Tear Film, Contact Lens, and Patient Factors Associated with Corneal Staining

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PURPOSE. The purpose of this study was to examine ocular surface and tear film, contact lens, care solution, medical, and patient-related factors that are associated with corneal staining in contact lens wearers.

METHODS. In this cross-sectional/nested case-control study, in addition to the assessment of corneal staining with fluorescein, a variety of tear film and ocular surface, contact lens, and patient-related factors were examined. Poisson regression models were used to examine the relation between corneal staining and these factors.

RESULTS. Data from 413 patients were eligible for the analyses described. The average age was 30.6 ± 11.1 years, and 277 (67.1%) of the patients were women. Several factors were shown to be related to increased corneal staining in multivariate modeling, including increased daily wearing times ($P = 0.0006$), lower income ($P = 0.0008$), lissamine green conjunctival staining ($P = 0.002$), contact lens deposition ($P = 0.007$), increased tear meniscus height ($P = 0.007$), and decreased hydrogel nominal water content ($P = 0.02$). The wearing of silicone hydrogels (as opposed to hydrogels) was protective against corneal staining ($P = 0.0004$). Notably, neither contact lens care solutions nor disinfectants were associated with corneal staining.

CONCLUSIONS. Corneal staining in contact lens wearers continues to be a frequent, but not well understood, outcome. These data suggest that contact lens factors (water content, material, wearing time, and deposition) are more generally associated with corneal staining than are contact lens care solutions or other ocular surface and tear film, demographic, or medical factors. (*Invest Ophthalmol Vis Sci.* 2011;52:1127-1137) DOI: 10.1167/iovs.10-5757

Corneal staining has long been thought to be associated with conditions of the ocular surface, such as dry eye disease, in addition to contact lens wear, although it is often observed in otherwise normal individuals as well.¹⁻⁸ As the research community continues to focus on conditions and treatments associated with the anterior segment, regulatory agencies such as the United States Food and Drug Administration (FDA) are both questioning and implementing endpoints to optimize drug and device testing. There has been a significant interest in corneal staining as such an endpoint, but there

remain many unanswered questions about corneal staining. One question that is unanswered is exactly what corneal staining is and what it shows. Likewise, there are questions as to the clinical relevance of corneal staining, in that studies have generally failed to show a correlation with patient symptoms and there has yet to be any evidence that it is associated with an increased risk of corneal infection.^{2,9} There is preliminary evidence that corneal staining is associated with (but not necessarily the cause of) infiltrates observed in the cornea.¹⁰

There appears to be somewhat of a paucity of information about the factors associated with corneal staining in contact lens wearers. One factor that has received significant attention, however, is the role of contact lens care solutions and their disinfectants.^{2,11-21} Thus, the purposes of this report were to examine tear film, contact lens, and other patient factors (e.g., sociodemographics and medical conditions) associated with corneal staining.

MATERIALS AND METHODS

Study Design, Patient Sample, and Outcome Assessment

This research was approved by the Biomedical Institutional Review Board of The Ohio State University, in accordance with the tenets of the Declaration of Helsinki. The study was a two-phase, cross-sectional survey with a nested case-control design that is described elsewhere.^{22,23} In phase I, individuals from a large, university-based ophthalmology clinic, in addition to the surrounding community, were surveyed with the Contact Lens Dry Eye Questionnaire (CLDEQ),²⁴ the results of which have been described.^{25,26} Clinic-based patients completing the questionnaire were those presenting only for routine ophthalmic care; patients presenting to the clinic for follow-up or problem-based care were not eligible to complete the questionnaire. During the survey, patients were asked if they would like to return for an examination visit (phase II).

In phase II, patients returned for an examination visit and completed a variety of other clinical and questionnaire assessments (described later). All clinical tests were performed on the right eye of the patient, with appropriate rest intervals associated with the more invasive tests that might induce tearing. Clinical tests and questionnaire outcomes and their order have been described extensively elsewhere.^{22,24,27} As part of the battery of outcomes assessed during the examination, the patients were asked to complete a sociodemographic survey, a contact lens and ocular history survey, and a general medication survey (including medication usage). Likewise, clinical measures obtained during the examination phase have been described extensively elsewhere and included pre-lens lipid layer thickness and pre-lens tear film thinning time, soft contact lens water content and refractive index, tear film osmolality, slit lamp biomicroscopy of the anterior segment, tear meniscus height, phenol red thread testing, meibography, and corneal and conjunctival staining. As corneal staining was used as the outcome in this analysis, further description is warranted. A 5- μ L sample of 2% liquid fluorescein was applied to the bulbar conjunctiva with a Finn timer micropipette. After instillation, a yellow filter (~520 nm) was used to enhance contrast when assessing

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FIGURE 1. Overall distribution of summed corneal staining scores from 413 patient observations.

staining of the cornea. The extent of the corneal surface area stained was graded for each of the five locations, according to the Cornea and Contact Lens Research Unit Grading Scales as follows: grade 0, none; grade 1, 1% to 15% surface area; grade 2, 16% to 30% surface area; grade 3, 31% to 45% surface area; and grade 4, >45% surface area. A total surface area staining score was generated (of 20 possible units).

Statistical Analyses

For continuous variables, means were used to characterize central tendency, and standard deviations were used to characterize dispersion. For categorical variables, contingency tables were used to characterize the distribution of variable values (all analyses performed with Statistical Analysis Software [SAS], ver. 9.2; SAS Institute, Cary, NC).

Generalized linear regression was used to model the relation between corneal staining and independent variables (predictors). The process of building a multiple regression model began with a univariate analysis of each possible predictor. For continuous and categorical patient-related and ophthalmic data, univariate Poisson regression models were fitted to describe the relationship between each predictor variable and the outcome (corneal staining). For continuous variables, the median value associated with the full range of values was typically used to categorize each predictor for univariate analysis. On completion of the univariate analyses, a predictive model of staining using multiple predictors was developed. For this model building, all variables in the univariate analyses that had $P \leq 0.25$ and did not pertain to a subgroup of the CLADES (Contact Lens and Dry Eye Study) sample (e.g., hormone replacement therapy, as it pertains only to women, and the percentage of lens dehydration, as the dehydration of silicone hydrogel lenses cannot be measured with refractometry) were considered, resulting in a list of 24 variables. The initial multiple regression model was the result of a stepwise procedure, with entry and exit criteria set at $\alpha \leq 0.25$. A second stepwise multiple regression model was fitted using the variables selected by the first stepwise procedure. The second stepwise procedure used a stricter criterion of $\alpha \leq 0.10$ for inclusion. All variables identified by using the criterion of $\alpha \leq 0.10$ were included in a model with all their possible two-way interactions. Interactions were sequentially removed if they did not reach $P < 0.05$ or if they had no biological plausibility. The final model included all main effects with $P \leq 0.05$ and statistically significant interactions. For the final model, P values, rate ratios, and 95% confidence intervals are presented.

RESULTS

Patient Sample and Corneal Staining Response

Four hundred fifteen patients were enrolled in phase II of the study, although 413 patients were included in the sample analyses, as 2 had missing data on corneal staining. The average age of the patients in the sample was 30.6 ± 11.1 years, and 277 (67.1%) were women. The overall average length of contact lens wear was 12.7 ± 9.0 years; 378 (91.5%) were hydrogel lens wearers, and 35 (8.5%) were gas-permeable lens wearers.

The distribution of corneal staining can be seen in Figure 1. Overall, approximately 54% of the patients had corneal staining present and the average overall summed corneal staining score was 1.96 ± 3.40 (range, 0.00–20.00). Figure 2 summarizes the frequency of staining by region. The most frequent area of the cornea with staining present was the inferior region (39.7% of patients), and the second most common region was the temporal region (24.9% of patients). Likewise, corneal staining had the highest average grade in the inferior region (0.72 ± 1.11), followed by the temporal region (0.47 ± 0.98).

Univariate Analyses

Table 1 displays means, standard deviations, and sample sizes for possible predictors of staining stratified by the level of each variable, in addition to results for univariate Poisson regression models for each variable. Average weekly lens wear duration was associated with corneal staining ($P < 0.0001$), in that those with more corneal staining were more likely to wear their lenses on a full-time basis (~ 7 days per week). Consistent with weekly lens wear, daily lens wear duration was also statistically significant ($P < 0.001$); longer daily wearing times were more likely to be associated with increased corneal staining. Increased contact lens surface deposition was associated with increased corneal staining ($P = 0.01$), as was concurrent presence of lissamine green staining ($P = 0.04$) and the inability to wear lenses as long as desired ($P = 0.04$). Factors associated with reduced corneal staining included the pres-

FIGURE 2. Region specific corneal staining responses of the 413 patients observed. The percentage of patients having any staining present in each region is provided in addition to the average $\pm$ SD response for that region.

TABLE 1. Univariate Poisson Regression Analyses of Ophthalmic, General Medical, and Demographic Variables Possibly Associated with Corneal Staining

Predictors (<i>n</i>)	Average $\pm$ SD Corneal Staining	Rate Ratio (95% CI)	<i>P</i>
Weekly lens wear duration, d			
1 (13)	0.54 $\pm$ 0.88		
2 (13)	0.77 $\pm$ 1.30		
3 (9)	0.56 $\pm$ 1.01		
4 (19)	0.47 $\pm$ 0.84	1.28 (1.14–1.43)	<0.0001
5 (34)	1.94 $\pm$ 2.90		
6 (40)	1.90 $\pm$ 2.66		
7 (285)	2.24 $\pm$ 3.77		
Daily lens wear duration, h			
<14 Hours (170)	1.62 $\pm$ 2.72	1.09 (1.04–1.14)	0.001
$\geq$ 14 Hours (243)	2.21 $\pm$ 3.79		
Deposits			
0 (333)	1.82 $\pm$ 3.18		
1 (38)	1.84 $\pm$ 3.42		
2 (20)	3.55 $\pm$ 5.03	1.30 (1.05–1.61)	0.01
3 (6)	6.00 $\pm$ 7.01		
4 (4)	2.50 $\pm$ 1.73		
Asthma			
No (359)	2.09 $\pm$ 3.58		
Yes (47)	1.17 $\pm$ 1.58	0.56 (0.33–0.95)	0.03
Lissamine green staining			
<4 (176)	1.78 $\pm$ 3.5	1.03 (1.00–1.06)	0.04
$\geq$ 4 (235)	2.11 $\pm$ 3.33		
Lids scrubs/compresses			
No (384)	1.85 $\pm$ 3.11		
Yes (29)	3.45 $\pm$ 5.91	1.86 (1.04–3.35)	0.04
FDA group			
1 (41)	2.90 $\pm$ 4.75	REF	
2 (71)	2.20 $\pm$ 4.15	0.76 (0.41–1.39)	0.04
4 (187)	1.46 $\pm$ 2.02	0.50 (0.29–0.89)	
Silicone hydrogel (76)	2.09 $\pm$ 4.01	0.72 (0.40–1.31)	
Ability to wear lenses as long as desired			
Yes (128)	1.51 $\pm$ 2.78	1.44 (1.02–2.03)	0.04
No (285)	2.17 $\pm$ 3.63		
Lid margin vascularization			
1 (295)	2.15 $\pm$ 3.73		
2 (86)	1.55 $\pm$ 2.44	0.78 (0.60–1.00)	0.05
3 (32)	1.41 $\pm$ 2.08		
Tear meniscus height, mm			
<0.20 (128)	1.63 $\pm$ 2.83	3.82 (0.92–15.88)	0.06
$\geq$ 0.20 (282)	2.10 $\pm$ 3.61		
Race			
White (326)	1.81 $\pm$ 3.17	1.42 (0.97–2.07)	0.07
Non-white (86)	2.57 $\pm$ 4.11		
Lipid layer thickness			
Absent, 0–13 nm (30)	3.07 $\pm$ 4.13		
Open meshwork, 13–50 nm (84)	2.71 $\pm$ 3.86		
Closed meshwork, 13–50 nm (73)	1.25 $\pm$ 1.67		
Wave/flow, 50–70 nm (134)	1.77 $\pm$ 3.68	0.92 (0.83–1.01)	0.08
Amorphous, 80–90 nm (44)	1.84 $\pm$ 3.12		
Colored fringe brown, 90–140 nm (34)	1.15 $\pm$ 2.64		
Colored fringe blue, >140 nm (13)	3.31 $\pm$ 4.07		
Income			
\$0–\$44,999 (143)	2.41 $\pm$ 3.73	REF	
\$44,999–\$74,999 (149)	1.56 $\pm$ 2.92	0.65 (0.45–0.94)	0.08
\$75,000+ (118)	1.96 $\pm$ 3.53	0.81 (0.55–1.20)	
Hormone replacement therapy, women only			
No (259)	2.12 $\pm$ 3.40	0.50 (0.23–1.10)	0.08
Yes (18)	1.06 $\pm$ 1.55		
Δ Water content, %			
<–4.05 (140)	1.39 $\pm$ 2.27	1.05 (0.99–1.11)	0.09
$\geq$ –4.05 (140)	2.16 $\pm$ 3.53		
Nominal water content, %			
<50 (115)	2.30 $\pm$ 4.24	0.99 (0.98–1.00)	0.10
$\geq$ 50 (249)	1.66 $\pm$ 2.81		

(continues)

TABLE 1 (continued). Univariate Poisson Regression Analyses of Ophthalmic, General Medical, and Demographic Variables Possibly Associated with Corneal Staining

Predictors (<i>n</i>)	Average $\pm$ SD Corneal Staining	Rate Ratio (95% CI)	<i>P</i>
Lens type			
Soft (378)	1.88 $\pm$ 3.33		
Gas permeable (35)	2.91 $\pm$ 4.02	0.64 (0.37–1.11)	0.11
Nasal steroids			
No (392)	2.01 $\pm$ 3.46		
Yes (21)	1.10 $\pm$ 1.55	0.54 (0.25–1.17)	0.12
Meibomian gland count			
<7.5 glands (178)	2.30 $\pm$ 3.64		
$\geq$ 7.5 glands (218)	1.78 $\pm$ 3.28	0.96 (0.92–1.01)	0.13
Education			
High school or less (89)	1.53 $\pm$ 2.35	0.89 (0.55–1.44)	
Associates or bachelors degree (233)	2.22 $\pm$ 3.93	1.29 (0.87–1.91)	
Masters+ (91)	1.73 $\pm$ 2.70	REF	0.14
Dry eye treatments, <i>n</i>			
0 (185)	1.66 $\pm$ 3.09		
1 (178)	2.28 $\pm$ 3.75		
2 (35)	2.31 $\pm$ 3.59	1.20 (0.94–1.52)	
3+ (6)	1.50 $\pm$ 1.76		0.14
Doctor recommended discontinuation of lens wear			
Yes (262)	1.82 $\pm$ 2.91		
No (145)	2.30 $\pm$ 4.17	1.27 (0.92–1.75)	0.15
Hypothyroid			
No (393)	2.01 $\pm$ 3.46		
Yes (18)	1.17 $\pm$ 1.65	0.58 (0.26–1.31)	0.19
Dry eye status			
No (161)	2.17 $\pm$ 3.78		
Yes (198)	1.77 $\pm$ 2.97	0.79 (0.56–1.12)	0.19
Antihypertensive medications			
No (391)	1.91 $\pm$ 3.32		
Yes (21)	3.00 $\pm$ 4.67	1.57 (0.79–3.14)	0.20
Cancer			
No (401)	1.99 $\pm$ 3.43		
Yes (11)	1.00 $\pm$ 1.79	0.5 (0.17–1.45)	0.20
Nominal refractive index			
<1.41 (87)	2.14 $\pm$ 3.88		
$\geq$ 1.41 (277)	1.78 $\pm$ 3.15	1.83 (0.69–4.87)	0.22
Measured refractive index			
<1.43 (177)	1.77 $\pm$ 3.03		
$\geq$ 1.43 (178)	2.10 $\pm$ 3.74	1.88 (0.63–5.64)	0.26
Seasonal allergies			
No (190)	2.15 $\pm$ 3.68		
Yes (223)	1.80 $\pm$ 3.14	0.84 (0.61–1.15)	0.27
Tranquilizer medicines			
No (367)	1.90 $\pm$ 3.30		
Yes (46)	2.50 $\pm$ 4.09	1.32 (0.81–2.15)	0.27
Overnight lens wear			
No (370)	1.89 $\pm$ 3.25		
Yes (42)	2.52 $\pm$ 4.52	1.33 (0.80–2.22)	0.27
Cataract			
No (393)	1.94 $\pm$ 3.33		
Yes (13)	1.15 $\pm$ 1.99	0.59 (0.23–1.55)	0.29
Antihistamine use			
No (352)	2.03 $\pm$ 3.52		
Yes (61)	1.61 $\pm$ 2.60	0.79 (0.51–1.24)	0.31
Sterility			
No (379)	1.93 $\pm$ 3.38		
Yes (30)	2.60 $\pm$ 3.78	1.35 (0.75–2.43)	0.32
Over-the-counter cough medications			
No (364)	1.90 $\pm$ 3.28		
Yes (49)	2.41 $\pm$ 4.19	1.26 (0.78–2.04)	0.33
Overall satisfaction with current contact lenses			
Very dissatisfied (6)	0.33 $\pm$ 0.52		
Dissatisfied (25)	1.80 $\pm$ 2.20		
Satisfied (231)	1.97 $\pm$ 3.36	1.13 (0.87–1.47)	
Very satisfied (151)	2.04 $\pm$ 3.67		0.36

(continues)

TABLE 1 (*continued*). Univariate Poisson Regression Analyses of Ophthalmic, General Medical, and Demographic Variables Possibly Associated with Corneal Staining

Predictors (<i>n</i>)	Average $\pm$ SD Corneal Staining	Rate Ratio (95% CI)	<i>P</i>
Modality			
Daily disposable (32)	1.47 $\pm$ 2.03	0.86 (0.46–1.62)	0.38
Two week (202)	1.70 $\pm$ 2.85	REF	
Monthly (120)	2.23 $\pm$ 4.10	1.32 (0.91–1.90)	
Quarterly+ (23)	2.22 $\pm$ 4.11	1.31 (0.65–2.63)	
Limbal injection			
None (268)	2.09 $\pm$ 3.75	0.90 (0.71–1.15)	0.41
Mild (113)	1.67 $\pm$ 2.45		
Moderate (30)	1.97 $\pm$ 3.29		
Severe (1)	2.00		
Smoking, cigarettes or pipe			
Not at all (365)	1.90 $\pm$ 3.40	1.15 (0.82–1.60)	0.41
Some days (30)	1.73 $\pm$ 2.38		
Every day (16)	2.94 $\pm$ 3.34		
Hyperlipidemia			
No (371)	1.93 $\pm$ 3.36	1.23 (0.73–2.08)	0.43
Yes (40)	2.38 $\pm$ 3.82		
Sleep medication			
No (402)	1.94 $\pm$ 3.31	1.45 (0.56–3.75)	0.44
Yes (11)	2.82 $\pm$ 5.84		
Sex			
Male (136)	1.79 $\pm$ 3.55	1.14 (0.81–1.60)	0.44
Female (277)	2.05 $\pm$ 3.32		
Recent contact lens refitting			
No (376)	1.92 $\pm$ 3.36	1.24 (0.72–2.13)	0.44
Yes (37)	2.38 $\pm$ 3.79		
Eye sensitivity to smog			
Not at all (274)	1.99 $\pm$ 3.26	0.90 (0.69–1.18)	0.45
Occasionally (111)	2.05 $\pm$ 3.80		
Often (24)	1.54 $\pm$ 3.30		
All the time (3)	0.00		
Dryness and irritation on the day after alcohol consumption			
Not at all or occasionally (321)	1.95 $\pm$ 3.35	1.12 (0.73–1.72)	0.48
Often or all the time (22)	2.77 $\pm$ 5.10	1.58 (0.74–3.41)	
No alcohol consumption (68)	1.75 $\pm$ 2.98	REF	
Arthritis			
No (371)	1.93 $\pm$ 3.36	1.21 (0.71–2.04)	0.48
Yes (40)	2.33 $\pm$ 3.84		
Ophthalmic medication			
No (399)	1.94 $\pm$ 3.35	1.32 (0.57–3.1)	0.52
Yes (14)	2.57 $\pm$ 4.77		
Diuretic medicines			
No (403)	1.98 $\pm$ 3.42	0.71 (0.25–2.04)	0.52
Yes (10)	1.40 $\pm$ 2.07		
Tear debris			
None (259)	1.90 $\pm$ 3.46	1.08 (0.84–1.38)	0.55
Mild (123)	2.07 $\pm$ 3.36		
Moderate (29)	2.03 $\pm$ 3.20		
Severe (1)	5.00		
Diet medicines			
No (182)	1.86 $\pm$ 3.05	1.10 (0.80–1.51)	0.55
Yes (230)	2.05 $\pm$ 3.66		
PLTF thinning time, s			
<7.57 (206)	2.18 $\pm$ 3.36	0.99 (0.97–1.01)	0.56
$\geq$ 7.57 (207)	1.75 $\pm$ 3.43		
Osmolality, mOsm			
<299 (179)	2.02 $\pm$ 3.79	1.00 (0.99–1.01)	0.57
$\geq$ 299 (186)	1.95 $\pm$ 3.04		
Phenol red thread, mm			
<21 (206)	1.76 $\pm$ 2.93	1.01 (0.99–1.03)	0.57
$\geq$ 21 (207)	2.17 $\pm$ 3.81		
Disinfectant from care solution			
Generic (31)	1.55 $\pm$ 1.79	0.80 (0.42–1.52)	0.57
Hydrogen Peroxide (20)	2.20 $\pm$ 4.53	1.14 (0.54–2.41)	
None (71) (e.g., daily disposable or extended wear)	2.48 $\pm$ 3.87	1.28 (0.82–2.00)	
PHMB (165)	1.93 $\pm$ 3.65	REF	
Polyquad (122)	1.75 $\pm$ 2.84	0.9 (0.62–1.33)	

(continues)

TABLE 1 (continued). Univariate Poisson Regression Analyses of Ophthalmic, General Medical, and Demographic Variables Possibly Associated with Corneal Staining

Predictors (<i>n</i>)	Average $\pm$ SD Corneal Staining	Rate Ratio (95% CI)	<i>P</i>
Hypertension			
No (382)	1.94 $\pm$ 3.35	1.18 (0.66–2.13)	0.58
Yes (31)	2.29 $\pm$ 4.03		
Eye sensitivity to heating and cooling			
Not at all (138)	2.28 $\pm$ 3.97	0.95 (0.81–1.13)	0.58
Occasionally (171)	1.76 $\pm$ 2.78		
Often (77)	1.58 $\pm$ 3.02		
All the time (27)	2.70 $\pm$ 4.56		
Measured water content, %			
<51.1% (183)	1.93 $\pm$ 3.41	0.99 (0.97–1.02)	0.61
$\geq$ 51.1% (187)	1.79 $\pm$ 3.02		
Age when started lens wear, y			
<16 years (202)	1.86 $\pm$ 3.46	0.99 (0.97–1.02)	0.63
$\geq$ 16 years (211)	2.06 $\pm$ 3.34		
Care solution			
Complete Moisture Plus (Advanced Medical Optics, Inc., Santa Ana, CA) (42)	2.26 $\pm$ 4.32	1.29 (0.73–2.27)	0.67
Generic (31)	1.55 $\pm$ 1.79	0.88 (0.46–1.70)	
None (71) (e.g., daily disposable or extended wear)	2.48 $\pm$ 3.87	1.41 (0.88–2.26)	
Opti-Free Express (Alcon Laboratories, Fort Worth TX) (120)	1.76 $\pm$ 2.86	REF	
Other (32)	2.00 $\pm$ 3.85	1.14 (0.60–2.15)	
Renu Multiplus (Bausch & Lomb, Rochester, NY) (115)	1.85 $\pm$ 3.48	1.05 (0.69–1.60)	
OTC pain medications			
No (212)	2.02 $\pm$ 3.47	0.94 (0.69–1.29)	0.71
Yes (200)	1.90 $\pm$ 3.33		
Frequency of needing to remove lenses (due to lenses bothering the eyes)			
Never (3)	1.67 $\pm$ 2.08	1.04 (0.81–1.35)	0.74
Less than once per week (37)	1.08 $\pm$ 1.48		
Weekly (35)	2.09 $\pm$ 4.26		
Several times per week (33)	1.64 $\pm$ 2.78		
Once per day (16)	1.38 $\pm$ 1.26		
Several times per day (4)	1.25 $\pm$ 1.26		
Blink			
Normal (321)	1.99 $\pm$ 3.52	0.94 (0.64–1.37)	0.75
Abnormal (92)	1.87 $\pm$ 2.93		
Postmenopausal women			
No (242)	2.05 $\pm$ 3.35	0.91 (0.51–1.63)	0.75
Yes (31)	1.87 $\pm$ 3.19		
Age, y			
<26 years (204)	2.17 $\pm$ 3.78	1.00 (0.98 to 1.01)	0.76
$\geq$ 26 years (209)	1.77 $\pm$ 2.97		
Bulbar injection			
None (143)	2.03 $\pm$ 3.80	1.02 (0.83–1.27)	0.84
Mild (192)	1.81 $\pm$ 2.99		
Moderate (77)	2.26 $\pm$ 3.60		
Severe (1)	0.00		
Cholesterol medications			
No (397)	1.96 $\pm$ 3.44	1.09 (0.48–2.44)	0.84
Yes (16)	2.13 $\pm$ 2.13		
Dry eye diagnosis/symptoms without lens wear			
Yes (347)	1.98 $\pm$ 3.41	0.96 (0.62–1.48)	0.84
No (65)	1.89 $\pm$ 3.40		
Eye sensitivity to smoke			
Not at all (75)	1.88 $\pm$ 3.15	0.98 (0.83–1.16)	0.83
Occasionally (208)	2.17 $\pm$ 3.49		
Often (75)	1.25 $\pm$ 2.55		
All the time (55)	2.27 $\pm$ 4.22		
Meibomian gland capping			
1 (266)	2.02 $\pm$ 3.53	0.98 (0.78–1.23)	0.85
2 (109)	1.77 $\pm$ 2.83		
3 (36)	2.14 $\pm$ 4.04		
4 (2)	2.00 $\pm$ 2.83		
Multivitamins			
No (233)	1.99 $\pm$ 3.56	0.97 (0.71–1.34)	0.87
Yes (190)	1.94 $\pm$ 3.21		
Δ refractive index			
<0.02 (173)	1.79 $\pm$ 3.02	0.87 (0.08–9.17)	0.91
$\geq$ 0.02 (174)	2.07 $\pm$ 3.75		

(continues)

TABLE 1 (*continued*). Univariate Poisson Regression Analyses of Ophthalmic, General Medical, and Demographic Variables Possibly Associated with Corneal Staining

Predictors (<i>n</i>)	Average $\pm$ SD Corneal Staining	Rate Ratio (95% CI)	<i>P</i>
Prior infection associated with lens wear			
Yes (348)	1.97 $\pm$ 3.43		
No (64)	1.94 $\pm$ 3.27	0.98 (0.64–1.52)	0.94
Oral contraceptives, women only			
No (182)	2.04 $\pm$ 3.19		
Yes (95)	2.06 $\pm$ 3.57	1.01 (0.69–1.48)	0.95
Diabetes			
No (401)	1.97 $\pm$ 3.42		
Yes (12)	1.92 $\pm$ 2.75	0.98 (0.38–2.49)	0.96
Overall vision with current lenses			
Very dissatisfied (5)	0.60 $\pm$ 0.89		
Dissatisfied (22)	1.95 $\pm$ 3.11		
Satisfied (218)	2.05 $\pm$ 3.63	1.01 (0.77–1.31)	0.96
Very satisfied (168)	1.89 $\pm$ 3.18		
Artificial tears/rewetting drops			
No (214)	1.96 $\pm$ 3.68		
Yes (199)	1.96 $\pm$ 3.07	1.00 (0.73–1.37)	0.99
Total years lenses worn			
<11 years (201)	2.16 $\pm$ 3.71		
$\geq$ 11 years (212)	1.77 $\pm$ 3.07	1.00 (0.98–1.02)	0.99
Meibomian gland dropout			
1 (no partial glands) (224)	2.09 $\pm$ 3.84		
2 (<25% partial glands) (126)	1.67 $\pm$ 2.54		
3 (25% to 75% partial glands) (45)	2.22 $\pm$ 2.98	1.00 (0.83–1.21)	0.99
4 (>75% partial glands) (12)	2.50 $\pm$ 4.58		
Previous conjunctivitis			
No (235)	1.97 $\pm$ 3.28		
Yes (176)	1.96 $\pm$ 3.57	1.00 (0.72–1.37)	0.99
Retinopathy			
No (411)	1.96 $\pm$ 3.40		
Yes (1)	4.00	NA	NA
Heart disease			
No (405)	1.97 $\pm$ 3.42		
Yes (3)	1.67 $\pm$ 2.89	NA	NA
Osteoporosis			
No (405)	1.98 $\pm$ 3.42		
Yes (4)	1.00 $\pm$ 2.00	NA	NA
Glaucoma			
No (406)	1.97 $\pm$ 3.42		
Yes (4)	1.75 $\pm$ 2.22	NA	NA
Steroid medicines			
No (406)	1.98 $\pm$ 3.42		
Yes (7)	1.14 $\pm$ 1.21	NA	NA
Arthritis medicines			
No (406)	1.99 $\pm$ 3.42		
Yes (7)	0.57 $\pm$ 0.79	NA	NA
Retinal detachment			
No (403)	1.95 $\pm$ 3.40		
Yes (8)	1.50 $\pm$ 2.07	NA	NA
Lupus			
No (409)	1.97 $\pm$ 3.41		
Yes (3)	1.33 $\pm$ 1.53	NA	NA
Macular degeneration			
No (404)	1.92 $\pm$ 3.39		
Yes (1)	1.00	NA	NA
Humidifier			
No (404)	1.98 $\pm$ 3.42		
Yes (7)	1.43 $\pm$ 1.99	NA	NA
Punctal occlusion			
No (410)	1.96 $\pm$ 3.41		
Yes (2)	4.00 $\pm$ 1.41	NA	NA
Ointment			
No (405)	1.98 $\pm$ 3.43		
Yes (1)	2.00	NA	NA

ence of asthma ($P = 0.03$), the wearing of FDA group 4 lenses (compared to FDA group 1 lenses, $P = 0.04$), and lid margin vascularization ($P = 0.05$).

Noteworthy factors that were not associated with corneal staining included hydrogel refractive index (either nominal or measured; $P = 0.22$ and 0.26 , respectively), any systemic disease or medication usage (all $P > 0.05$), contact lens modality ($P = 0.38$), smoking ($P = 0.83$), tear film thinning time ($P = 0.56$), osmolality ($P = 0.57$), contact lens care solution disinfectants ($P = 0.57$) or specific brands of care solutions ($P = 0.67$), measured water content ($P = 0.61$), and dry eye status ($P = 0.19$).

Multivariate Analyses

Again, the initial step in multivariate analyses was the inclusion of variables from univariate analyses that met the $\alpha \leq 0.25$ entry criteria; 24 variables from Table 1 were included in the initial step. After inclusion in a multivariate model, 9 of the 24 variables were retained (at $\alpha \leq 0.25$) which included asthma, deposition, FDA group, lissamine green staining, income, tear meniscus height, cumulative treatments for dry eye with lenses, nominal water content, and average daily lens wear duration. These nine variables were then resubmitted for stepwise selection with the criterion tightened to $\alpha \leq 0.10$, and eight variables were retained (all nine, except asthma). All the possible two-way interactions were then added to these eight variables, and stepwise selection was used to develop the final model, with the selection criterion set at $\alpha \leq 0.05$. No biologically plausible interactions were selected.

The final model included the seven variables found in Table 2. As displayed, the FDA group was related to corneal staining (overall $P = 0.0004$). When adjusted for other predictors in the model, the wearing of silicone hydrogel lenses was protective against corneal staining (rate ratio = 0.29; 95% CI, 0.14–0.61; $P = 0.001$). Other predictors were daily lens wear duration (i.e., wearing lenses for longer periods increased corneal staining; overall $P = 0.0006$; rate ratio = 1.09; 95% CI, 1.04–1.15); income (overall $P = 0.0008$), lissamine green staining (overall $P = 0.002$; rate ratio = 1.05; 95% CI, 1.02–1.09), deposition (overall $P = 0.007$; rate ratio = 1.41; 95% CI, 1.10–1.80), tear meniscus height (overall $P = 0.007$; rate ratio = 9.12; 95% CI, 1.81–45.82), and nominal water content (overall $P = 0.02$; rate ratio = 0.96; 95% CI, 0.92–0.99).

This model fits the data significantly better than the null model (i.e., the intercept-only model). To show this, the null

model was fitted and compared to this final multiple regression model by using a χ^2 test of the difference of log likelihoods. The log likelihood for the full regression model was -587.6 and was -615.0 for a model of staining with no predictors ($\chi^2 = 54.9$; $df = 10$; $P < 0.0001$). The dispersion-based R^2 for the final model was 0.27.

DISCUSSION

Frequency of Corneal Staining

As noted in Figure 1, approximately 54% of contact lens wearers in this large, cross-sectional study had corneal staining present (whereas approximately 46% of lens wearers had no corneal staining present). This result is in excellent agreement with another large, multicenter, cross-sectional study in which the frequency of corneal staining was evaluated in a sample of 500 contact lens wearers and found to be present 56% of the sample.² Moderate staining (grade 3 or more) was noted in 26% of patients in the present study, whereas it was noted in 8% to 33% of patients in prior studies.^{1,2} The corresponding average of the summed corneal staining score across the regions of the cornea was 1.96 in this study, whereas it ranged from 0.50 to 0.93 in prior studies.^{1,2} Staining was located most frequently and graded the worst in the inferior region of the cornea in the present study, which was also the case in the aforementioned studies (and in all studies, the temporal region was the second most frequent and the worse).^{1,2}

Contact Lens Factors and Corneal Staining

As noted from the multivariate analyses, contact lens factors that were related to corneal staining included the contact lens materials (silicone hydrogels and high-water-content lenses were protective against corneal staining), daily wearing time (whereby increased daily wearing time was associated with increased corneal staining), and contact lens deposition (increased contact lens deposition was associated with increased corneal staining).

Some of these findings confirm prior thoughts about the relation between contact lens factors and corneal staining, although other findings refute prior thoughts and ideas on the topic. For instance, it has been thought for years that high-water-content lenses (particularly high-water-content lenses with thin center thicknesses) are associated with corneal staining.^{3,28,29} It is thought that front surface evaporation dehy-

TABLE 2. Statistically Significant Predictors of Staining in a Multivariate Poisson Regression Analysis

Variable	Overall Effect P	Rate Ratio (95% CI)	Level-Specific P
Contact Lens FDA Grouping			
1	0.0004	REF	REF
2		1.94 (0.70–5.40)	0.20
4		0.83 (0.38–1.82)	0.65
Silicone hydrogel		0.29 (0.14–0.61)	0.001
Daily lens wear duration, h	0.0006	1.09 (1.04–1.15)	NA
Income			
\$0–\$29,999	0.0008	REF	REF
\$29,999–\$74,999		0.53 (0.36–0.78)	0.001
\$75,000+		0.49 (0.32–0.76)	0.001
Lissamine Green Staining	0.002	1.05 (1.02–1.09)	NA
Deposition	0.007	1.41 (1.10–1.80)	NA
Tear meniscus height (mm)	0.007	9.12 (1.81–45.82)	NA
Nominal water content (%)	0.02	0.96 (0.92–0.99)	NA

All variables identified through step-wise regression using the criterion of ≤ 0.10 were included in a model with all their possible two-way interactions. Interactions were sequentially removed if they did not have $P < 0.05$. In addition, interactions between FDA group and care solution, FDA group and disinfectant from care solution, and smoking and income were evaluated, although none yielded statistical significance. The final model included all main effects with $P \leq 0.05$.

drates a thin hydrogel contact lens leading to an uptake and loss of the post-lens tear film and subsequent corneal staining.^{3,22,30} However, these results suggest that high-water-content lenses ($\geq 50\%$ per the FDA definition and our analysis) are protective against corneal staining. It is important to note that there was no measure of contact lens thickness in this study, and it was therefore impossible to categorize thick versus thin high-water-content lenses in these analyses. That being said, it appears that these data suggest on the whole that high-water-content lenses generally protect against corneal staining. Further, as already mentioned, some earlier studies have suggested a relation between higher modulus and corneal staining (SEALs, for example). However, these results show that silicone hydrogels are protective against corneal staining. The high-water-content and silicone hydrogel contact lenses may be protective because both types of contact lens provide higher oxygen levels to the cornea (than other nonsilicone hydrogel and lower water content lenses). This increased oxygenation may be associated with improved maintenance of the corneal barrier function or epithelial cell viability.^{31,32}

Likewise, it has been suggested in the literature that contact lens deposition is related to corneal staining, and the results from this study suggest that increased deposition was related to increased corneal staining.³³ In this regard, the mechanism for the relation between contact lens deposition and corneal staining may be purely mechanical or due to the disruption of one of the tear film components that normally protects the ocular surface (i.e., mucins). Interestingly, a prior large-scale evaluation of factors associated with corneal staining found the replacement schedule to be related to corneal staining, with the conventional modality being more likely to be associated.² However, contact lens deposition was not evaluated in that study, and in that regard, replacement schedule may have served as a surrogate for deposition (with the lengthier replacement schedules being related to corneal staining). Last, and not surprisingly, increased corneal staining was related to the amount of time each day that a patient wore contacts lenses. As shown by the data from this study, each additional hour of wear was associated with a 9% increase in corneal staining.

There were numerous contact lens factors that were not related to corneal staining in multivariate modeling, including weekly lens wear duration (which is correlates highly with daily wearing time and thus likely dropped from the multivariate model due to the covariance), contact lens dehydration (again, likely due to covariance with nominal water content), lens type (soft versus GP), overnight lens wear, contact lens modality (which may be due to covariance with deposition), a recent contact lens refitting, perceived vision or satisfaction with contact lenses, or years of lens wear. The lack of an association between some of these contact lens factors and corneal staining are worthy of further discussion, particularly as it relates to contact lens care solutions and associated disinfectants, given the significant clinical and research interest in that topic. Contact lens care solution (by brand), disinfectant, or the interaction between contact lens FDA group and care solution were not related to corneal staining. The lack of an association between contact lens care solution disinfectant and corneal staining was also reported in the prior large-scale analysis by Nichols et al.²

Historically, contact lens care systems that included thimerosal or chlorhexidine were thought to be associated with toxicity or hypersensitivity of the ocular surface, caused at least in part by loss of the epithelial microvilli and conjunctival goblet cells that produce mucin.^{34–52} These early problems led to an ongoing effort to improve contact lens solutions, especially relative to the development of more biocompatible disinfectants. Despite the introduction of newer contact lens care solutions, reports linking corneal staining with care solutions

continue to be published. More specifically, when a relation between corneal staining and a care system has been reported, it most typically links the biguanide disinfectants used in combination with some silicone hydrogel lenses.^{11,12,15–18,53–57}

It is important to note that the aforementioned studies linking corneal staining and contact lens care solutions had significant design differences from the methodology used in this study. For instance, the link between care solution disinfectant and corneal staining has been shown to occur most often when corneal staining is evaluated within 2 to 4 hours after the presoaked contact lens has been applied to the eye. In this study, corneal staining was measured with habitual contact lens wear and care solution use, whereas other studies have measured corneal staining shortly after patients changed solution and/or materials. These short-term studies may evoke a variety of transient and self-limiting factors associated with corneal staining. The present study was conducted from a cross-sectional vantage point, and the findings suggest potential adaptation of the cornea to any immediate, but transient, ocular surface changes, specifically because the staining in the study was not diffusely observed across the cornea. Another study design difference is that some of the prior study methodologies were essentially ongoing, open-label studies that may introduce examiner and selection biases. Thus, in a study such as the present one, in which corneal staining was assessed at various time points in a large cross-sectional manner, it may not be surprising that neither contact lens solutions nor specific disinfectants were related to corneal staining. Our findings have been corroborated by one other large, cross-sectional, multicenter study that showed no relation between contact lens care solution and corneal staining.²

Ocular Surface Factors and Corneal Staining

As noted from the multivariate analyses, tear film factors related to increased corneal staining included lissamine green conjunctival staining and an increased tear meniscus height. In a prior study that was smaller in scope, we showed a trend in a correlation between corneal staining and rose bengal staining, which seems clinically intuitive.⁵⁸ The relation between increased tear meniscus height and corneal staining seems counterintuitive at first glance. However, one potential explanation of this is that increased corneal staining may be associated with upregulation of nervous feedback to the lacrimal gland, which may stimulate aqueous tear secretion (thus increasing the pooling of tears found in the meniscus).

More surprising were the numerous ocular surface factors not related to corneal staining, including pre-lens tear film thinning time, incomplete blinking, osmolality, all putative measures of the tear film lipids or blepharitis (e.g., lipid layer thickness, lid margin vascularization, meibomian gland capping, and meibomian gland dropout), tear debris, and conjunctival and limbal injection. Interesting as well was that dry eye status (by subjective report) was not related to corneal staining. Dry eye status and many other clinical symptoms or signs have not correlated well with corneal staining in prior studies.^{58–61}

Patient-Related Factors

We also found that annual income below \$30,000, a designator of lower socioeconomic status, nearly doubles the amount of corneal staining. This relationship is intriguing, because it is nonocular in nature and may suggest a relation with general health or financial well-being. Interestingly, neither the age nor the sex of the subject was related to corneal staining, although that finding has been shown in other studies as well.^{2,60}

In the multivariate model, there was no relationship between corneal staining and any tested health conditions or

medications, which is consistent with another large-scale analysis of factors associated with corneal staining in contact lens wearers.² Several systemic medications were evaluated including antihistamines, analgesics, antihypertensives, antidiarrheals, oral contraceptives, hormone replacement therapy, and tricyclic antidepressants. Many of these medications are traditionally thought to decrease tear production.⁶² In prior analyses of data from this study in which dry eye status was the outcome, over-the-counter pain medication was related to dry eye status but no other medications were related.²² However, those analyses also found rapid pre-lens tear film thinning time, limbal injection, and increased tear film osmolality were related to dry eye status in contact lens wearers, whereas these factors were not related to corneal staining in these analyses. In other population-based studies, self-reported dry eye has been related to arthritis and to medications such as antihistamines, antianxiety drugs, antidepressants, and oral steroids.^{63,64} Again, these dry eye factors do not seem to be related to corneal staining in contact lens wearers.

The strength of this study is that a large number of intrinsic and extrinsic factors were simultaneously assessed for their importance in contact lens-associated corneal staining. The cross-sectional design allows for observation of these factors in a large number of patients in their habitual contact lenses. A potential limitation of this study is the relatively mild amount of corneal staining found in most patients. However, the study design did not necessarily introduce a selection bias that suggests patients are different from the general contact lens wearing population. Related to this, one of the issues in analyzing corneal staining (or graded outcomes over several tissue regions) is that there is not necessarily an optimal way to aggregate the data into a statistically useful outcome. For instance, with corneal staining there are several analytical approaches one might consider including summing the severity scores across the entire region (as was done in this work), or alternatively, simply categorizing patients into two groups (those with and without corneal staining, for example). One limitation in the approach used in this study is that two patients with differing clinical grades were considered the same from an analytical standpoint (for example, a patient with a grade 1 in four regions would be counted the same as a patient with a grade 4 in one region). However, the alternative approach of categorizing patients into two groups is associated with a loss of information, as the ability to examine how the predictor affects the magnitude of the outcome would be lost. In fact, in preliminary statistical analyses, logistic regression models were conducted using "no staining versus staining" as the outcome, and very little information was gleaned. Thus, we chose to examine the impact of the predictors on the amount of corneal staining using Poisson models, rather than presence or absence of corneal staining as it provided more meaningful insights. A second limitation is that it is unknown whether the staining observed in this study had the propensity for pathogenicity (e.g., microbial keratitis), although work in this area is ongoing. In summary, low levels of corneal staining are common in contact lens wearers and several factors were identified as being related to this corneal staining.

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