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Climatic and Environmental Correlates of Dry Eye Disease Severity: A Report From the Dry Eye Assessment and Management (DREAM) Study

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Purpose: Correlate climate, weather parameters, and environmental exposures with the severity of symptoms and signs of dry eye disease (DED) in Dry Eye Assessment and Management (DREAM) study participants.

Methods: Participants from five distinct climates completed the Ocular Surface Disease Index (OSDI) and were examined for corneal and conjunctival staining, tear breakup time (TBUT), and Schirmer's testing at baseline, 3, 6, and 12 months. Climate, weather parameters, and pollutants including ozone (O_3), carbon monoxide (CO), nitrous oxides (NO_2, NO_x, NO_y), sulfur dioxide (SO_2), particulate matter, and optical depth were obtained from governmental databases. Multivariate analysis and partial correlation coefficients (ρ) were used to assess associations, adjusted for age, sex, and the presence of Sjögren disease.

Results: Among 535 participants, 81% were female and mean age was 58 years. Participants from the Mediterranean climate demonstrated better corneal fluorescein staining, better TBUT, and higher Schirmer's test scores throughout the calendar year (each $P < 0.0001$). Greater corneal fluorescein staining was associated with lower humidity ($P < 0.0038$). TBUT measurements positively correlated with temperature, humidity, and dewpoint and inversely correlated with NO_2 levels ($P < 0.0038$). Paradoxically, some airborne pollutants were associated with less severe signs of dry eye ($P < 0.0038$). Windspeed was not correlated with signs of DED, and OSDI scores did not correlate with individual environmental exposures.

Conclusions: Dry eye signs differed between climates and local humidity levels. With the exception of NO_2, airborne pollutants were not associated with detrimental dry eye features.

Translational Relevance: These results support limiting dry air exposure for patients with DED.

Introduction

Dry eye disease (DED) is a physically and mentally troubling disorder of the ocular surface estimated to affect over 16 million adults in the United States.[1] A common reason to present for eye care,[2] DED is a multifactorial disorder that affects women more often than men[3] and is associated with symptoms of blurred vision, ocular discomfort, and gritty sensation while reading, driving, and working with computers.[4] Society's financial burden to manage this chronic disease has been estimated to cost over $55 billion per year in the United States alone[5]; thus, identifying the etiologies of DED is an important consideration.

Longstanding hypotheses suggest that air quality and pollution are factors in DED.[6,7] DED prevalence based upon International Classification of Diseases (ICD) code data from US Veterans Health Administration eye clinics has been linked to atmospheric pressure and air pollution in urban areas.[8] Retrospective data from South Korea suggest higher ozone and lower humidity levels are correlated with an increased prevalence of DED.[9] The corneal and conjunctival epithelium is continuously barraged by contaminants in ambient air that negatively affect goblet cell density in vitro.[10] Low humidity in a controlled chamber has also been shown to exert pathologic effects on the tear film.[11] Relative humidity, which describes the percentage saturation within the air, may correlate with signs and symptoms of DED; however, dewpoint may be a better metric for environmental dryness as it represents an absolute quantity of moisture contained within the air.

Airborne pollution consists of both particles and gases that result in respiratory system inflammation, contribute to smog and acid rain, and can be absorbed in mucous membranes such as conjunctiva. Per the World Health Organization, key air pollutants include ozone (O_3), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and particulate matter (PM).[12] PM is a category of minute elements, of which one of the most studied categories is particles less than 2.5 microns in diameter (PM 2.5), which derive from automobile combustion engines and agricultural, industrial, and residential wood burning. Increases in PM 2.5 and O_3 have been correlated with increased adult mortality.[13] Additional pollutants studied in this investigation included carbon monoxide (CO), NO_x (which includes nitric oxide and NO_2), NO_y (which includes NO_x and compounds produced by oxidation of NO_x), Geostationary Operational Environmental Satellite Aerosol/Smoke Product daily aerosol optical depth (GASP daily AOD), and moderate resolution imaging spectroradiometer (MODIS) optical depth.[14] The GASP daily AOD and the MODIS optical depth are satellite-based measurements of airborne dust, haze, smoke, and pollution, with lower values signifying a "cleaner" atmosphere.

Smoking status and medical history have been studied as risk factors for DED,[15,16] yet the characteristics of DED compared across cities and the possible contributory role(s) of climate remain understudied. Given the role of air pollution such as PM and O_3 in nonophthalmic disease processes, correlations between environmental variables and DED signs and symptoms were analyzed.

In this study, prospectively collected data over a 12-month period in the Dry Eye Assessment and Management (DREAM) study were examined. The association between the severity of DED signs and symptoms and retrospectively retrieved same-day local and temporal meteorologic data and air pollutants (O_3, CO, NO_2, NO_x, NO_y, SO_2, PM 2.5, and optical depth) were evaluated.

Methods

The DREAM study was a US-based double-masked, randomized, placebo-controlled multicenter clinical trial funded by the National Eye Institute to determine whether oral omega-3 fatty acid supplements improve the signs or symptoms of DED. Patients were randomly assigned in a 2:1 ratio to either 3 g of omega-3 fatty acids per day (2 g eicosapentaenoic acid plus 1 g docosahexaenoic acid) or 5 g of refined olive oil as a placebo. There were significant changes from baseline in Ocular Surface Disease Index (OSDI) and signs of DED for both placebo and treatment groups, although the changes were not different between treatment groups; results did not show benefit of the omega-3 fatty acid treatment arm over the placebo arm in either symptoms or signs. Details regarding study methodology, inclusion and exclusion criteria, definition of DED, and main results have been previously published.[17] Participants included adults with ocular dryness for at least 6 consecutive months who had moderate to severe symptoms (score 25–80) as measured by the OSDI questionnaire, a tool ranging from 0 to 100 with a higher score indicative of more severe DED symptoms.[18,19] In addition, patient eligibility criteria required two of the following signs of DED in at least one eye during both screening and confirmation of eligibility visits: conjunctival lissamine green staining ≥ 1 (0–6 scale), corneal fluorescein staining ≥ 4 (0–15 scale), tear breakup time (TBUT) ≤ 7 seconds, and a 5-minute anesthetized Schirmer's test between 1 and 7 mm.

The DREAM study adhered to the tenets of the Declaration of Helsinki[20] and was approved by the institutional review board associated with each study center. Written informed consent was obtained from patients after an explanation of the nature and consequences of participation. The clinical trial was registered with ClinicalTrials.gov (NCT02128763).

Clinical Examination

Prior to study conduct, DED clinicians completed a certification program on the standardized procedures for assessing signs of DED.[21] Instillation of 2% fluorescein dye and 1% lissamine green dye was standardized by the use of an Eppendorf micropipette to instill 5 μL of dye into the inferior cul-de-sac. Measurements of TBUT began approximately 30 seconds after the addition of fluorescein dye. Clinicians viewed the cornea using slit-lamp microscopy with broad-beam cobalt blue illumination and a yellow barrier filter. After instructing the patient to blink, the time to the first discontinuity in the tear film was measured. The measurement was repeated two more times, and the average was used for analysis. Short measurements were indicative of more severe DED. Approximately 2 to 3 minutes after fluorescein dye instillation, the clinician scored central corneal staining and each of the four surrounding quadrants on a scale of 0 (no staining) to 3 (severe staining). One to 2 minutes after lissamine green dye instillation, the clinician viewed the conjunctiva using slit-lamp microscopy using white light and graded punctate staining from 0 to 3 both temporally and nasally. The sum of the scores for each eye was used as the total corneal and conjunctival staining (maximum of 15 and 6, respectively). Higher corneal and conjunctival staining scores were indicative of more severe DED. Approximately 5 minutes after the instillation of a topical anesthetic, a Schirmer's test strip was hung onto the lower conjunctival sac in the temporal one-third of each eyelid and the patient was asked to close both eyes for 5 minutes. The length of wetting on the strip was then recorded in millimeters. Shorter measurements were indicative of more severe DED.

Weather and Pollution Data

Daily meteorologic data corresponding to each respective study site location and date of the visit were retrospectively abstracted from the National Centers for Environmental Information (NCEI) public database, a service of the National Oceanic and Atmospheric Administration.[22] Local climatological data had been directly measured by each NCEI data center and included 24-hour averages for temperature, relative humidity, windspeed, and dewpoint. The distance from a DREAM study site to the closest NCEI data reporting center ranged from 2 to 32 miles with a mean of 13.8 miles (Table 1). The testing centers were grouped into six climate zones according to the three-letter Koppen climate classification system: Humid Continental (DFA), Humid Continental (DFB), Humid Subtropical (CFA), Subtropical Desert (BWH), Semi-Arid (BSH), and Mediterranean (CSB).[23]

Levels of gaseous pollutants were accessed from the public Environmental Protection Agency (EPA) database using an area of ±0.2 degrees (an approximate 9-mile radius) around the city center nearest to each corresponding DREAM study site. The distance from each DREAM testing center to its respective city center ranged from 1 to 25 miles with a mean of 4.8 miles. Recorded pollutant data encompassed 24-hour averages on the day of examination and testing.

Statistical Analysis

Descriptive statistics of patient characteristics, environmental exposures, and DED symptoms and signs were summarized using means, standard deviations, and percentages. The cross-sectional associations of meteorologic and environmental pollutant variables with DED symptoms and signs were evaluated using Pearson correlation coefficients (ρ) and P values. For TBUT, Schirmer's test, and corneal and conjunctival staining scores, the worst score of the patient's two eyes at each study visit was used as the score for a person in the analysis. These correlation analyses were initially performed for each separate time point (screening, baseline, and months 3, 6, and 12). Because the DREAM study did not find a difference between treatment and placebo groups in symptoms or signs, analyses were performed using combined data from all time points to improve the statistical power to detect correlations.

The partial correlation coefficient was calculated after adjusting for time (screening, baseline, months 3, 6, and 12), treatment group (placebo or study drug), age, sex, and the presence of Sjögren disease, and the P value was calculated using the generalized estimating equation approach that accounts for the correlation from repeated measures. Similar analyses were performed for the changes of environmental exposures with changes of DED symptoms and signs. The comparison of dry eye signs and symptoms across climates was performed using analysis of covariance that adjusted for age, sex, and the presence of Sjögren disease. The Bonferroni correction was used to account for the 13 environmental measures so that only P values less than 0.0038 were considered statistically significant. All statistical analyses were performed in SAS v9.4 (SAS Institute, Inc., Cary, NC).

Table 1. Climate and Location of Study Site with Respect to the Corresponding NCEI Climate Center and EPA City Center Radius (in Miles)

Climate	City	State	Distance from NCEI Location	Distance from EPA City Center	No. of Patients
Humid continental (DFA)					
Cold, without dry season, hot summer	Indianapolis	IN	10	10	1
	Cleveland	OH	23	15[a]	36
	Chicago	IL	14	2	1
	Racine	WI	17	7	4
	Ann Arbor	MI	30	1	41
	Minneapolis	MN	15	11	44
	Kansas City	KS	15	3	14
	Kansas City	MO	18	6	11
	Creve Coeur	MO	7	1	19
Humid continental (DFB)					
Cold, without dry season, warm summer	Boston	MA	4	3	37
	Rochester	NY	2	2	19
Humid subtropical (CFA)					
Temperate, without dry season, hot summer	New York City	NY	2	6	59
	Philadelphia	PA	6	2	32
	Morrow	GA	8	1	28
	Memphis	TN	7	2	17
	Largo	FL	16	1	20
	Raleigh	NC	13	4	19
Subtropical desert (BWH)					
Arid, desert, hot	Scottsdale	AZ	14	8	48
Semiarid (BSH)					
Arid, steppe, hot	Oceanside	CA	32	4	18
Mediterranean (CSB)					
Temperate, warm and dry summer	Azusa	CA	32	2	43
	Oakland	CA	19	1	20
	Torrance	CA	10	2	4

[a]Two centers located 4 and 25 miles from the EPA city center.

Results

The DREAM study included 535 patients (81% female, mean baseline age 58 years) with mild to moderate DED as defined by OSDI and clinical symptoms. The baseline mean values of environmental measures and DED signs and symptoms are reported in Table 2. Some environmental measures were not reported for the given test date so the total number of patients for those measures is fewer than 535. A comparison of environmental measures by climate zone is at the baseline study visit in Table 3.

Table 4 lists the mean dry eye symptoms and signs for each climate for all visit time points (baseline [0], 3, 6, and 12 months); OSDI and conjunctival staining showed no correlation with climate zone. However, as Figure 1 further illustrates, patients in the Mediterranean climate zone (CSB) of the United States demonstrated significantly decreased (better) corneal dryness as measured by mean corneal fluorescein staining compared with other climates throughout the calendar year. On the other hand, in patients from the semiarid (BSH) climate, corneal fluorescein staining was significantly worse throughout the calendar year when compared with patients from all other Koppen climate zones. Patients from study sites in the Mediterranean (CSB) climates of the United States demonstrated generally longer TBUT throughout the year (as depicted in Fig. 2), in contrast to patients from the

Table 2. Environmental Measures and Dry Eye Signs and Symptoms at Baseline

Characteristic	Baseline No. of Patients	Baseline Mean (SD)
Environmental measures		
Daily temperature		
Maximum	535	71 (18)
Minimum	535	53 (17)
Average	535	62 (18)
Daily average humidity	535	62 (17)
Daily average windspeed	535	8.0 (3.6)
Daily average dewpoint	535	47 (17)
CO (ppm)	466	314 (153)
NO_2 (ppb)	485	14 (7.9)
NO_x (ppb)	478	20 (18)
NO_y (ppb)	335	21 (21)
Ozone (ppb)	526	28 (10)
PM 2.5 (μg/m^3)	529	9.2 (4.7)
SO_2 (ppb)	404	1.0 (1.4)
GASP daily AOD	368	0.2 (0.2)
MODIS optical depth	252	0.3 (0.2)
Dry eye signs and symptoms		
Conjunctival staining score	535	3.4 (1.5)
Corneal staining score	535	4.4 (3.1)
Tear breakup time (seconds)	535	2.7 (1.4)
Schirmer's test score (mm/5 min)	535	8.1 (6.2)
OSDI		
Total score	535	42 (16)

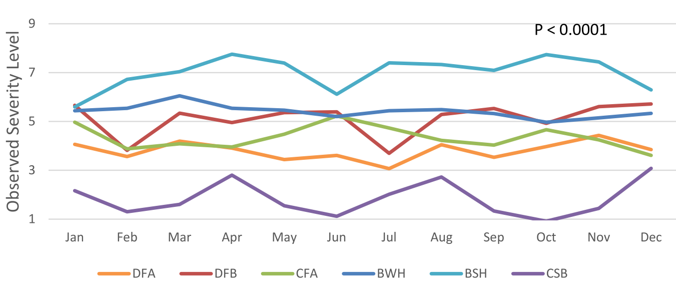

Figure 1. Monthly average corneal fluorescein score by region of the United States. The worst score of the patient's two eyes was used as the score of a person, adjusted by baseline age, sex, and Sjögren disease.

subtropical desert (BWH) climate who demonstrated diminished TBUT scores (all $P < 0.0001$). Additionally, Schirmer's test scores were higher in patients from the Mediterranean (CSB) and semiarid (BSH) climates ($P < 0.0001$ for all study visits except for $P = 0.0001$ at the 6-month visit; Table 4).

Table 5 illustrates that when all study time points (screening, baseline, and months 3, 6, and 12) across all study sites were considered together, the subjective OSDI symptom scores did not correlate with either specific weather exposures or pollutants. Average daily temperature was not significantly associated with total OSDI score ($\rho = -0.01$), even when further adjusted by humidity ($\rho = -0.02$).

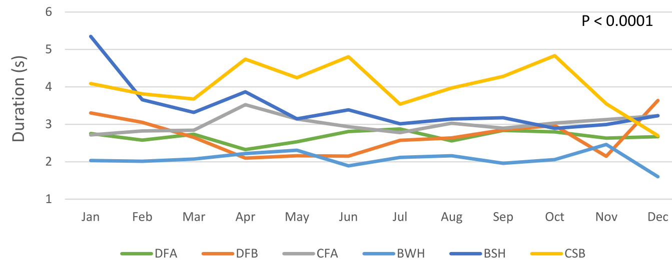

Figure 2. Monthly average TBUT score by region of the United States. The worst score of the patient's two eyes was used as the score of a person, adjusted by baseline age, sex, and Sjögren disease.

Table 6 depicts several cross-sectional associations between environmental measures and objective DED signs. More severe conjunctival staining was unexpectedly associated with decreased GASP daily AOD ($\rho = -0.06$) and decreased NO_y ($\rho = -0.06$, $P < 0.0038$). More severe corneal staining was associated with lower daily average humidity ($\rho = -0.09$) and, paradoxically, decreased NOx ($\rho = -0.08$) and decreased PM 2.5 ($\rho = -0.08$, all $P < 0.0038$). TBUT was significantly correlated with several weather and pollution variables. Shorter (worse) TBUT correlated with lower average daily temperature ($\rho = 0.08$). When the average daily temperature was adjusted for humidity, the partial correlation coefficient remained significant and increased from 0.08 to 0.11 ($P < 0.0038$). TBUT correlated with average daily dewpoint ($\rho = 0.17$) and humidity ($\rho = 0.18$, both $P < 0.0038$). Longer TBUT correlated with decreased NO_2 levels ($\rho = -0.14$). Paradoxically, longer TBUT was associated with both increased O_3 levels ($\rho = 0.07$) and PM 2.5 ($\rho = 0.06$, both $P < 0.0038$). Schirmer's test results were not associated with any environmental measurement.

Lastly, Table 7 further examines to see if a change in environmental parameters correlates with a change in dry eye symptoms and signs. No correlation was detected for a $P < 0.0038$ level. This lack of association refutes a possible causal relationship between humidity and other weather parameters and dry eye parameters.

Discussion

The DREAM study afforded a unique first opportunity to study DED symptoms and signs in a geographically diverse population in the United States.

Table 3. Comparison of Environmental Measures at Baseline by Climate

Environmental Measure	Humid Continental (DFA, $n = 171$)	Humid Continental (DFB, $n = 56$)	Humid Subtropical (CFA, $n = 175$)	Subtropical Desert (BWH, $n = 48$)	Semiarid (BSH, $n = 18$)	Mediterranean (CSB, $n = 67$)	*P* Value
Daily temperature							
Maximum	66 (18)	62 (20)	73 (17)	90 (17)	69 (7)	69 (8)	<0.0001
Minimum	47 (17)	46 (18)	56 (17)	69 (16)	56 (8)	56 (6)	<0.0001
Average	56 (17)	54 (19)	65 (17)	79 (17)	63 (7)	63 (7)	<0.0001
Daily average humidity	65 (13)	62 (16)	63 (15)	34 (15)	59 (13)	73 (14)	<0.0001
Daily average windspeed	9.3 (3.7)	9.8 (3.4)	6.6 (2.9)	6.7 (2.1)	5.3 (2.9)	8.2 (4.2)	<0.0001
Daily average dewpoint	43 (17)	41 (19)	51 (19)	44 (15)	47 (11)	52 (8)	<0.0001
CO (ppm)	266 (105)	251 (66)	328 (176)	379 (151)	NA	371 (173)	<0.0001
NO_2 (ppb)	11 (6)	12 (5)	14 (9)	19 (8)	8 (5)	17 (9)	<0.0001
NO_x (ppb)	13 (13)	18 (8)	25 (21)	17 (14)	11 (7)	28 (21)	<0.0001
NO_y (ppb)	19 (23)	20 (12)	24 (23)	19 (18)	NA	NA	0.25
Ozone (ppb)	29 (10)	31 (9)	25 (10)	33 (11)	33 (7)	29 (10)	<0.0001
PM 2.5 (µg/m^3)	8.6 (4.2)	8.1 (3.6)	9.4 (4.4)	7.1 (2.8)	7.7 (2.8)	12.7 (6.7)	<0.0001
SO_2 (ppb)	1.8 (2.2)	0.7 (0.6)	0.6 (0.6)	0.6 (0.5)	NA	1.1 (0.3)	<0.0001
GASP daily AOD	0.24 (0.17)	0.21 (0.14)	0.25 (0.18)	0.23 (0.22)	0.14 (0.09)	0.17 (0.11)	0.03
MODIS optical depth	0.23 (0.17)	0.22 (0.15)	0.26 (0.17)	0.49 (0.17)	0.09 (0.05)	0.22 (0.09)	<0.0001

The values are mean (SD). NA, Not Available.

Table 4. Multivariate Analysis for the Comparison of Dry Eye Symptoms and Signs by Climate over Time

		Mean (SE) by Region[a]						
Measures	Month of Visit	Humid Continental (DFA, $n = 171$)	Humid Continental (DFB, $n = 56$)	Humid Subtropical (CFA, $n = 175$)	Subtropical Desert (BWH, $n = 48$)	Semi-Arid (BSH, $n = 18$)	Mediterranean (CSB, $n = 67$)	*P* Value[a]
OSDI total score	0	40.1 (1.2)	46.0 (2.1)	42.7 (1.2)	44.5 (2.2)	40.3 (3.7)	40.7 (1.9)	0.13
	3	32.5 (1.5)	38.4 (2.6)	32.1 (1.4)	31.2 (2.7)	35.6 (4.4)	28.8 (2.5)	0.14
	6	31.8 (1.5)	38.1 (2.6)	31.4 (1.5)	31.6 (2.8)	34.6 (5.1)	29.1 (2.8)	0.21
	12	30.9 (1.4)	38.9 (2.5)	28.3 (1.4)	29.8 (2.7)	30.5 (4.7)	27.8 (2.5)	0.01
Conjunctival staining	0	3.32 (0.11)	3.72 (0.20)	3.22 (0.11)	3.19 (0.21)	3.14 (0.35)	3.70 (0.18)	0.09
	3	3.09 (0.12)	3.70 (0.22)	2.93 (0.12)	2.94 (0.23)	3.08 (0.38)	3.48 (0.21)	0.02
	6	2.98 (0.13)	3.67 (0.22)	2.73 (0.12)	2.87 (0.23)	3.04 (0.42)	3.07 (0.23)	0.01
	12	2.85 (0.13)	3.49 (0.22)	2.68 (0.12)	2.92 (0.23)	2.82 (0.41)	2.78 (0.22)	0.06
Corneal staining	0	4.05 (0.22)	5.60 (0.38)	4.56 (0.22)	5.53 (0.41)	6.75 (0.67)	2.59 (0.35)	<0.0001
	3	3.83 (0.21)	4.38 (0.37)	4.13 (0.21)	5.28 (0.40)	6.91 (0.66)	1.82 (0.36)	<0.0001
	6	3.67 (0.23)	4.17 (0.39)	4.15 (0.22)	5.17 (0.42)	6.24 (0.76)	1.88 (0.42)	<0.0001
	12	3.14 (0.22)	4.77 (0.38)	4.26 (0.21)	4.84 (0.40)	6.72 (0.70)	1.42 (0.37)	<0.0001
Tear breakup time (seconds)	0	2.53 (0.10)	2.33 (0.17)	2.69 (0.10)	1.86 (0.18)	3.64 (0.30)	3.59 (0.16)	<0.0001
	3	2.70 (0.14)	2.65 (0.25)	3.12 (0.14)	2.09 (0.27)	3.08 (0.44)	4.12 (0.24)	<0.0001
	6	2.68 (0.14)	2.89 (0.25)	3.35 (0.14)	2.23 (0.27)	3.91 (0.48)	4.64 (0.26)	<0.0001
	12	2.88 (0.15)	2.84 (0.26)	3.25 (0.14)	2.57 (0.27)	3.66 (0.47)	4.74 (0.25)	<0.0001
Schirmer's test (mm/5 min)	0	8.12 (0.45)	4.46 (0.78)	7.81 (0.44)	7.77 (0.84)	12.4 (1.38)	10.6 (0.72)	<0.0001
	3	9.11 (0.44)	4.31 (0.78)	7.94 (0.44)	6.56 (0.83)	10.9 (1.36)	12.7 (0.75)	<0.0001
	6	8.77 (0.47)	5.77 (0.79)	8.29 (0.46)	7.34 (0.85)	11.6 (1.55)	10.9 (0.86)	0.0001
	12	8.78 (0.43)	5.08 (0.76)	7.78 (0.43)	7.47 (0.80)	10.6 (1.40)	12.4 (0.75)	<0.0001

[a] Adjusted by age, gender, and presence of Sjogren disease.

Table 5. Correlation of Environment Measures with OSDI Score Combining Screening, Baseline, and 3, 6, and 12 months, Adjusted for the Correlation from Repeated Measures, Time, and Treatment Group

	Partial Correlation Coefficient for Cross-Sectional Correlation[a]	
Environment Measure	No. of Measures	OSDI Total Score
Average daily temperature	2542	−0.01
Daily average humidity	2542	−0.02
Daily average windspeed	2542	0.01
Daily average dewpoint	2542	−0.03
CO (ppm)	2178	−0.05
NO_2 (ppb)	2276	−0.02
NO_x (ppb)	2264	−0.01
NO_y (ppb)	1605	−0.03
O_3 (ppb)	2485	−0.01
PM 2.5 (μg/m^3)	2471	−0.04
SO_2 (ppb)	1948	−0.01
GASP daily AOD	1846	−0.01
MODIS optical depth	1172	−0.03

No partial correlation coefficients were statistically significant after correction for multiple comparisions ($P < 0.0038$).

[a]Adjusted by visit, treatment group, age, sex, and presence of Sjögren disease.

Using NCEI and EPA public databases, a number of correlations were identified between symptoms and signs of DED and atmospheric variables that may be relevant to future research design and clinical management.

Dry eye research chambers have been used to create arid indoor environments of low humidity mimicking the arid climate in this study.[24,25] This study's findings support the notion that DED signs correlate to some degree with the local climate, as described in published retrospective studies. It was previously reported that patients residing in areas of increased relative humidity and higher windspeed were less likely to carry an ICD-9 diagnosis code for DED.[8]

Galor et al.[6] hypothesized that higher windspeeds would presumably disperse pollution to reduce its negative effects on DED. The results of the present study lend some support to humidity and dewpoint as protective factors for the ocular surface; higher humidity levels were associated with improved corneal fluorescein staining and improved TBUT while higher dewpoint similarly correlated with improved TBUT. However, windspeed was not found to be significantly associated with DED symptoms or signs. On the other hand, average daily temperature was shown to positively correlate with TBUT independently of humidity. Further examination of the relationship between windspeed, temperature, and DED signs and symptoms seems warranted.

As clinicians have long suggested, climate was associated with a significant difference in the signs of DED. Patients from the semiarid (BSH) and subtropical desert (BWH) climates exhibited higher levels of corneal dryness measured through fluorescein staining, while patients from the Mediterranean (CSB) climates had milder corneal staining. Notably, Mediterranean climate demonstrated both the highest mean daily average humidity (73%) and daily average dewpoint (52 degrees). A climate difference in TBUT was also seen. Patients from Mediterranean climates generally demonstrated longer (better) TBUT throughout the calendar year, achieving a breakup time up to 3 seconds longer than patients from the subtropical desert (BWH) climate. However, these differences did not translate into patient DED symptoms. There was no difference in the patient-reported OSDI scores among the various climate zones at the baseline visit ($P = 0.13$, Table 4).

Speculation exists regarding a possible association between ocular surface inflammation and high levels of atmospheric pollution.[6] Several paradoxical findings regarding the presence of pollutants and signs of DED were discovered. Although some of the correlations were statistically significant from zero, all of the correlations were weak, with the magnitude of the correlation coefficient <0.20. The rationale for these findings cannot be explained at this time. In addition, there were unexpected correlates with noxious gases (NO_2, NO_x, O_3) and the signs of DED in ways that are not understood (Table 6). Such nonintuitive associations may be a manifestation of reflex tearing, a protective mechanism in areas of high pollution or ocular irritation. Alternatively, patients may be inclined to spend more time indoors when pollution levels are high, cued by mass media pollution advisories. The interpretation of the associations identified among the correlations of environmental factors and DED signs in Table 6 is further complicated by the lack of correlation between changes in environmental factors and changes in signs (Table 7), which weakens the argument for a causal relationship. There may be another regional variable in play, such as UV exposure, that was not examined in this study.

Several limitations must be considered. The distance between each study center to its respective NCEI climate recording site ranged from 2 to 32 miles. The

Table 6. Correlation of Environment Measures with Dry Eye Signs for All Times Combined (Screening, Baseline, and 3, 6, and 12 Months), Adjusted for the Correlation from Repeated Measures, Time, and Treatment Group

		Partial Correlation Coefficient for Cross-Sectional Correlation between Environment Measures with Dry Eye Signs Combining Screening, Baseline, and 3, 6, and 12 Months[a]			
Environment Measure	No. of Measures	Conjunctival Staining	Corneal Staining	Tear Breakup Time	Schirmer's Test
Average daily temperature	2542	0.03	0.02	**0.08**	0.01
Average daily temperature (humidity adjusted)	2542	0.04	0.01	**0.11**	0.01
Daily average humidity	2542	0.02	**−0.09**	**0.18**	0.03
Daily average windspeed	2542	−0.01	−0.03	−0.00	−0.05
Daily average dewpoint	2542	0.04	−0.03	**0.17**	0.03
CO (ppm)	2178	−0.04	−0.04	−0.06	0.02
NO_2 (ppb)	2276	−0.01	−0.06	**−0.14**	0.03
NO_x (ppb)	2264	−0.02	**−0.08**	−0.06	0.03
NO_y (ppb)	1605	**−0.06**	−0.03	−0.03	0.04
O_3 (ppb)	2485	0.03	−0.02	**0.07**	0.02
PM 2.5 (μg/m^3)	2471	0.03	**−0.08**	**0.06**	0.05
SO_2 (ppb)	1948	0.02	0.01	−0.02	−0.02
GASP daily AOD	1846	**−0.06**	0.04	−0.01	−0.03
MODIS optical depth	1172	−0.06	−0.01	−0.06	−0.03

Bold indicates significant (raw $P < 0.0038$) to correct for multiple comparisons.
[a]Adjusted by visit, treatment group, age, gender, and presence of Sjogren disease.

climate measured at the NCEI location may have differed from the actual climate at the study center, and thus the data are limited by the location of government reporting stations. The same holds true for the EPA data surrounding a city center. Patients may have traveled by car from surrounding cities to a study site in order to participate in the trial, and thus the weather and pollution data may not accurately reflect one's experience in their own typical climate. The duration or intensity of an individual patient's exposure to the outdoor elements could not be analyzed, and the quality of indoor air and use of fans that create moving air in patients' homes or workplaces were not assessed.

The indoor humidity and air quality of the testing center may also play a role in affecting DED research parameters and should be further studied. Additional potential modifying factors such as patient exercise, eye-rubbing, and diet were not investigated but may be of interest in subsequent studies. In addition to PM 2.5, the larger-diameter marker of atmospheric pollution that is also well studied, PM 10, was not analyzed. Rural and urban centers were not compared, and the relationship between atmospheric pressure and DED symptoms and signs was not investigated. By separating the total patient population into six subpopulations based on climate zones, some climates had relatively low patient numbers.

One strength of this study is the prospective, standardized collection of data by trained DED clinicians in the context of a randomized clinical trial. Sites were distributed among the various climates across the continental United States. Given the geographic variability, these results may be generalized with a high degree of reliability in patients with preexisting diagnoses of DED. Environmental data on a day-to-day basis were retrospectively analyzed and correlated with same-day examination findings from a patient cohort that included participants with confirmed DED based on both clinical signs and subjective symptoms.

Environmental pollutants may not show effects until late-stage exposure in sensitive individuals. Subsequent research could explore different temporal scales such as a rolling 1- or 2-week average or a lag time effect in the change of symptoms after exposure to an offending pollutant or climate variable that presents in a delayed fashion. This population's exposure may

Table 7. Correlation between Change from Baseline in Environment Measures and Change in Dry Eye Symptoms and Signs

		Partial Correlation Coefficient for Change in Environment Measures and Change in Dry Eye Symptoms and Signs[a]				
Environment Measure	No. of Measures[b]	OSDI Total Score	Conjunctival Staining	Corneal Staining	Tear Breakup Time	Schirmer's Test
Daily average temperature	2007	−0.03	0.07	−0.03	−0.03	0.04
Daily average humidity	2007	−0.01	−0.01	−0.05	0.03	0.06
Daily average windspeed	2007	0.03	−0.02	0.03	0.03	−0.05
Daily average dewpoint	2007	−0.04	0.05	−0.05	−0.02	0.05
CO (ppm)	1694	−0.04	−0.01	0.02	−0.06	−0.04
NO_2 (ppb)	1774	−0.02	−0.01	0.03	−0.01	−0.06
NO_x (ppb)	1748	−0.02	0.00	0.03	−0.01	−0.02
NO_y (ppb)	1228	−0.08	−0.02	−0.01	0.06	0.04
O_3 (ppb)	1931	−0.02	0.02	−0.04	−0.01	−0.03
PM 2.5 (μg/m^3)	1935	−0.06	0.01	0.01	−0.01	−0.02
SO_2 (ppb)	1518	−0.02	−0.04	0.03	0.02	−0.02
GASP daily AOD	1027	0.01	−0.08	−0.08	0.06	0.02
MODIS optical depth	444	−0.14	0.02	−0.07	0.09	−0.03

No partial correlation coefficients were statistically significant after correction for multiple comparisions ($P < 0.0038$).
[a]Adjusted by visit, treatment group, age, sex, and presence of Sjögren disease.
[b]Changes from baseline for measurements taken at the screening visit and 3, 6, and 12 months.

not be sufficiently severe or clinical effects may have been masked if meibomian gland function was intact. The human eye is naturally resilient and has evolved to sustain extremes of temperatures and inclement weather conditions. Maintaining homeostasis day-to-day changes in atmospheric variables, the eye may require long-term and repeated exposures to generate meaningful changes in current DED criteria. Anecdotally, changing humidity in the local environment does not correct DED for some patients who move from one geographic location to another. Perhaps patients in the DREAM study with diagnoses of DED had lost the ability to maintain ocular homeostasis, and no objective changes in DED measurements were perceived due to this reason; the DREAM study lacked a healthy control comparison group that may have responded in a more dramatic fashion to seasonal changes in weather patterns.

This subanalysis of DREAM data help confirms long-term suspicions that a moist climate is healthier for dry eye patients. More research is recommended to obtain more precise measurements of the local environment to affirm these results. These results also conflict with the past observation that pollution correlates with worse DED symptoms. Climate and environmental factors are difficult to modify and intervene. However, moisture chambers and scleral contacts can help reduce the impact of environment on the ocular surface. This study supports looking more closely at ways to limit dry environmental exposures. Lastly, future dry eye research should include a range of arid-to-humid climates, when feasible, to properly reflect a more accurate national demographic.

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