ocular Comfort Index (OCI),[24] and Work Productivity and Activity Impairment (WPAI) questionnaire.[25] Respondents assigned to survey A completed the Impact of Dry Eye on Everyday Life (IDEEL) questionnaire[17] exclusively, while only those assigned to survey B completed the Dry Eye Questionnaire 5 (DEQ-5)[26] and Standardized Patient Evaluation of Eye Dryness (SPEED),[27] McMonnies index,[28,29] and Symptom Assessment in Dry Eye (SANDE) questionnaires.[30]

Survey contents, as well as the features and properties of all but 2 of the questionnaires (McMonnies and SANDE), have been described previously (P. Hossain, unpublished data, 2019). The most recent scoring algorithm (modified Rasch-scored 28-item Visual Function Questionnaire [VFQ-28R]) was applied to the data collected in the NEI VFQ-25 and 6 additional items to evaluate activity limitation and socioemotional functioning associated with dry eye.[22] Higher scores on the EQ-5D-5L represent better health states (0 = dead; 1 = full health).[31]

Because eye dryness varies over time and respondents likely answer questionnaires based on their most recent experience of DED, respondents with DED completed the EDS VAS over the previous 24 hours. The EDS VAS was developed in conjunction with clinical trials of patients with DED. Eye dryness has been reported by many patients as an important symptom of DED,[32,33] and the EDS identifies the severity of this component of DED symptomatology.[2,34] The EDS and symptom severity/frequency VAS was rated according to level of discomfort (0 = no discomfort; 100 = maximal discomfort). For the other PROMs, a score of >6 on the DEQ-5 suggests dry eye (range 0-22),[26] higher OCI scores (range 0-72) represent more severe or frequent discomfort,[24] higher SPEED scores indicate more frequent and/or more severe symptoms (range 0-28),[27] and higher WPAI scores (range 0%-100%) indicate greater impairment and less productivity.[25] IDEEL scores on each dimension range from 0 to 100, with higher impact scores representing less impact, satisfaction scores indicating greater satisfaction, symptom bother scores indicating greater bother, and treatment-related bother scores indicating less treatment-related bother.[17]

The McMonnies index is a 14-item questionnaire that assesses symptoms and risk factors common to people who experience dry eye.[35] Weighted scores are summed to give an overall index that ranges from 0 to 45, where a higher score is more suggestive of DED than a lower score.[35] The SANDE incorporates 2 questions with answers presented in a 100-mm horizontal linear VAS that assesses the frequency and intensity of DED.[30] The measurement of symptom frequency ranges from "rarely" to "all of the time," while symptom severity ranges from "very mild" to "very severe."[30] The SANDE global score is calculated by multiplying the frequency score by the severity score and obtaining the square root.[30]

• **RESPONDENTS:** Individuals were aged ≥18 years and resided in the United States at the time of survey completion. All individuals spoke, read, and understood English. Those assigned to the DED group self-reported either a diagnosis of DED or symptoms of DED. We aimed to recruit 1000 individuals with self-reported DED and 1000 individuals without DED via e-mail. Individuals without DED were identified based on having <2 common signs or symptoms of dry eye.

Potential respondents answered study eligibility questions via a web-based screener and consented electronically before beginning the survey. Screening included questions about sex and age to fulfill recruitment targets, as well as 1 multiple-choice question regarding specific medical conditions that included DED. If the respondent indicated that they did not have a DED diagnosis, follow-up questions were asked to determine if they experienced symptoms of DED (ie, eye discomfort, including feelings of dryness, grittiness, or soreness; burning sensation; feeling like something is in the eye; eyelids that stick together upon awakening; or temporary blurred vision that usually improves when blinking).

• **STATISTICAL ANALYSIS:** The response rate was defined as the number of surveys completed divided by the number of individuals who received the online screener questions. Demographic characteristics and health-related QoL (VFQ-28R and EQ-5D-5L) were described in respondents with and without a self-report of DED. The crosswalk method, based on nonparametric calculations, was used to map the EQ-5D-5L data to the EQ-5D-3-Levels US value set before calculating the utility index score.[31]

Respondents with DED were classified as follows: EDS <40, 40≤ EDS <60, and EDS ≥60. Scores for PROMs relating to functional vision, health status, ocular discomfort, and work productivity were calculated in each EDS category among respondents with DED. For categorical variables, data were reported by frequencies; for continuous variables, data were reported by means (standard deviation [SD]) and medians (interquartile range [IQR]). Missing data and/or missing assessments in the questionnaires were not imputed. All data analysis was performed using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina, USA).

RESULTS

• **DISPOSITION:** A large number of individuals did not qualify for the survey after completing the screener (n = 1134; DED n = 637, non-DED n = 497). In addition, 817 individuals started the survey and did not complete it (DED n = 300; non-DED n = 24; unknown n = 493). A total of 2009 respondents completed the survey. Hence, the response rate to the survey was 51%.

Of these 2009 respondents, 1003 reported they had DED or symptoms of DED (herein referred to as the DED group) and 1006 reported they did not. More than half of the DED group (52.9%) were identified as having DED because they endorsed symptoms of the disease in the screener, while the remaining 47.1% reported having DED in the screener. Surveys A and B were completed by 501 and 502 respondents with DED, respectively. Nearly half of the respondents with DED (n = 492, 49.1%) had an EDS <40, while 199 (19.8%) and 312 (31.1%) respondents with DED had EDS values between 40 and <60 and ≥60, respectively.

• **DEMOGRAPHICS AND CLINICAL CHARACTERISTICS:** Respondents with and without DED were well matched with respect to age and sex distributions (owing to recruitment targets) and race/ethnicity distribution. The mean (SD) age of survey respondents was 55 (15) years. Most respondents were female (63.5%) and white (89.5%). Clinical characteristics that were common to respondents with and without DED included the use of digital screens (~89% in both groups), daily activities such as reading (~82% to 86% across groups), and regular exposure to air conditioning or recirculated air (~64% to 66% across groups) (Table 1). However, daily exposure to low humidity, wind or moving air, and polluted air or tobacco smoke was more commonly reported among respondents with DED.

Medical comorbidities were more frequently reported by respondents with DED than respondents without DED (Table 1), with arthritis (43.8% vs 19.6%) being the most commonly reported comorbid medical condition on the screener form overall. Cataracts, which were the only ocular comorbidity assessed directly in the screener, were more frequently reported by respondents with DED (16.4%) than respondents without DED (3.0%).

Patterns of diagnosis, eye-related comorbidities, and eye-related procedures by EDS score among respondents with self-reported DED are summarized in Table 2. Of the 1003 respondents with DED, 688 (68.6%) were diagnosed by a healthcare professional. This frequency increased as the EDS increased (EDS <40, 61.4%; 40≤ EDS <60, 71.4%; EDS ≥60, 78.2%). Of respondents with DED who were diagnosed by a healthcare professional, 86.8% (597/688) were diagnosed by an ophthalmologist or optometrist.

Of 1003 respondents with DED, 180 (17.9%) reported that they had never been treated for DED. All 1003 respondents with DED provided data regarding dry eye treatment in the 12 months before survey administration: 76.2% and 25.6% reported use of artificial tears and ocular gels/ointments, respectively. Over the same timeframe, the percentage of respondents with DED who reported that they had used prescription-only medicines (topical cyclosporine and lifitegrast) were 19.2% and 10.6%, respectively. More than one-quarter of respondents with DED had used oral treatments containing fish oil (28.8%) or omega-3 fatty acids

TABLE 1. Survey Respondent Sociodemographics at Screening

Variable	Respondents With DED[a] (n = 1003)	Respondents Without DED (n = 1006)
Age, years		
Mean (SD)	56.0 (14.7)	54.5 (15.6)
Median (IQR)	60 (47-67)	59 (44-66)
Female, n (%)	652 (65.0)	623 (61.9)
Race/ethnicity, n (%)[b]		
White	907 (90.4)	892 (88.7)
Hispanic/Latino	63 (6.3)	37 (3.7)
Black/African American	46 (4.6)	54 (5.4)
Asian	38 (3.8)	42 (4.2)
Other	28 (2.8)	25 (2.5)
Preferred not to answer	6 (0.6)	8 (0.8)
Typical daily environment, n (%)[b]		
Using digital screens	887 (88.4)	891 (88.6)
Activities (eg, reading)	859 (85.6)	820 (81.5)
Air conditioning/recirculated air	661 (65.9)	644 (64.0)
Forced air/heat	625 (62.3)	579 (57.6)
Low humidity (very dry)	405 (40.4)	231 (23.0)
Wind/moving air	273 (27.2)	175 (17.4)
Polluted air/tobacco smoke	113 (11.3)	68 (6.8)
Other factors	33 (3.3)	24 (2.4)
Reported medical conditions, n (%)[b]		
Dry eye disease	531 (52.9)	0 (0.0)
Arthritis	439 (43.8)	197 (19.6)
Hearing loss	232 (23.1)	82 (8.2)
Cataracts	164 (16.4)	30 (3.0)
Asthma	146 (14.6)	74 (7.4)
Irritable bowel disease	133 (13.3)	36 (3.6)
Psoriasis	102 (10.2)	39 (3.9)
COPD	50 (5.0)	21 (2.1)
Multiple sclerosis	22 (2.2)	6 (0.6)
Parkinson disease	4 (0.4)	2 (0.2)
None of the above	145 (14.5)	633 (62.9)

COPD = chronic obstructive pulmonary disease; DED = dry eye disease; IQR = interquartile range; SD = standard deviation.
[a]A total of 501 respondents completed survey A and 502 respondents completed survey B.
[b]Several answers were possible; thus total percentage is >100%.

(28.4%). Fifty-six respondents with DED (5.6%) had used an ocular device and 31 (3.1%) had undergone eye-related procedures. For respondents with DED who were undergoing treatment at the time of the survey, 80.6% (663/823) were treated by an ophthalmologist or optometrist. Most respondents with DED sought care because of "burning eyes" (54.8%) or problems with their vision (40.5%).

The most frequently reported eye-related conditions were cataract (23.9%) and glaucoma (11.3%). The most frequently reported eye-related procedures were cataract surgery (23.5%) and refractive procedures (13.0%). More than half of respondents with DED (58.9%) reported having none of the eye-related conditions listed in Table 2, and approximately two-thirds (65.6%) reported not having eye-related procedures. Respondents who reported having uveitis (58.3%), meibomian gland dysfunction (58.0%), and Sjögren syndrome (57.9%) were most likely to have an EDS score ≥60.

• **VISION-RELATED FUNCTIONING AND HEALTH STATUS IN RESPONDENTS WITH AND WITHOUT DRY EYE DISEASE:** Figure 1 shows the VFQ-28R scores in respondents with and without DED. The respondents with DED had a lower (worse) mean total VFQ-28R score than respondents without DED (68.8 [11.9] vs 81.2 [12.7]). Consistent findings were observed for mean VFQ-28R domain scores for activity limitations and socioemotional functioning (Figure 1).

Respondents with DED, compared with respondents without DED, had greater problems with mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as measured by the EQ-5D-5L items (Figure 2). The

TABLE 2. Respondents With Dry Eye Disease: Diagnosis and Medical History

Variable	EDS Group			All Respondents With DED (N = 1003)
	EDS <40 (n = 492)	40≤ EDS <60 (n = 199)	EDS ≥60 (n = 312)	
Diagnosed by HCP, n (%)	302 (61.4)	142 (71.4)	244 (78.2)	688 (68.6)
Mean (SD) time since diagnosis of DED, years	6.4 (8.2)	5.7 (8.6)	6.5 (7.5)	6.3 (8.1)
HCP-diagnosed DED, n (%)[a]				
Ophthalmologist	148 (49.0)	78 (54.9)	138 (56.6)	364 (52.9)
Optometrist	101 (33.4)	50 (35.2)	82 (33.6)	233 (33.9)
Primary care doctor	3 (1.0)	2 (1.4)	2 (0.8)	7 (1.0)
Eye care specialist[b]	38 (12.6)	10 (7.0)	17 (7.0)	65 (9.4)
Nurse	3 (1.0)	1 (0.7)	1 (0.4)	5 (0.7)
Pharmacist	1 (0.3)	0	1 (0.4)	2 (0.3)
Other	8 (2.6)	1 (0.7)	3 (1.2)	12 (1.7)
Eye-related conditions, n (%)				
Cataracts	99 (20.1)	62 (31.2)	79 (25.3)	240 (23.9)
Glaucoma	45 (9.1)	23 (11.6)	45 (14.4)	113 (11.3)
Meibomian gland dysfunction	11 (2.2)	10 (5.0)	29 (9.3)	50 (5.0)
Macular degeneration	16 (3.3)	12 (6.0)	16 (5.1)	44 (4.4)
Sjögren syndrome	9 (1.8)	7 (3.5)	22 (7.1)	38 (3.8)
Ocular graft-vs-host disease	18 (3.7)	2 (1.0)	18 (5.8)	38 (3.8)
Blepharitis	12 (2.4)	5 (2.5)	13 (4.2)	30 (3.0)
Diabetic retinopathy	7 (1.4)	6 (3.0)	12 (3.8)	25 (2.5)
Uveitis	7 (1.4)	3 (1.5)	14 (4.5)	24 (2.4)
None of the above	317 (64.4)	101 (50.8)	173 (55.4)	591 (58.9)
Eye-related procedures, n (%)				
Cataract surgery	99 (20.1)	44 (22.1)	93 (29.8)	236 (23.5)
Refractive procedures/surgeries	50 (10.2)	26 (13.1)	54 (17.3)	130 (13.0)
Glaucoma surgery	27 (5.5)	16 (8.0)	31 (9.9)	74 (7.4)
None of the above	342 (69.5)	133 (66.8)	183 (58.7)	658 (65.6)

DED = dry eye disease; EDS = eye dryness score; HCP = healthcare professional; SD = standard deviation.
[a]For participants diagnosed by HCP.
[b]Type of eye care specialist is unknown.

proportion of respondents who had any problems associated with all 5 dimensions was higher in respondents with DED than those without DED. The mean EQ-5D index score based on the 5 items was lower (worse) among respondents with DED than respondents without DED (0.82 [0.13] vs 0.88 [0.14]), suggestive of slightly lower health status in the former group.

• **SYMPTOMS, VISION-RELATED FUNCTIONING, HEALTH STATUS, AND WORK PRODUCTIVITY IN RESPONDENTS WITH DRY EYE DISEASE:** The 24-hour mean (SD) EDS in respondents with DED was 41.7 (30.6). Other than eye dryness, the highest 24-hour mean VAS score for DED symptoms was tired eyes (34.8 [30.0]). Mean VAS scores pertaining to DED symptoms over the past 24 hours and past week increased with an increase in the EDS. Distributions of both "past 24 hours" and "past week" mean VAS scores were highly comparable for each symptom with respect to EDS category. Over the past 24 hours and during the past week, eye discomfort and eyes sensitive to light were the symptoms that showed the greatest difference in mean VAS score when respondents with an EDS <40 were compared with those with an EDS ≥60.

Burden associated with DED worsened as a function of EDS category based on scores for commonly used PROMs (Figures 3-5). The mean (SD) OCI score in respondents with DED was 30.9 (15.0), with eye discomfort worsening with respect to increasing EDS (Figure 3). Among respondents with DED who completed survey B, mean scores for the DEQ-5, SPEED, McMonnies, and SANDE questionnaires worsened with an increase in EDS.

As summarized in Figure 4, the mean VFQ-28R total score as well as the domain scores were found to decrease with an increase in the EDS, signifying worsening of vision-related QoL. Similarly, the EQ-5D index scores also decrease with increasing disease severity as measured by EDS. The mean (SD) EQ-5D index scores were 0.84 (0.13), 0.80 (0.14), and 0.79 (0.14) for respondents with

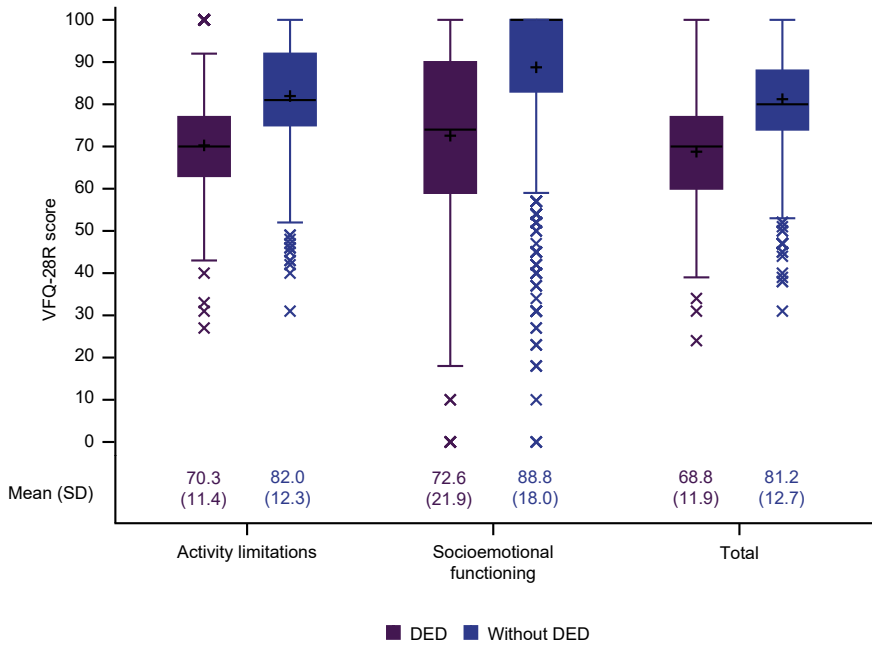

FIGURE 1. Vision-related quality of life in respondents with and without dry eye disease (DED; n = 2009). Higher score represents better vision-related quality of life. The box signifies the interquartile range, the band ("-") inside the box is the median, the plus ("+") inside the box is the mean, and the whisker ends denote the minimum and maximum values. SD = standard deviation; VFQ-28R = modified Rasch-scored 28-item Visual Functioning Questionnaire.

DED with an EDS <40, ≥40 to <60, and ≥60, respectively. Among respondents with DED, mean (SD) WPAI score for "percent activity impairment due to a problem" was 22.4 (24.6), for "percent impairment while working due to a problem" was 25.6 (26.3), for "percent overall work impairment due to a problem" was 28.5 (29.5), and for "percent work time missed due to problem" was 7.9 (18.7). Mean WPAI scores increased as EDS increased for "percent activity impairment due to a problem," "percent impairment while working due to a problem," and "percent overall work impairment due to a problem" (Figure 5).

Among respondents with DED who completed the IDEEL questionnaire, mean (SD) scores were 77.5 (19.8) for Impact on Daily Activities, 77.3 (22.3) for Impact on Work, and 78.6 (21.9) for Emotional Impact score. Mean (SD) IDEEL scores were 53.1 (25.1) for Satisfaction with Treatment Effectiveness score, 44.9 (19.6) for Symptom Bother, and 76.6 (21.9) for Treatment-Related Bother. Mean scores from each IDEEL domain deteriorated with increasing EDS.

DISCUSSION

TO OUR KNOWLEDGE, THIS CROSS-SECTIONAL STUDY OF survey respondents with and without self-reported DED represents the most comprehensive study assessing patient burden in the United States to date. By capturing the patient's voice and perspective on overall disease burden, the findings add to the existing evidence base that DED is associated with decreased vision-related and disease-specific QoL,[5,9,14,17–19] general (beyond ocular) health status,[5,18] and work productivity.[11,13,18,20] Our data are broadly consistent with information on the overall burden of DED reported in previous studies conducted in North America,[5,9–11,13,17–20] Europe,[10] and Asia.[10,36]

One of the main findings was the extent to which functional vision and health status in respondents with DED deviated from those without DED, as assessed by the VFQ-28R and EQ-5D-5L scores. The mean VFQ-28R total score was 12.4 points lower among respondents with DED than among those without DED. Although no minimally important difference has been established for VFQ-28R total score in the DED population, the difference between respondents with and without DED exceeds half a standard deviation (11 points) and thus may represent clinically meaningful worse functional vision. In addition, respondents with DED reported greater problems in all 5 dimensions of the EQ-5D-5L than respondents without DED. Pain/discomfort was the dimension with which most respondents with DED had more problems, compared with respondents without DED (73% patients with DED reported having slight, moderate, severe, or extreme pain/discomfort vs 46% without DED). Although it is plausible that these between-group differences on the EQ-5D-5L may be accounted for by the presence of DED, the higher frequency of comorbidities in the DED group is likely a contributing factor. For instance, arthritis, a known risk factor for DED,[5] was reported by a

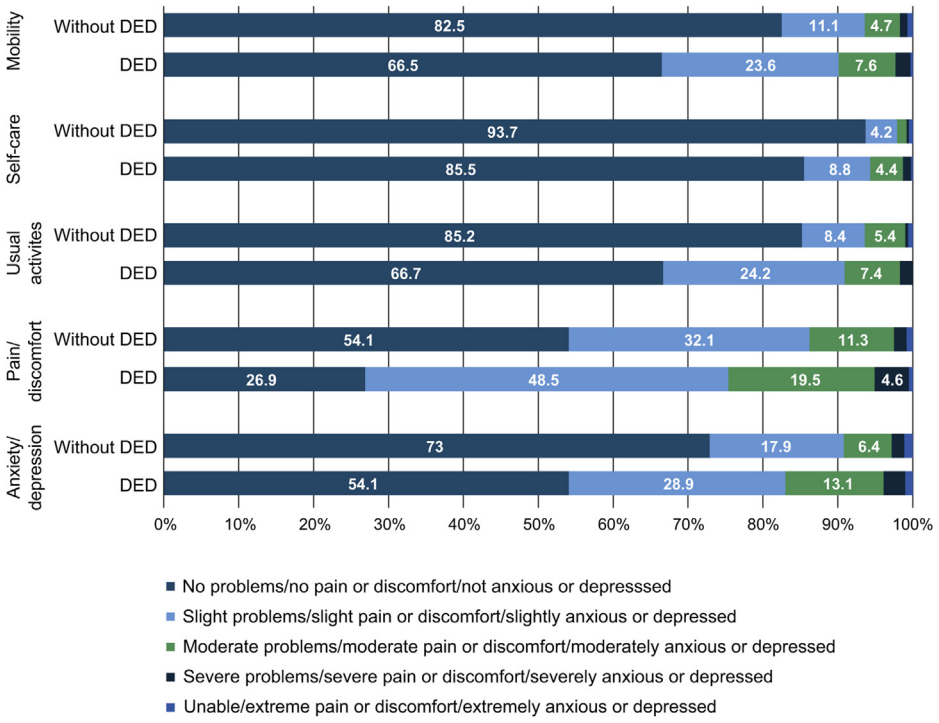

FIGURE 2. Proportion of respondents for different levels of the EuroQol 5-dimensions 5-levels questionnaire by dimension and presence/absence of dry eye disease (DED). Percentage values not shown in figure were < 3%.

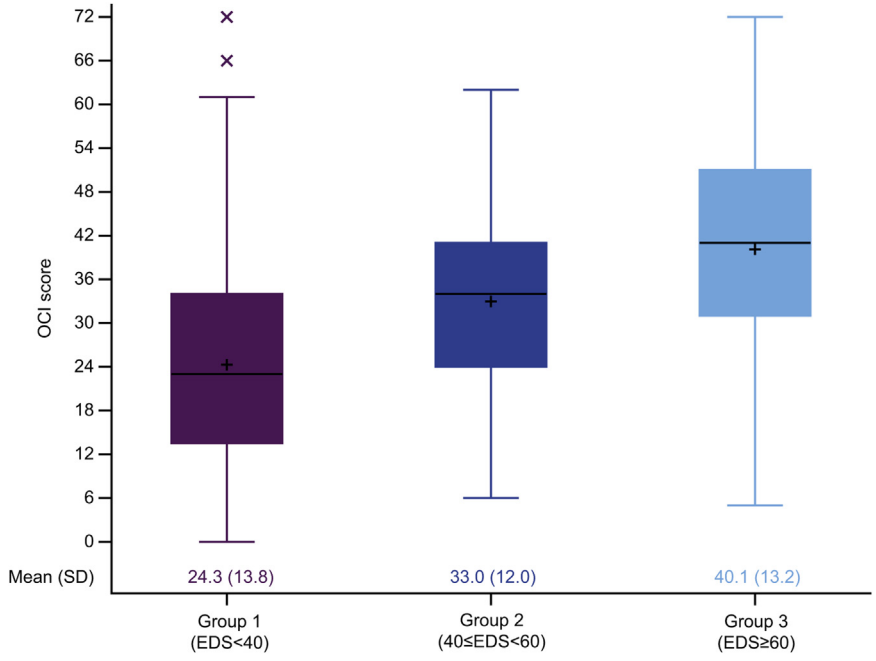

FIGURE 3. Ocular Comfort Index (OCI) questionnaire scores by eye dryness score (EDS) severity category in respondents with dry eye disease (DED; n = 1003). Higher OCI score represents more severe or frequent discomfort. The box signifies the interquartile range, the band ("-") inside the box is the median, the plus ("+") inside the box is the mean, and the whisker ends denote the minimum and maximum values. SD = standard deviation.

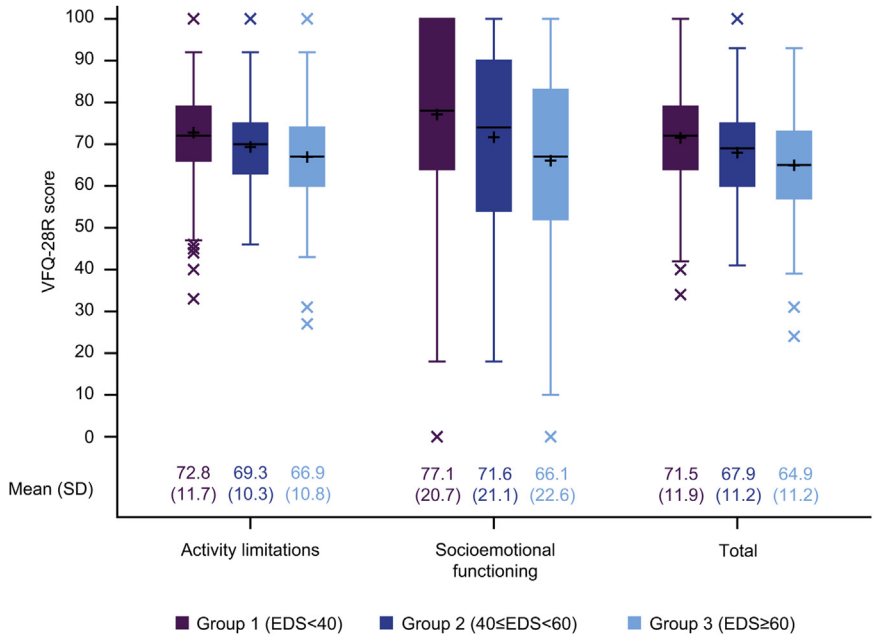

FIGURE 4. Modified Rasch-scored 28-item Visual Functioning Questionnaire (VFQ-28R) scores by eye dryness score (EDS) severity category in respondents with dry eye disease (DED; n = 1003). Higher VFQ-28R score represents better vision-related quality of life. The box signifies the interquartile range, the band ("-") inside the box is the median, the plus ("+") inside the box is the mean, and the whisker ends denote the minimum and maximum values. SD = standard deviation.

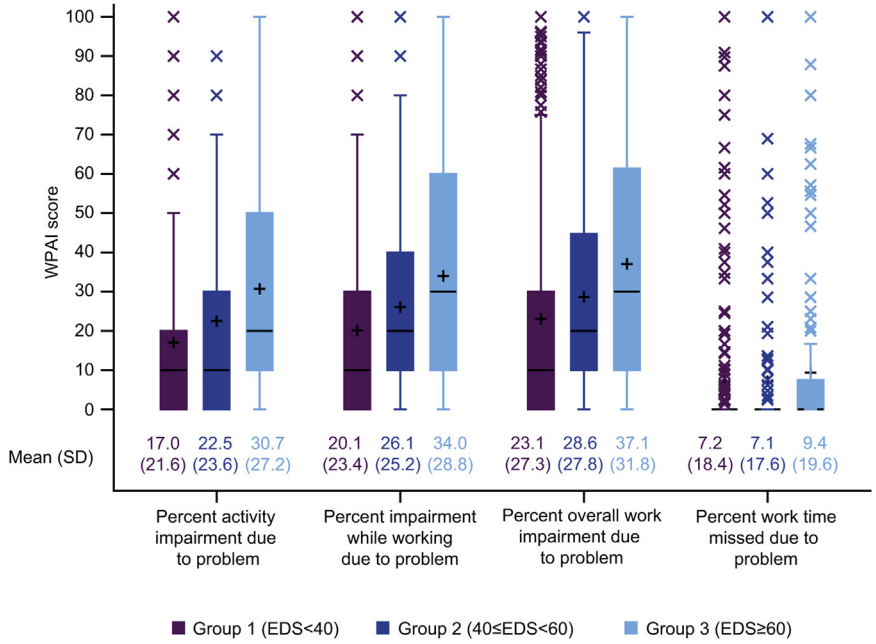

FIGURE 5. Work Productivity and Activity Impairment (WPAI) subscale questionnaire scores by eye dryness score (EDS) severity category in respondents with dry eye disease (DED; n = 1003). Higher WPAI score represents greater impairment and less productivity. The box signifies the interquartile range, the band ("-") inside the box is the median, the plus ("+") inside the box is the mean, and the whisker ends denote the minimum and maximum values. SD = standard deviation.

greater proportion of respondents with DED than respondents without DED (43.8% vs 19.6%).

Increased EDS was associated with a greater negative impact on common DED scales measuring the frequency and intensity of dry eye symptoms (OCI, DEQ-5, SPEED, and SANDE), presence of dry eye (McMonnies), vision-related QoL (VFQ-28R), disease-specific QoL (IDEEL), general health status (EQ-5D-5L), and work productivity (WPAI). The burden of DED among our US respondents was very similar to a related survey in the United Kingdom (P. Hossain, unpublished data, 2019), in which respondents with DED and an EDS ≥60 had worse discomfort, vision-related functioning, and productivity than respondents with DED and an EDS <40. The same relationship was observed between EDS category and patient-reported outcome scores for dry eye symptoms and impact (IDEEL), dry eye symptom frequency and intensity (DEQ-5, SPEED, and SANDE), and presence of dry eye (McMonnies). The differences in scores between EDS groups were approximately equivalent to or greater than half a standard deviation of the score, a common distribution-based indicator of meaningfulness. In addition, previous studies have shown that the degree of health-related QoL impairment (vision-related, disease-specific, and overall) and work productivity impairment increases with worsening DED.[10,11,13–15,17–19]

Given the uniform trend of worse outcomes as a function of increasing EDS, our preliminary findings indicate that the EDS may have utility as a single-item question for assessing severity of dry eye symptoms in individuals with DED. Further research needs to be conducted nonetheless to evaluate the relative value of EDS compared to the questionnaires included in the survey, which have proven to be suitable to categorize patients with DED based on severity. However, some of the PROMs—for example, the McMonnies questionnaire—are not likely to correlate with the EDS, since the former was not designed to categorize the participants as mild, moderate, or severe.[35] This property could explain the smaller differences observed between EDS severity categories in the McMonnies questionnaire than observed with other questionnaires.

Cutoffs for EDS categories may require further refinement when classifying individuals as having mild, moderate, or severe DED. In survey B, mean DEQ-5 scores were >6 in all 3 EDS categories, indicating that DED was heavily present in all groups. This finding validates our sample of respondents with DED to some extent, because the DEQ-5 discriminates between patients with a DED diagnosis at this threshold score.[26] However, close examination of the DEQ-5 score distribution in the cohort with an EDS <40 revealed that the first-quartile DEQ-5 score was 7 (ie, 25% of respondents with DED and an EDS <40 had a score ≤7). In addition, a non-negligible proportion of survey B respondents with DED and an EDS <40 had a DEQ-5 score ≤6, indicating that those respondents may not have DED.

The study sample was well balanced, as enrollment targets were applied to obtain comparable samples of respondents with DED as respondents without DED. However, some caution is required when interpreting the findings of this study. Although the breakdown of sex and age was broadly similar to those observed in other large observational studies of DED,[3–6] nonwhite individuals were underrepresented in our study.[4,6] Additionally, a greater proportion of respondents with than without DED reported being exposed to air conditioning/recirculated air, low humidity, wind or moving air, and polluted air/tobacco smoke. It is not possible to determine if respondents with DED were exposed to more of these environmental factors or were more sensitive to them. As this was an online study, recruitment was skewed toward individuals with internet access, and survey completion was skewed toward individuals motivated to respond to a 45-minute survey and whose DED was not severe enough to prevent looking at a digital screen for this time period. Thus, the sample may not be entirely representative of the DED population.

Because all of the data presented in this study come from self-reported information from respondents with or without DED, accuracy may be limited by recall bias and by individual abilities to report health-related information accurately. Although respondents with or without DED were screened for age and sex to ensure balance, matching or adjusting for other sociodemographic variables and comorbidities was not undertaken. Of note, the EDS is not validated as an instrument to discriminate between levels of DED severity. An inherent limitation of our study is that the relationship between DED and burden can only be inferred.

In summary, the burden of DED reported by patients on functional vision, general health status, and productivity is substantial. DED symptom severity and impact, functional vision, and productivity worsened with increasing EDS.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

REZA DANA: CONCEPTUALIZATION, METHODOLOGY, SUpervision. **Juliette Meunier:** Software, Formal analysis, Data curation. **Jessica T. Markowitz:** Software, Formal analysis, Data curation. **Corey Joseph:** Conceptualization, Methodology, Supervision, Project administration. **Csaba Siffel:** Conceptualization, Methodology, Supervision, Project administration.

FUNDING/SUPPORT: THIS STUDY WAS SUPPORTED BY TAKEDA AND NOVARTIS PHARMACEUTICAL CORPORATION, NJ, USA.
Financial Disclosures: Reza Dana is a consultant for Aldeyra, Dompé, GSK, Kala, and Shire, a Takeda company; holds equity in Aramis and Claris;

and has received research support from Allergan and the National Eye Institute. Juliette Meunier is an employee of Modus Outcomes and consulted for Shire, a Takeda company, on this study. Jessica T. Markowitz is an employee of Modus Outcomes and consulted for Shire, a Takeda company, on this study. Corey Joseph and Csaba Siffel are employees of and own stock/stock options in Takeda. All authors attest that they meet the current ICMJE criteria for authorship.

Other Acknowledgments: The authors thank the patients for participating in the survey. The authors acknowledge Ipek Özer Stillman, from Takeda, for her assistance with survey conceptualization and development, data interpretation, and study operations; and Patrick Marquis from Modus Outcomes for his assistance with survey conceptualization and development. The authors thank Lisa O'Brien, PharmD, of Excel Scientific Solutions, who provided medical writing assistance, supported by Takeda and Novartis Pharmaceutical Corporation, NJ, USA.

REFERENCES

1. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification report. *Ocul Surf* 2017;15(3):276–283.
2. Akpek EK, Amescua G, Farid M, et al. American Academy of Ophthalmology Preferred Practice Pattern Cornea and External Disease Panel. Dry Eye Syndrome Preferred Practice Pattern. *Ophthalmology* 2019;126(1):P286–P334.
3. Dana R, Bradley JL, Guerin A, et al. Estimated prevalence and incidence of dry eye disease based on coding analysis of a large, all-age United States health care system. *Am J Ophthalmol* 2019;202:47–54.
4. Farrand KF, Fridman M, Stillman IÖ, Schaumberg DA. Prevalence of diagnosed dry eye disease in the United States among adults aged 18 years and older. *Am J Ophthalmol* 2017;182:90–98.
5. Paulsen AJ, Cruickshanks KJ, Fischer ME, et al. Dry eye in the Beaver Dam Offspring Study: prevalence, risk factors, and health-related quality of life. *Am J Ophthalmol* 2014;157(4):799–806.
6. Schein OD, Muñoz B, Tielsch JM, Bandeen-Roche K, West S. Prevalence of dry eye among the elderly. *Am J Ophthalmol* 1997;124(6):723–728.
7. Moss SE, Klein R, Klein BE. Long-term incidence of dry eye in an older population. *Optom Vis Sci* 2008;85(8):668–674.
8. Bradley JL, Özer Stillman I, Pivneva I, Guerin A, Evans AM, Dana R. Dry eye disease ranking among common reasons for seeking eye care in a large US claims database. *Clin Ophthalmol* 2019;13:225–232.
9. Miljanović B, Dana R, Sullivan DA, Schaumberg DA. Impact of dry eye syndrome on vision-related quality of life. *Am J Ophthalmol* 2007;143(3):409–415.
10. McDonald M, Patel DA, Keith MS, Snedecor SJ. Economic and humanistic burden of dry eye disease in Europe, North America, and Asia: a systematic literature review. *Ocul Surf* 2016;14(2):144–167.
11. Mertzanis P, Abetz L, Rajagopalan K, et al. The relative burden of dry eye in patients' lives: comparisons to a U.S. normative sample. *Invest Ophthalmol Vis Sci* 2005;46(1):46–50.
12. Uchino M, Schaumberg DA. Dry eye disease: impact on quality of life and vision. *Curr Ophthalmol Rep* 2013;1(2):51–57.
13. Nichols KK, Bacharach J, Holland E, et al. Impact of dry eye disease on work productivity, and patients' satisfaction with over-the-counter dry eye treatments. *Invest Ophthalmol Vis Sci* 2016;57(7):2975–2982.
14. Schiffman RM, Walt JG, Jacobsen G, Doyle JJ, Lebovics G, Sumner W. Utility assessment among patients with dry eye disease. *Ophthalmology* 2003;110(7):1412–1419.
15. Yu J, Asche CV, Fairchild CJ. The economic burden of dry eye disease in the United States: a decision tree analysis. *Cornea* 2011;30(4):379–387.
16. Reddy P, Grad O, Rajagopalan K. The economic burden of dry eye: a conceptual framework and preliminary assessment. *Cornea* 2004;23(8):751–761.
17. Abetz L, Rajagopalan K, Mertzanis P, Begley C, Barnes R, Chalmers R. Impact of Dry Eye on Everyday Life (IDEEL) Study Group. Development and validation of the impact of dry eye on everyday life (IDEEL) questionnaire, a patient-reported outcomes (PRO) measure for the assessment of the burden of dry eye on patients. *Health Qual Life Outcomes* 2011;9:111.
18. Rajagopalan K, Abetz L, Mertzanis P, et al. Comparing the discriminative validity of two generic and one disease-specific health-related quality of life measures in a sample of patients with dry eye. *Value Health* 2005;8(2):168–174.
19. Fairchild CJ, Chalmers RL, Begley CG. Clinically important difference in dry eye: change in IDEEL-symptom bother. *Optom Vis Sci* 2008;85(8):699–707.
20. Farrand KF, Fridman M, Schaumberg DA. The burden of dry eye disease: quality of life, work, activity outcomes, and healthcare resource use. *Invest Ophthalmol Vis Sci* 2016;57(12):6195.
21. Turk T, Elhady MT, Rashed S, et al. Quality of reporting web-based and non-web-based survey studies: what authors, reviewers and consumers should consider. *PLoS One* 2018;13(6):e0194239.
22. Petrillo J, Bressler NM, Lamoureux E, Ferreira A, Cano S. Development of a new Rasch-based scoring algorithm for the National Eye Institute Visual Functioning Questionnaire to improve its interpretability. *Health Qual Life Outcomes* 2017;15(1):157.
23. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20(10):1727–1736.
24. Johnson ME, Murphy PJ. Measurement of ocular surface irritation on a linear interval scale with the ocular comfort index. *Invest Ophthalmol Vis Sci* 2007;48(10):4451–4458.
25. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993;4(5):353–365.
26. Chalmers RL, Begley CG, Caffery B. Validation of the 5-Item Dry Eye Questionnaire (DEQ-5): discrimination across self-assessed severity and aqueous tear deficient dry eye diagnoses. *Cont Lens Anterior Eye* 2010;33(2):55–60.
27. Ngo W, Situ P, Keir N, Korb D, Blackie C, Simpson T. Psychometric properties and validation of the standard patient evaluation of eye dryness questionnaire. *Cornea* 2013;32(9):1204–1210.

28. McMonnies CW, Ho A. Responses to a dry eye questionnaire from a normal population. *J Am Optom Assoc* 1987;58(7):588–591.
29. McMonnies C, Ho A, Wakefield D. Optimum dry eye classification using questionnaire responses. *Adv Exp Med Biol* 1998;438:835–838.
30. Schaumberg DA, Gulati A, Mathers WD, et al. Development and validation of a short global dry eye symptom index. *Ocul Surf* 2007;5(1):50–57.
31. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012;15(5):708–715.
32. Begley CG, Chalmers RL, Abetz L, et al. The relationship between habitual patient-reported symptoms and clinical signs among patients with dry eye of varying severity. *Invest Ophthalmol Vis Sci* 2003;44(11):4753–4761.
33. Nichols KK, Nichols JJ, Mitchell GL. The lack of association between signs and symptoms in patients with dry eye disease. *Cornea* 2004;23(8):762–770.
34. Holland EJ, Luchs J, Karpecki PM, et al. Lifitegrast for the treatment of dry eye disease: results of a phase III, randomized, double-masked, placebo-controlled trial (OPUS-3). *Ophthalmology* 2017;124(1):53–60.
35. Nichols KK, Nichols JJ, Mitchell GL. The reliability and validity of McMonnies Dry Eye Index. *Cornea* 2004;23(4):365–371.
36. Le Q, Zhou X, Ge L, Wu L, Hong J, Xu J. Impact of dry eye syndrome on vision-related quality of life in a non-clinic-based general population. *BMC Ophthalmol* 2012;12:22.