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Age Associations with Dry Eye Clinical Signs and Symptoms in the Dry Eye Assessment and Management (DREAM) Study

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Purpose: To evaluate how increasing age is associated with dry eye disease (DED) signs and symptoms in the Dry Eye Assessment and Management (DREAM) study. This study was undertaken to better understand how DED signs and symptoms differ across decades of life with goals to help assess detection and treatment of DED.

Design: Secondary analysis of the DREAM study.

Subjects: One hundred twenty, 140, 185, and 90 participants aged < 50, 50 to 59, 60 to 69, and ≥ 70 years, respectively.

Methods: We performed a secondary analysis of data from the DREAM study, a multicenter randomized clinical trial, to evaluate the effect of omega-3 fatty acid supplementation for the treatment of DED. At baseline, 6 months, and 12 months follow-up, participants underwent an assessment of DED symptoms and signs using Ocular Surface Disease Index, Brief Pain Inventory, tear break-up time (TBUT) (in seconds), Schirmer test with anesthesia (mm/5 minutes), conjunctival staining, corneal staining, meibomian gland dysfunction evaluation, and tear osmolarity (mOsm/l). Multivariable generalized linear regression models were used to compare DED symptoms and signs across the 4 age groups among all participants and by sex.

Main Outcome Measures: Scores of DED symptoms, individual signs, and composite scores of DED signs.

Results: Among 535 patients with DED, increasing age was significantly associated with worse TBUT ($P = 0.01$), corneal staining ($P < 0.001$), a composite severity score of DED signs ($P = 0.007$), and tear osmolarity ($P = 0.001$). Similar significant differences were found across 4 age groups of 334 women in TBUT, corneal staining score, composite severity score of DED signs, and tear osmolarity (all $P < 0.05$) but not in men.

Conclusion: We found that corneal staining, TBUT, tear osmolarity, and a composite severity score of DED signs were significantly more severe with increasing age in women but not in men; worsening symptoms did not increase with increasing age.

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Dry eye disease (DED) has a severe impact on patients' quality of life[1,2] and has a prevalence that increases with age in both sexes.[3–8] Prevalence differences across age groups present a distinct disparity: only 8.4% of individuals younger than 60 report a diagnosis of DED compared with 15% in individuals from 70 to 79 years of age and 20% in individuals older than 80.[9,10] With an increasingly aging population across the world, DED will continue to grow as a public health issue.

However, there is uncertainty regarding whether aging is a DED causal factor or if DED is simply an age-related disease. The effects of aging on DED seem to be multifaceted. For example, aging appears to cause various changes on the ocular surface. Aging has been found to be a risk factor for increased goblet cell loss,[11–16] as well as for profound lacrimal gland and ocular surface alterations.[11,13,17–23] From a structural standpoint, aging may also cause other anatomic changes, such an anterior shift of Marx's line.[24] Theorized mechanisms that contribute to the increased prevalence of DED in older age include immunosenescence, or aging of the immune system, causing effects such as a decrease in naive T cells and an increased state of chronic inflammation.[25–28]

In addition, aging may affect various ocular surface signs in different ways. For example, in a study of 140 volunteers (70 men and 70 women) with no ocular symptoms or ocular surface disorders, Ozdemir et al[29] found a significant decrease in tear break-up time (TBUT) with increasing age across the 7 decades spanning 11 to 86 years of age, with an especially highly significant difference between the younger and older decades. However, the same group found that, although Schirmer test results decreased with increasing age, these changes were not significant.[29] In another study, Maïssa et al[30] reported that, in individuals

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without DED, tear film stability was impacted by age, with a significantly shorter TBUT in older individuals. Additionally, the lipid layer was significantly thinner for patients older than 45. In particular, older women had significantly thinner lipid layers in comparison to younger women and older men.[30] Obata et al[31,32] also reported that signs of lacrimal gland deterioration, as indicated by diffuse fibrosis and atrophy in orbital lobes, increase with age and may be more frequent in women than in men. We previously reported on sex-related differences in DED in the Dry Eye Assessment and Management (DREAM) study, noting that women demonstrate more severe signs in comparison to men and that postmenopausal women have more severe signs in comparison to premenopausal women.[33]

Overall, a more comprehensive overview that includes a wide range of DED signs and symptoms regarding age-related differences is needed to improve our understanding of associations of DED and age differences. This study aims to provide a detailed analysis of age-related effects on DED symptoms and signs by conducting a secondary analysis of rich data from the DREAM study. The DREAM study, a multicenter randomized clinical trial assessing the efficacy and safety of oral omega-3 supplementation for treatment of DED, provides standard comprehensive assessment of DED symptoms and signs in a large and well-defined cohort.[34] As a result, an in-depth analysis of this well-established cohort may provide insight into clinically relevant differences in the dry eye symptoms and signs across various age groups among patients with DED.

Methods

This is a secondary analysis of data from the DREAM study (ClinicalTrials.gov identifier, NCT02128763). The results of the DREAM study were previously published and showed that the active treatment group that received omega-3 supplementation did not show a significant difference in DED signs and symptoms compared with the placebo group that received olive oil pills.[34] Briefly, 535 patients with moderate to severe DED and who were $\geq$ 18 years of age were enrolled in the study. All enrolled patients had moderate to severe DED symptoms for at least 6 months before the screening visit, use or desired use of artificial tears twice daily in the 2 weeks before the screening visit, and an Ocular Surface Disease Index (OSDI) score of 25 to 80 at the screening visit and 21 to 80 at the baseline visit. Full details on the inclusion and exclusion criteria and outcome measures can be found in the previously published primary results of the DREAM study.[34] The study was approved by the institutional review board/ethics committee at each center (centers listed in Credit Roster for the DREAM study, available at www.opthalmologyscience.org), followed the tenets of the Declaration of Helsinki, and written informed consent was obtained from all patients.

Dry eye symptom outcome measures taken at baseline, 6 months, and 12 months follow-up included the OSDI score (scale of 0 to 100) and the Brief Pain Inventory score,[35] with higher scores indicative of more severe symptoms. The measures for dry eye signs (measured per eye) included conjunctival staining scores (ranging from 0 to 6) and corneal staining scores (0 to 15), TBUT, and Schirmer test with anesthesia. More severe signs were indicated by lower TBUT, lower Schirmer test score, higher conjunctival staining score, higher corneal staining score, and higher tear osmolarity.

Tear film osmolarity was measured from both eyes at baseline, 6 months, and 12 months at 19 of the 27 clinical centers that had the TearLab Osmolarity System (OcuSense Inc).

Each patient was also administered the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) version 2.0 at baseline, 6 months, and 12 months follow-up. Two summary scores were generated from the survey: the physical component summary and mental component summary (MCS). The MCS is scored between 0 and 100, with higher scores indicating greater psychological well-being. The recommended cutoff of 42 in MCS score has sensitivity of 73.7% and specificity of 80.6% for identifying clinical depression.[36]

Statistical Analysis

To evaluate how the age is associated with DED symptoms and signs that can be nonlinear, we categorized age into 4 age groups, including $<$ 50, 50 to 59, 60 to 69, and $\geq$ 70 years. We compared the demographics, comorbidities, scores for dry eye symptoms, and signs across these 4 age groups using generalized linear regression models for continuous measurements and the χ^2 test or Fisher exact test for categorical measurements. For the comparison of dry eye symptoms and signs, the generalized linear regression models were performed with and without an adjustment for sex, race, smoking status, and several comorbidities that were previously found to be associated with the severity of dry eye symptoms and signs in the DREAM study, including facial rosacea, rheumatoid arthritis, peripheral artery disease, Sjögren syndrome,[37] and depression defined as MCS score $\leq$ 42.[38] We performed these analyses using the combined data of baseline, 6 months, and 12 months with time modeled as a categorical variable to improve statistical power. The correlations from repeated measures across visits and between eyes within the same participant (for comparison of eye-specific dry eye signs) were accounted for using generalized estimating equations. Similar analyses were performed for each time point separately to check the consistency of results across time. Because omega-3 supplementation did not show a significant effect on DED signs and symptoms compared with placebo,[34] all these evaluations were based on the data from the 2 treatment groups combined.

For the comparison of each DED sign across age groups, individual signs from both eyes of all time points were used. In addition, we adapted a method from previous studies[37,38] to calculate a composite dry eye severity score of signs by transforming the individual score of each of the 5 dry eye signs (TBUT, Schirmer testing, corneal staining, conjunctival staining, and meibomian gland dysfunction [MGD]) to a common unit severity score between 0 (no DED signs) and 1 (most severe signs). A composite signs severity score for each eye was then calculated by averaging severity scores of the 6 individual DED signs. The composite sign severity score ranges from 0 to 1, with 1 indicating the most severe dry eye signs. This composite score allows for 1 continuous metric of assessing objective DED sign severity based on 5 separate dry eye sign measures.[39,40]

All statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc), and 2-sided $P < 0.05$ was considered statistically significant.

Results

Table 1 shows the comparison of baseline characteristics among the 4 age groups of DREAM participants. Across

Table 1. Comparison of Baseline Characteristics among Different Age Groups

	Age (yrs)				
	< 50 (n = 120)	[50, 59] (n = 140)	[60, 69] (n = 185)	≥ 70 (n = 90)	P
Sex, n (%)					0.23*
Female	95 (79.2)	113 (80.7)	158 (85.4)	68 (75.6)	
Male	25 (20.8)	27 (19.3)	27 (14.6)	22 (24.4)	
Ethnicity, n (%)					**< 0.001**†
Hispanic or Latino	26 (21.7)	24 (17.1)	15 (8.1)	3 (3.3)	
Not Hispanic or Latino	93 (77.5)	115 (82.1)	170 (91.9)	85 (94.4)	
Unable to answer	1 (0.8)	1 (0.7)	0 (0.0)	2 (2.2)	
Race, n (%)					**< 0.001**†
White	81 (67.5)	97 (69.3)	146 (78.9)	74 (82.2)	
Black	11 (9.2)	21 (15.0)	23 (12.4)	9 (10.0)	
Asian	9 (7.5)	3 (2.1)	5 (2.7)	2 (2.2)	
American Indian or Alaskan Native	0 (0.0)	0 (0.0)	1 (0.5)	2 (2.2)	
More than 1 race	4 (3.3)	1 (0.7%)	3 (1.6)	1 (1.1)	
Unable to answer	15 (12.5)	18 (12.9)	7 (3.8)	2 (2.2)	
Cigarette smoking, n (%)					**< 0.001***
Never	97 (80.8)	97 (69.3)	123 (66.5)	50 (55.6)	
Former	15 (12.5)	33 (23.6)	58 (31.4)	36 (40.0)	
Current	8 (6.7)	10 (7.1)	4 (2.2)	4 (4.4)	
Taking statin, n (%)					**0.009***
No	112 (93.3)	115 (82.1)	126 (68.1)	53 (58.9)	
Yes	8 (6.7)	25 (17.9)	59 (31.9)	37 (41.1)	**< 0.001***
Rosacea (facial), yes (%)	19 (15.8)	22 (15.7)	44 (23.8)	24 (26.7)	0.07
Sjögren syndrome met 2012 ACR criteria, yes (%)	11 (9.2)	16 (11.4)	16 (8.6)	9 (10.0)	0.90*
Self-reported peripheral artery disease, ongoing (%)	9 (7.5)	5 (3.6)	20 (10.8)	13 (14.4)	**0.002**†
Self-reported thyroid dysfunction, ongoing (%)	15 (12.5)	23 (16.4)	37 (20.0)	19 (21.1)	0.07†
Self-reported hypertension, ongoing (%)	11 (9.2)	34 (24.3)	67 (36.2)	37 (41.1)	**< 0.001**†
Self-reported diabetes, ongoing (%)	7 (5.8)	13 (9.3)	24 (13.0)	13 (14.4)	0.25†
Self-reported rheumatoid arthritis, ongoing (%)	8 (6.7)	16 (11.4)	14 (7.6)	9 (10.0)	0.53†
Self-reported irritable bowel, ongoing (%)	13 (10.8)	12 (8.6)	11 (5.9)	8 (8.9)	0.64†
Self-reported osteoarthritis, ongoing (%)	7 (5.8)	21 (15.0)	62 (33.5)	44 (48.9)	**< 0.001**†
Self-reported hypercholesterolemia, ongoing (%)	10 (8.3)	41 (29.3)	80 (43.2)	40 (44.4)	**< 0.001**†
Self-reported depression, ongoing (%)	19 (15.8)	26 (18.6)	27 (14.6)	15 (16.7)	0.98*
Taking antidepressants, yes (%)	26 (21.7)	35 (25.0)	37 (20.0)	20 (22.2)	0.76*
Summary component measures of physical health, mean (SD)	48.8 (9.85)	47.9 (10.29)	46.7 (9.56)	46.7 (8.47)	0.23‡
Summary component measures of mental health, mean (SD)	49.6 (9.50)	50.8 (10.03)	54.5 (8.31)	54.1 (8.98)	**< 0.001**‡
MCS ≤ 42, yes (%)	21 (17.5)	30 (21.4)	22 (11.9)	11 (12.2)	0.09*
Treatments used for DED§, n (%)					
Artificial tears or gel	86 (71.7)	103 (73.6)	154 (83.2)	81 (90.0)	**0.002***
Cyclosporine drops	12 (10.0)	29 (20.7)	43 (23.2)	21 (23.3)	**0.02***
Warm lid soaks	17 (14.2)	23 (16.4)	51 (27.6)	23 (25.6)	**0.01***
Lid scrubs or baby shampoo	16 (13.3)	19 (13.6)	31 (16.8)	17 (18.9)	**0.61***
Other	26 (21.7)	43 (30.7)	72 (38.9)	35 (38.9)	**0.009***

ACR = American College of Rheumatology; ANOVA = analysis of variance; DED = dry eye disease; MCS = mental component summary; SD = standard deviation. Boldface indicates statistical significance.
*χ^2 test.
†Fisher exact test.
‡ANOVA F-test.
§Participants can take > 1 treatment for DED at the same time.

Table 2. Association of DED Symptoms and Signs and Age among DREAM Participants (Combining Baseline, 6 Mos, and 12 Mos)

	< 50		[50, 59]		[60, 69]		≥ 70				
Dry Eye Symptoms and Signs	*n*	*Mean (SD)*	*n*	*Mean (SD)*	*n*	*Mean (SD)*	*n*	*Mean (SD)*	**P**	**Adjusted P***	**Adjusted P†**
OSDI total score	324	35.73 (18.71)	392	36.19 (19.70)	525	34.92 (17.75)	263	33.26 (17.61)	0.24	0.18	0.16
BODI score	324	26.06 (17.51)	392	27.65 (19.10)	525	24.47 (17.46)	263	25.74 (17.86)	0.44	0.67	0.92
BODI #3 pain score	324	36.36 (21.20)	391	38.13 (21.57)	525	36.50 (20.92)	263	38.06 (22.01)	0.66	0.63	0.56
Tear break-up time (sec)	648	4.06 (3.27)	784	3.59 (2.22)	1050	3.26 (2.02)	526	3.36 (2.01)	**0.001**	**0.005**	**0.01**
Schirmer test (mm in 5 min)	646	11.22 (7.82)	776	9.85 (7.50)	1046	9.08 (6.42)	524	9.46 (5.59)	**0.007**	**0.03**	0.07
Corneal staining score	648	2.47 (2.33)	784	3.37 (3.12)	1050	3.60 (2.87)	526	4.31 (3.01)	**< 0.001**	**< 0.001**	**< 0.001**
Conjunctival staining score	648	2.47 (1.54)	784	2.94 (1.68)	1050	2.56 (1.59)	526	2.79 (1.53)	0.40	0.27	0.29
Meibomian gland abnormality	648	2.69 (1.91)	784	2.85 (1.82)	1048	3.10 (1.98)	526	3.05 (1.84)	**0.03**	**0.01**	0.13
Composite dry eye severity score based on signs	648	0.42 (0.27)	784	0.52 (0.30)	1050	0.53 (0.29)	526	0.53 (0.28)	**< 0.001**	**0.001**	**0.007**
Tear osmolarity (mOsms/l)	490	300.19 (14.99)	539	303.62 (18.33)	772	302.99 (16.73)	364	305.76 (18.72)	**0.006**	**0.004**	**0.001**

BODI = Brief Pain Inventory; DED = dry eye disease; DREAM = Dry Eye Assessment and Management; MCS = mental component summary; OSDI = Ocular Surface Disease Index; SD = standard deviation.
All the *P* values are from the linear trend test. Boldface indicates statistical significance.
*Adjusted by sex and race.
†Adjusted by sex, race, smoking status, Sjögren syndrome, facial rosacea, rheumatoid arthritis, peripheral artery disease, and depression defined by MCS ≤ 42.

4 age groups (< 50, 50−59, 60−69, ≥ 70 years), older age groups had a higher percent of White race (67.5% vs. 69.3% vs. 78.9% vs. 82.2%, $P < 0.001$) and a higher percent of non-Hispanic or Latino ethnicity (77.5% vs. 82.1% vs. 91.9% vs. 94.4%, $P < 0.001$). Older age groups had a lower percent of never smokers (80.8% vs. 69.3% vs. 66.5% vs. 55.6%, $P < 0.001$), a higher percent of self-reported ongoing peripheral artery disease (7.5% vs. 3.6% vs. 10.8% vs. 14.4%, $P = 0.002$), and a higher percent of hypertension (12.5% vs. 16.4% vs. 20.0% vs. 21.1%, $P < 0.001$). Older age groups also had a higher percent with osteoarthritis (5.8% vs. 15.0% vs. 33.5% vs. 48.9%, $P < 0.001$), with hypercholesteremia (8.3% vs. 29.3% vs. 43.2% vs. 44.4%, $P < 0.001$), and taking statin medications (6.7% vs. 17.9% vs. 31.9% vs. 41.1%, $P < 0.001$) and a higher mean summary component measure of mental health (49.6 vs. 50.8 vs. 54.5 vs. 54.1, $P < 0.001$). Regarding treatment for dry eye, older age groups had a higher percent of using tears or gel (71.7% vs. 73.6% vs. 83.2% vs. 90.0%, $P = 0.002$) and using more cyclosporine drops (10.0% vs. 20.7% vs. 23.2% vs. 23.3%, $P = 0.02$) and warm liquid soaks (14.2% vs. 16.4% vs. 27.6% vs. 25.6%, $P = 0.01$). They also used more other dry eye treatments beyond artificial tears or gel, cyclosporine drops, warm lid soaks, lid scrubs, or baby shampoo (21.7% vs. 30.7% vs. 38.9% vs. 38.9%, $P = 0.009$).

Dry eye disease symptoms and signs across the 4 age groups were compared using the combined data (Table 2) from baseline (Table 3), 6-month visit (Table 4), and 12-month visit (Table 5). In both the unadjusted and adjusted analysis, there were no significant differences across age groups in dry eye symptom scores as measured by the OSDI and Brief Pain Inventory. In analyses adjusted by sex and race, the older age group had more severe signs, including lower mean TBUT (4.06 vs. 3.59 vs. 3.26 vs. 3.36 seconds; $P = 0.001$), lower Schirmer test score (11.22 vs. 9.85 vs. 9.08 vs. 9.46; $P = 0.007$), higher mean score in corneal staining (2.47 vs. 3.37 vs. 3.60 vs. 4.31; $P < 0.001$), and more meibomian gland abnormality (2.69 vs. 2.85 vs. 3.10 vs. 3.05; $P = 0.03$). Composite dry eye severity scores based on signs (0.42 vs. 0.52 vs. 0.53 vs. 0.53; $P < 0.001$) were higher in older age groups. Tear osmolarity (300.2 vs. 303.6 vs. 303.0 vs. 305.8; $P = 0.006$) was also significantly greater in older groups. Even after adjusting for sex, race, smoking status, Sjögren syndrome, facial rosacea, rheumatoid arthritis, peripheral artery disease, and depression, these significant differences across 4 age groups still remained significant for TBUT ($P = 0.01$), corneal staining ($P < 0.001$), composite dry eye severity score based on signs ($P = 0.007$), and tear osmolarity ($P = 0.001$), whereas the differences in Schirmer test scores ($P = 0.07$) and meibomian gland abnormality ($P = 0.13$) were no longer significant.

When analyzing combined data from baseline, 6-month, and 12-month visits for female patients with an adjustment for demographic and comorbidities (Table 6), older age groups had a lower mean TBUT (4.08 vs. 3.48 vs. 3.18 vs. 3.18 sec; $P = 0.002$), higher mean corneal staining score (2.37 vs. 3.72 vs. 3.77 vs. 4.55; $P < 0.001$), higher composite dry eye severity score based on signs (0.42 vs. 0.55 vs. 0.55 vs. 0.55; $P = 0.003$), and higher tear osmolarity (299.7 vs. 303.7 vs. 303.3 vs. 307.8; $P < 0.001$). However, in male participants, there were no significant differences in any DED symptoms or signs or symptoms across the 4 age groups (Table 7). Furthermore, there was no significant interaction of each covariate with age for each outcome of signs and symptoms.

When we compared the 4 age groups for changes in symptoms and signs from baseline at 6-month and 12-month visits, there were no significant differences across age groups (Table 8). When analyzing women and men separately, only change from baseline in TBUT was significantly different in women, with the older age group having less change (0.85 vs. 0.66 vs. 0.61 vs. 0.12, $P = 0.04$, Table S9, available at

Table 3. Association of DED Symptoms and Signs and Age among DREAM Participants at Baseline

	< 50		[50, 59]		[60, 69]		≥ 70				
Dry Eye Symptoms and Signs	*n*	*Mean (SD)*	*n*	*Mean (SD)*	*n*	*Mean (SD)*	*n*	*Mean (SD)*	**P**	**Adjusted P***	**Adjusted P†**
OSDI total score	120	43.13 (15.54)	140	43.10 (16.34)	185	41.67 (15.23)	90	39.83 (14.71)	0.10	0.12	0.13
BODI score	120	32.13 (17.51)	140	32.66 (17.53)	185	29.34 (16.47)	90	29.49 (16.30)	0.09	0.15	0.32
BODI #3 pain score	120	42.08 (18.83)	139	44.17 (19.33)	185	42.43 (19.05)	90	42.56 (19.58)	0.94	0.91	0.86
Tear break-up time (sec)	240	3.51 (2.01)	280	3.12 (1.56)	370	2.88 (1.48)	180	3.19 (2.07)	0.053	0.10	0.21
Schirmer test (mm in 5 min)	240	11.28 (8.30)	280	9.50 (7.70)	370	8.79 (6.17)	180	8.97 (5.38)	**0.004**	**0.03**	**0.047**
Corneal staining score	240	2.83 (2.39)	280	3.92 (3.22)	370	3.97 (2.81)	180	4.56 (3.21)	**< 0.001**	**< 0.001**	**< 0.001**
Conjunctival staining score	240	2.73 (1.44)	280	3.21 (1.58)	370	2.89 (1.57)	180	2.94 (1.46)	0.62	0.34	0.37
Meibomian gland abnormality	240	2.94 (1.90)	280	3.05 (1.72)	370	3.21 (1.93)	180	3.10 (1.79)	0.28	0.14	0.48
Composite dry eye severity score based on signs	240	0.42 (0.27)	280	0.53 (0.30)	370	0.53 (0.28)	180	0.51 (0.30)	**0.01**	**0.01**	**0.04**
Tear osmolarity (mOsms/l)	186	300.66 (16.22)	197	302.41 (16.50)	283	302.83 (15.57)	128	305.55 (16.91)	**0.045**	0.06	**0.04**

BODI = Brief Pain Inventory; DED = dry eye disease; DREAM = Dry Eye Assessment and Management; MCS = mental component summary; OSDI = Ocular Surface Disease Index; SD = standard deviation.
All the *P* values are from the linear trend test. Boldface indicates statistical significance.
*Adjusted by sex and race.
†Adjusted by sex, race, smoking status, Sjögren syndrome, facial rosacea, rheumatoid arthritis, peripheral artery disease, and depression defined by MCS ≤ 42.

www.ophthalmologyscience.org). However, the TBUT change from baseline in men was not significant ($P = 0.91$, Table S10, available at www.ophthalmologyscience.org).

Discussion

In this secondary analysis of data from the DREAM study of subjects with moderate to severe DED, we found that there were significant differences across the 4 age groups (< 50, 50−59, 60−69, and ≥ 70 years) for TBUT, meibomian gland abnormalities, corneal staining, and tear osmolarity and for a composite severity score of DED signs, with older age groups having more severe dry eye signs. These differences across the age groups held true for the cohort of women but not for men in the DREAM study. We did not find any significant difference in dry eye symptoms across age groups in either men or women.

Our finding that dry eye signs worsen with increasing age is mostly consistent with previous studies. For example, Lemp et al[41] studied 314 subjects between 18 and 82 years of age and found that the relative level of severity and rate of people with DED increased with increasing age. Similarly, in a large Iranian study that included patients 40 to 64 years of age, Hashemi et al[42] found that the prevalence of abnormal TBUT, corneal staining, and Schirmer test score increased significantly with age. However, Hashemi et al[42] looked at a smaller age range, and therefore, our study may be more informative by examining DED signs and symptoms across broader age groups. Furthermore, in contrast to Hashemi et al,[42] who evaluated the prevalence of abnormal values across clinical DED signs and

Table 4. Association of DED Symptoms and Signs and Age among DREAM Participants at 6 Mos

	< 50		[50, 59]		[60, 69]		≥ 70				
Dry Eye Symptoms and Signs	*n*	*Mean (SD)*	*n*	*Mean (SD)*	*n*	*Mean (SD)*	*n*	*Mean (SD)*	**P**	**Adjusted P***	**Adjusted P†**
OSDI total score	101	32.13 (19.45)	127	33.61 (19.87)	168	32.08 (18.48)	85	30.26 (18.94)	0.43	0.30	0.33
BODI score	101	22.30 (14.99)	127	26.31 (19.42)	168	23.44 (17.65)	85	24.84 (18.78)	0.66	0.41	0.17
BODI #3 pain score	101	33.17 (21.30)	127	36.46 (21.21)	168	35.06 (20.82)	85	36.82 (22.48)	0.37	0.28	0.23
Tear break-up time (sec)	202	4.37 (4.09)	254	3.82 (2.69)	336	3.44 (2.12)	170	3.41 (1.97)	**0.007**	**0.01**	**0.02**
Schirmer test (mm in 5 min)	202	11.61 (7.72)	250	9.81 (7.19)	334	9.23 (6.77)	168	9.63 (5.78)	**0.02**	0.053	0.10
Corneal staining score	202	2.29 (2.16)	254	3.24 (3.08)	336	3.49 (2.89)	170	4.02 (2.85)	**< 0.001**	**< 0.001**	**< 0.001**
Conjunctival staining score	202	2.36 (1.63)	254	2.96 (1.67)	336	2.38 (1.57)	170	2.73 (1.60)	0.75	0.60	0.51
Meibomian gland abnormality	202	2.63 (1.91)	254	2.77 (1.85)	334	3.02 (2.00)	170	2.94 (1.89)	0.12	0.08	0.46
Composite dry eye severity score based on signs	202	0.42 (0.27)	254	0.52 (0.30)	336	0.52 (0.29)	170	0.54 (0.28)	**0.003**	**0.006**	**0.03**
Tear osmolarity (mOsms/l)	149	299.48 (13.49)	173	305.33 (21.21)	242	303.61 (16.37)	112	304.19 (18.16)	0.09	**0.03**	**0.01**

BODI = Brief Pain Inventory; DED = dry eye disease; DREAM = Dry Eye Assessment and Management; MCS = mental component summary; OSDI = Ocular Surface Disease Index; SD = standard deviation.
All the *P* values are from the linear trend test. Boldface indicates statistical significance.
*Adjusted by sex and race.
†Adjusted by sex, race, smoking status, Sjögren syndrome, facial rosacea, rheumatoid arthritis, peripheral artery disease, and depression defined by MCS ≤ 42.

Table 5. Association of DED Symptoms and Signs and Age among DREAM Participants at 12 Mos

	< 50		[50, 59]		[60, 69]		≥ 70				
Dry Eye Symptoms and Signs	*n*	*Mean (SD)*	*n*	*Mean (SD)*	*n*	*Mean (SD)*	*n*	*Mean (SD)*	**P**	**Adjusted P***	**Adjusted P†**
OSDI total score	103	30.65 (18.77)	125	31.06 (20.86)	172	30.42 (17.47)	88	29.45 (17.27)	0.63	0.45	0.32
BODI score	103	22.69 (17.99)	125	23.38 (19.34)	172	20.24 (17.14)	88	22.78 (17.99)	0.55	0.70	0.57
BODI #3 pain score	103	32.82 (22.42)	125	33.12 (22.84)	172	31.51 (21.49)	88	34.66 (23.34)	0.82	0.82	0.99
Tear break-up time (sec)	206	4.41 (3.46)	250	3.89 (2.25)	344	3.50 (2.35)	176	3.47 (1.99)	**0.003**	**0.01**	**0.02**
Schirmer test (mm in 5 min)	204	10.75 (7.34)	246	10.28 (7.59)	342	9.25 (6.34)	176	9.80 (5.63)	0.11	0.24	0.42
Corneal staining score	206	2.24 (2.38)	250	2.90 (2.96)	344	3.30 (2.87)	176	4.34 (2.95)	**< 0.001**	**< 0.001**	**< 0.001**
Conjunctival staining score	206	2.27 (1.51)	250	2.60 (1.75)	344	2.39 (1.58)	176	2.70 (1.54)	0.16	0.14	0.23
Meibomian gland abnormality	206	2.46 (1.90)	250	2.71 (1.87)	344	3.06 (2.00)	176	3.10 (1.85)	**0.003**	**0.003**	**0.02**
Composite dry eye severity score based on signs	206	0.42 (0.28)	250	0.50 (0.30)	344	0.53 (0.29)	176	0.55 (0.26)	**< 0.001**	**< 0.001**	**0.006**
Tear osmolarity (mOsms/l)	155	300.30 (14.88)	169	303.28 (17.11)	247	302.58 (18.33)	124	307.40 (20.88)	**0.02**	**0.03**	**0.006**

BODI = Brief Pain Inventory; DED = dry eye disease; DREAM = Dry Eye Assessment and Management; MCS = mental component summary; OSDI = Ocular Surface Disease Index; SD = standard deviation.
All the *P* values are from the linear trend test. Boldface indicates statistical significance.
*Adjusted by sex and race.
†Adjusted by sex, race, smoking status, Sjögren syndrome, facial rosacea, rheumatoid arthritis, peripheral artery disease, and depression defined by MCS ≤ 42.

symptoms, our study allowed us to examine significant differences in mean values, not whether or not they fall within a certain range. Thus, our study provides more detailed data of significant differences involving TBUT decreasing with age, corneal staining increasing with age, and Schirmer testing decreasing with age.

The evaluation of MGD with increasing age is of particular interest in relation to DED. For example, Tellefsen Nøland et al[43] compared tear osmolarity, TBUT, ocular surface staining, corneal staining, Schirmer test score, and meibomian expressibility and quality across 1823 DED Norwegian patients aged 20 to 39 years, 40 to 59 years, and ≥ 60 years. This study found that increasing age was significantly associated with a lower TBUT, a lower Schirmer test score, and worse meibum expressibility. The findings of this study are similar to our findings of significant associations of increasing age with lower TBUT, lower Schirmer scores, and greater meibomian abnormalities. However, in contrast to Tellefsen Nøland et al, we also found significantly higher corneal staining and higher composite dry eye severity scores.

In another recent study, Badian et al[44] analyzed 900 subjects who presented for DED evaluation and found that MGD was highly prevalent in over 93% of patients but that the prevalence was not associated with age or sex. However, there was an association between MGD and symptoms. Finally, a large Spanish study of 1000 participants found that the prevalence of asymptomatic MGD increased with age and was higher in men than in

Table 6. Association of DED Symptoms and Signs and Age among DREAM Female Participants (Combining Baseline, 6 Mos, and 12 Mos)

	< 50		[50, 59]		[60, 69]		≥ 70				
Dry Eye Symptoms and Signs	*n*	*Mean (SD)*	*n*	*Mean (SD)*	*n*	*Mean (SD)*	*n*	*Mean (SD)*	**P**	**Adjusted P***	**Adjusted P†**
OSDI total score	259	36.81 (19.26)	317	36.44 (19.41)	451	35.73 (17.60)	198	32.95 (17.74)	0.17	0.11	0.14
BODI score	259	27.36 (18.04)	317	27.22 (18.90)	451	24.27 (17.61)	198	25.41 (18.31)	0.17	0.28	0.57
BODI #3 pain score	259	37.99 (21.27)	316	38.26 (21.02)	451	36.45 (20.86)	198	38.23 (22.54)	0.81	0.79	0.99
Tear break-up time (sec)	518	4.08 (3.12)	634	3.48 (2.06)	902	3.18 (1.98)	396	3.18 (1.87)	**< 0.001**	**0.001**	**0.002**
Schirmer test (mm in 5 minutes)	516	10.76 (7.63)	626	8.99 (6.66)	898	8.64 (6.22)	394	9.19 (5.33)	0.03	0.11	0.18
Corneal staining score	518	2.37 (2.30)	634	3.72 (3.22)	902	3.77 (2.91)	396	4.55 (3.11)	**< 0.001**	**< 0.001**	**< 0.001**
Conjunctival staining score	518	2.42 (1.54)	634	3.01 (1.67)	902	2.65 (1.63)	396	2.85 (1.54)	0.20	0.13	0.13
Meibomian gland abnormality	518	2.71 (1.89)	634	2.93 (1.85)	900	3.16 (1.96)	396	3.09 (1.79)	**0.04**	**0.02**	0.10
Composite dry eye severity score based on Signs	518	0.42 (0.28)	634	0.55 (0.29)	902	0.55 (0.28)	396	0.55 (0.27)	**< 0.001**	**0.001**	**0.003**
Tear osmolarity (mOsms/l)	384	299.72 (14.35)	416	303.71 (16.77)	680	303.34 (16.90)	283	307.76 (19.47)	**< 0.001**	**< 0.001**	**< 0.001**

BODI = Brief Pain Inventory; DED = dry eye disease; DREAM = Dry Eye Assessment and Management; MCS = mental component summary; OSDI = Ocular Surface Disease Index; SD = standard deviation.
All the *P* values are from the linear trend test. Boldface indicates statistical significance.
*Adjusted by race.
†Adjusted by race, smoking status, Sjögren syndrome, facial rosacea, rheumatoid arthritis, peripheral artery disease, and depression defined by MCS ≤ 42.

Table 7. Association of DED Symptoms and Signs and Age among DREAM Male Participants (Combining Baseline, 6 Mos, and 12 Mos)

	< 50		[50, 59]		[60, 69]		≥ 70				
Dry Eye Symptoms and Signs	*n*	*Mean (SD)*	*n*	*Mean (SD)*	*n*	*Mean (SD)*	*n*	*Mean (SD)*	**P**	**Adjusted P***	**Adjusted P†**
OSDI total score	65	31.46 (15.74)	75	35.10 (20.96)	74	29.96 (18.01)	65	34.23 (17.31)	0.72	0.73	0.95
BODI score	65	20.88 (14.16)	75	29.47 (19.94)	74	25.70 (16.58)	65	26.76 (16.48)	0.23	0.19	0.30
BODI #3 pain score	65	29.85 (19.72)	75	37.60 (23.93)	74	36.76 (21.46)	65	37.54 (20.47)	0.16	0.13	0.18
Tear break-up time (sec)	130	4.01 (3.80)	150	4.08 (2.75)	148	3.76 (2.18)	130	3.89 (2.32)	0.68	0.81	0.85
Schirmer test (mm in 5 min)	130	13.04 (8.30)	150	13.43 (9.50)	148	11.77 (6.93)	130	10.28 (6.28)	0.08	0.11	0.09
Corneal staining score	130	2.88 (2.42)	150	1.92 (2.16)	148	2.53 (2.29)	130	3.58 (2.58)	0.14	0.21	0.50
Conjunctival staining score	130	2.68 (1.52)	150	2.62 (1.69)	148	2.06 (1.21)	130	2.62 (1.49)	0.50	0.56	0.63
Meibomian gland abnormality	130	2.62 (2.01)	150	2.52 (1.63)	148	2.74 (2.02)	130	2.92 (1.99)	0.42	0.37	0.87
Composite dry eye severity score based on signs	130	0.41 (0.24)	150	0.37 (0.29)	148	0.37 (0.26)	130	0.47 (0.30)	0.46	0.51	0.97
Tear osmolarity (mOsms/l)	106	301.89 (17.06)	123	303.31 (22.91)	92	300.42 (15.26)	81	298.77 (13.79)	0.30	0.38	0.90

BODI = Brief Pain Inventory; DED = dry eye disease; DREAM = Dry Eye Assessment and Management; MCS = mental component summary; OSDI = Ocular Surface Disease Index; SD = standard deviation.
All the *P* values are from the linear trend test.
*Adjusted by race.
†Adjusted by race, smoking status, Sjögren syndrome, facial rosacea, rheumatoid arthritis, peripheral artery disease, and depression defined by MCS ≤ 42.

women. The authors noted that the subjects with asymptomatic MGD also had higher abnormal TBUT and fluorescein staining than symptomatic MGD patients.[45] Thus, a lack of signs does not necessarily indicate the degree of ocular damage. Further investigation to help elucidate these mechanisms is needed.

There are several possible explanations as to why dry eye signs worsen with increasing age. One possibility explaining this trend involves the role of oxidative stress,[46] which develops with aging.[47] For example, Augustin et al[48] reported that oxidative reactions increased inflammatory markers in patients with more severe DED. They also found that the oxidative damage to the ocular surface was significantly correlated with increased lipid peroxidase in tear films. This study provides the basis for several theories of why DED severity may increase with age. There are also several other hypotheses as to why DED severity may increase with age. For example, it is possible that changes in epithelial damage and DNA alterations are exacerbated by inflammatory processes in the conjunctival epithelium, corneal epithelium, and accessory lacrimal glands,[49] which are more likely to occur with the progression of time in one's lifetime. Furthermore, it is possible that the healing process from oxidative damage is either partially or completely hindered by oxidative strain, leading to increased damage from these reactions.[50–52] Lifetime exposure to factors such as pollutants, ultraviolet radiation, ozone, and eyedrops are noted to increase

Table 8. Association of change in DED Symptoms and Signs from Baseline and Age among DREAM Participants (Combining 6 Mos and 12 Mos)

	< 50		[50, 59]		[60, 69]		≥ 70				
Dry Eye Symptoms and Signs	*n*	*Mean (SD)*	*n*	*Mean (SD)*	*n*	*Mean (SD)*	*n*	*Mean (SD)*	**P**	**Adjusted P***	**Adjusted P†**
OSDI total score	204	−12.19 (20.11)	252	−10.62 (20.13)	340	−10.84 (16.33)	173	−9.72 (15.56)	0.36	0.54	0.65
BODI score	204	−10.31 (18.55)	252	−7.03 (17.32)	340	−7.41 (16.81)	173	−5.28 (16.29)	0.052	**0.04**	0.07
BODI #3 pain score	204	−10.54 (22.53)	250	−8.60 (22.41)	340	−8.85 (21.01)	173	−6.30 (21.22)	0.18	0.14	0.24
Tear break-up time (sec)	408	0.94 (3.59)	504	0.72 (2.33)	680	0.64 (1.99)	346	0.31 (2.21)	0.053	0.07	0.09
Schirmer test (mm in 5 min)	406	0.09 (7.33)	496	0.53 (6.55)	676	0.57 (6.53)	344	0.72 (5.39)	0.41	0.51	0.53
Corneal staining score	408	−0.68 (2.05)	504	−0.73 (2.29)	680	−0.64 (2.34)	346	−0.42 (2.65)	0.34	0.42	0.37
Conjunctival staining score	408	−0.47 (1.33)	504	−0.42 (1.46)	680	−0.47 (1.31)	346	−0.23 (1.38)	0.22	0.36	0.64
Meibomian gland abnormality	408	−0.42 (1.83)	504	−0.26 (1.95)	678	−0.21 (2.01)	346	−0.08 (1.77)	0.08	0.16	0.21
Composite dry eye severity score based on signs	408	−0.02 (0.24)	504	−0.01 (0.24)	680	−0.01 (0.26)	346	0.03 (0.25)	0.11	0.22	0.31
Tear osmolarity (mOsms/l)	293	0.90 (16.71)	328	2.37 (21.00)	477	0.27 (19.57)	229	0.00 (21.42)	0.47	0.59	0.81

BODI = Brief Pain Inventory; DED = dry eye disease; DREAM = Dry Eye Assessment and Management; MCS = mental component summary; OSDI = Ocular Surface Disease Index; SD = standard deviation.
All the *P* values are from the linear trend test. Boldface indicates statistical significance.
*Adjusted by sex and race.
†Adjusted by sex, race, smoking status, Sjögren syndrome, facial rosacea, rheumatoid arthritis, peripheral artery disease, and depression defined by MCS ≤ 42.

oxidative stress and inflame the ocular surface, which may contribute to DED progression.[53] More importantly, these processes may contribute to the destruction of lacrimal glands as shown in mouse models.[54,55]

Although oxidative stress, inflammation, and environmental factors may be key components as to why there is increasing severity of DED with age, it is also notable that, in our study, we found that DED signs worsened with increasing age in women but not in men. There are limited reports in the literature that could partially explain this finding. One previous small study that evaluated the correlation between estrogen receptor-positive basal cells of the meibomian glands and age found that there was an increasing proportion of cells expressing estrogen receptors with increasing age, independent of sex. However, this study did not find any differences between men and women in correlation of estrogen receptor positivity with dry eye symptoms, TBUT, or Schirmer I and II results.[56] Thus, there are likely factors other than estrogen receptor expressivity involved with the relationship of DED signs in relation to both sex and increasing age.

In contrast to the notable associations between dry eye signs and age, our finding of a lack of association between DED symptoms and age is consistent with some reports in the literature, whereas it differs from others. Similar to our study, Lekhanont et al[57] found in their study of 550 Thai subjects that dry eye symptoms were not significantly associated with age. Additionally, Bourcier et al[58] found that age was not correlated with dry eye symptoms of itching, burning, or stinging across age groups of < 40, 40 to 55, and > 50 years. However, in contrast to our study, a recent Norwegian study found that increasing age was significantly associated with higher OSDI scores.[43] As Bourcier et al[58] showed in their study, the thresholds for mechanical, chemical, and thermal stimulation increase with age. Given these findings, decreased corneal sensitivity could be contributing to the lack of association between DED symptoms and age.[58]

Although this secondary analysis of the DREAM study data has provided greater insight regarding DED associations with age, there are limitations in this study. First, this study included only participants with moderate to severe DED, which excludes the comparison of signs and symptoms of patients with less severe DED. Moreover, because patients already have DED, we are unable to compare their DED signs and symptoms before the development of their disease.

Overall, we found that older age is associated with more severe dry eye signs but is not associated with dry eye symptoms. However, there are still many unanswered questions regarding the complex pathophysiology underlying these findings. Future studies that study the role of oxidative stress with increasing age and other potential factors affecting DED as patients get older would be helpful.

Footnotes and Disclosures

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Author Contributions:

Conception and design: Zhao, Yu, Ying, Asbell, Bunya

Analysis and interpretation: Yu, Ying

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Overall responsibility:

Abbreviations and Acronyms:

DED = dry eye disease; **DREAM** = Dry Eye Assessment and Management; **MCS** = mental component summary; **MGD** = meibomian gland dysfunction; **OSDI** = Ocular Surface Disease Index; **TBUT** = tear breakup time.

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