

UC Berkeley

UC Berkeley Previously Published Works

Title

Pain Sensitivity Associated With the Length of the Maximum Interblink Period

Permalink

<https://escholarship.org/uc/item/79x842m1>

Journal

Investigative Ophthalmology & Visual Science, 59(1)

ISSN

0146-0404

Authors

Li, Wing

Lin, Meng C

Publication Date

2018

DOI

10.1167/iovs.17-22950

Peer reviewed

Pain Sensitivity Associated With the Length of the Maximum Interblink Period

Wing Li¹ and Meng C. Lin^{1,2}

¹Clinical Research Center, School of Optometry, University of California, Berkeley, California, United States

²Vision Science Graduate Program, University of California, Berkeley, California, United States

Correspondence: Meng C. Lin, University of California, Berkeley, School of Optometry, 360 Minor Hall, Berkeley, CA 94720-2020, USA; mlin@berkeley.edu.

Submitted: September 9, 2017

Accepted: November 20, 2017

Citation: Li W, Lin MC. Pain sensitivity associated with the length of the maximum interblink period. *Invest Ophthalmol Vis Sci.* 2018;59:238-245. <https://doi.org/10.1167/iov.17-22950>

PURPOSE. Pain sensitivity has been identified as a factor that affects how individuals answer dry eye questionnaires, but it is unknown how it affects ocular discomfort. This study used the time that individuals could refrain from blinking as an indicator of ocular discomfort and set out to determine whether it was related to pain sensitivity, while adjusting for ocular surface conditions.

METHODS. Subjects first completed the Pain Sensitivity Questionnaire to quantify pain sensitivity levels. Exposed interpalpebral area, tear meniscus height, tear-film lipid layer thickness, ocular surface cooling, and noninvasive tear breakup were assessed. Subjects were then asked to refrain from blinking until the initial onset of discomfort, which was termed “the maximum interblink period” (MIBP), while ocular surface cooling rate was simultaneously measured. Subjects were seen for four visits over a course of 2 days.

RESULTS. Forty-two subjects (36 females, 6 males) completed the study, with a mean (SD) age of 23.2 (3.8) years. A longer MIBP was associated with decreased pain sensitivity ($P = 0.04$), lower ocular surface cooling rate ($P < 0.001$), and Asian ethnicity ($P = 0.005$). Based on the results from the mixed-effect model, it is estimated that individuals would be able to refrain from blinking for an additional 4 seconds if they had the lowest (0.6) compared to the highest (6.1) pain sensitivity in the study cohort.

CONCLUSIONS. The Pain Sensitivity Questionnaire was associated with the MIBP length even after adjusting for ocular surface conditions, which suggests that pain sensitivity plays a role in influencing how ocular discomfort is perceived.

Keywords: pain sensitivity, blink refrainment, ocular surface cooling, blink, dry eye

An extensive body of research has been done on dry eye, which has helped identify causative factors and elucidate its pathophysiology.¹ However, one enduring question yet to be solved is why discrepancies between signs and symptoms of dry eye are often noted.² It is not uncommon for patients to report symptoms of severe dry eye but with no clinical signs or, conversely, to present with significant clinical signs but be asymptomatic.^{3,4} This has complicated the diagnosis and management of dry eye⁵ and has been a major hindrance in the development of new treatment options.⁶

A possible reason for the discrepancy may be linked with the diverse levels of pain perception, where the same injury can be reported as mild irritation by some, but as severe pain by others. The perception of pain is thought to be primarily mediated by pain sensitivity, and its importance is highlighted by studies that have found pain sensitivity to be associated with how successful a medical treatment is rated, the level of opioid use after surgery,⁷ and as an independent risk factor for developing chronic pain.⁸ A recent study by Li et al.⁹ has found that increased sensitivity to pain, measured by using the Pain Sensitivity Questionnaire (PSQ), is associated with a higher Ocular Surface Disease Index (OSDI) score and greater reports of discomfort and dryness on a 100-point visual analog scale.

Although the study has found that pain sensitivity is related to how individuals respond to questionnaires, it is unknown if pain sensitivity merely affects the historic recall of ocular

discomfort on questionnaires⁹ or whether it actually influences the perception of ocular discomfort at the inception point, when noxious stimuli occur on the eye. Lacking this information, it is difficult to discern the exact role that pain sensitivity has on the relationship between signs and symptoms of dry eye. To gain greater insight, this study asked subjects to complete the PSQ and then assessed how they reacted to ocular discomfort. Ocular discomfort was induced by having subjects refrain from blinking until the initial experience of discomfort, which was termed “the maximum interblink period” (MIBP).

While having subjects refrain from blinking is not a conventional means of measuring ocular discomfort, it has been previously used in other studies and has several key advantages.^{10,11} The first advantage is that discomfort experienced during the MIBP closely mimics the pathophysiology and noxious stimuli in evaporative dry eye.^{12,13} A prolonged period of blink refrainment can contribute to localized disruption of the tear-film lipid layer that may cause a nearly 10-fold increase in tear-film evaporation, similar to evaporative dry eye.^{14,15} In addition, the increased tear evaporation leads to greater ocular surface cooling and tear hyperosmolarity, which are considered the primary noxious stimuli associated with evaporative dry eye.^{14,15} The second advantage is that as subjects were instructed to blink only with the initial sensation of ocular discomfort, the method provided a real-time assessment of



ocular discomfort, with length of blink refrainment as a measure of ocular discomfort. Therefore, the purpose of this study was to determine if pain sensitivity was associated with how long subjects could refrain from blinking. It was hypothesized that a subject with lower pain sensitivity would be less perceptive to ocular discomfort and could refrain from blinking for a longer period of time than a subject with higher pain sensitivity. It would also be important to factor in ocular surface parameters, as they have been shown to influence the length of blink refrainment, and to consider dry eye questionnaires, as they reflect the ocular discomfort that subjects encounter in their daily lives.^{10,11,16}

MATERIALS AND METHODS

Study Population

Subjects were recruited from the University of California, Berkeley, and the surrounding community. Subjects taking systemic or ocular medication, or having a history of systemic or ocular disease or surgery, were excluded from the study. Subjects were also excluded if they had undergone refractive surgery, had a history of ocular allergies, or had an eyelid or conjunctival abnormality.

Subjects aged 18 to 39 years were eligible for the study and consisted of individuals who were of Asian or non-Asian descent. These two groups were selected on the basis of studies that have found interethnic differences in pain sensitivity^{7,17} and dry eye prevalence rate.^{18,19} Individuals were considered to be Asians if they were of Chinese, Taiwanese, Japanese, or Korean descent, or a mixture of these ethnicities. Individuals were considered to be non-Asians if they were of any other ethnicity (e.g., European white, Latin American, Indian, African descent). Informed consent, with a complete description of the goals, risks, benefits, and procedures of the study was obtained from all participants. This study observed the tenets of the Declaration of Helsinki and was approved by the University of California, Berkeley Committee for Protection of Human Subjects.

Instrumentation and Measurements

Subject pain sensitivity was measured by using the PSQ, which has been validated in normal and chronic pain populations,^{20,21} and in ocular surface research.⁹ Subject symptoms associated with dry eye and contact lens discomfort were assessed by using the OSDI, Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8),²² and the University of California, Berkeley Clinical Research Center Dry Eye Flow Chart (DEFC).²³ These questionnaires were included as it was thought that subject symptomology might influence MIBP length. Anterior ocular surface health was evaluated with slit lamp biomicroscopy (SL120; Carl Zeiss Meditec, Inc., Jena, Germany) under white light. Noninvasive tear breakup time (NITBUT) was measured with the Medmont e300 corneal topographer (Medmont International Pty Ltd., Victoria, Australia). Tear meniscus height was measured by using the Oculus Keratograph 5m (Oculus, Inc., Arlington, WA, USA). Average tear-film lipid layer thickness was assessed by using the LipiView interferometry system (TearScience, Inc., Morrisville, NC, USA).

Ocular surface temperature was measured by using an FLIR A655sc (FLIR Systems, Inc., Wilsonville, OR, USA) uncooled microbolometer infrared thermographer, which has a 640 × 480 video resolution, 17- μ m pixel size, and 0.1°C thermal sensitivity. The thermographer, mounted on a tripod, was placed 8 to 10 inches from the eye, focused on the ocular surface, and aimed approximately at the geometric center of

the cornea, as based on visual inspection. FLIR+ ResearchIR Software Suite (FLIR Systems, Inc., Wilsonville, OR, USA) was used by an experienced observer (WL) to specify a user-defined region of interest corresponding to the cornea in the infrared recordings. The user-defined region in each video recording encompassed 3000 to 5000 temperature measurement points (due to anatomic variation in palpebral aperture size). The points were averaged and used to determine the ocular surface temperature profile over time, with a linear approximation used to obtain the ocular surface cooling rate in deg C/s. Although this methodology has some shortcomings, especially as it relies on the investigator to delineate the region of interest, it is generally considered the standard methodology in determining the ocular surface cooling rate.²⁴ Room temperature and humidity were measured by using a combination digital thermometer and hygrometer (General Tools & Instruments, Secaucus, NJ, USA). Room temperature and humidity were typically at 25°C and 48%, respectively.

Study Protocol

Seasoned contact lens wearers were administered a set of baseline questionnaires, which was composed of the PSQ, OSDI, CLDEQ-8, and the DEFC. Subjects were seen for four visits over the course of 2 days (two visits per day, consisting of a morning and an afternoon visit), providing four measurements per subject. All visits had the same set of procedures except that the afternoon visits included an assessment of corneal staining type, depth, and extent with sodium fluorescein instillation using the Cornea and Contact Lens Research Unit (CCLRU) grading scale. Subjects were asked to discontinue contact lens wear for at least 24 hours before their visits. All measurements were done on the right eye only and on an ocular surface without contact lenses. Digital photos were taken of the subject's eye in primary gaze position, using a smartphone (iPhone 6; Apple, Cupertino, CA, USA) while the subject held a United States 1-cent coin (diameter = 1.91 cm) in the same plane as the eye to help calibrate the magnification. Digital images were then processed with Adobe Photoshop CS5.5 (Adobe Systems, San Jose, CA, USA) to determine the exposed interpalpebral area (conjunctiva and cornea) in square centimeter (cm²) by pixel counting.²⁵

Anterior ocular health was assessed with slit lamp biomicroscopy under white light to ensure there was no evidence of active or preexisting ocular pathology (e.g., corneal scars, infiltrates, excessive corneal epithelial irritation). Subjects were then taken to a different examination room and acclimated to the ambient environment for a minimum of 10 minutes before testing started. Tear-film lipid layer thickness was measured first and then tear meniscus height was measured, with the investigator (WL) marking the height of the tear meniscus directly below the 6-o'clock position of the cornea. NITBUT was measured three times, with a 30-second break between each measurement and an endpoint consisting of the first visible disruption noted on the placido mires or upon a blink. Ocular surface temperature and MIBP measurements were conducted at the same time, where subjects were placed in a slit lamp head- and chinrest assembly, which minimized head movement during recordings; no slit lamp lighting was introduced during this measurement. Instructions to subjects during ocular surface temperature and MIBP measurements were scripted, so during each visit they were asked to "please close your eyes for 2 minutes and after opening your eyes, refrain from blinking until you experience the initial onset of ocular discomfort." The tone of voice for giving directions was standardized to a neutral affect in an attempt to minimize potential influence on the MIBP (e.g., subjects may try to hold their eyes for longer if the investigator

uses a more forceful voice). The ocular surface temperature recording was later reviewed to determine the MIBP length, using time stamps on the recording.

Statistical Methods

The PSQ provides three numerical values: the overall pain sensitivity score (PSQ-Total), and scores for sensitivity to situations with minor (PSQ-min) and moderate (PSQ-mod) pain. Our previous study determined that the PSQ-min score most accurately reflects the influence of pain sensitivity on dry eye questionnaires.⁹ Therefore, the analysis will only focus on the PSQ-min score and will be referred as the “PSQ score.”

Data were analyzed with R statistical package (version 3.3.2; R Foundation for Statistical Computing, Vienna, Austria).

A thorough exploratory and descriptive preliminary analysis was conducted by assessing bivariate plots and univariate models to examine for possible significant associations between explanatory and outcome variables, which guided how multivariate modeling was used. The statistical models factored the MIBP length as the outcome variable, with sex, ethnicity, exposed interpalpebral area, tear meniscus height, NITBUT, ocular surface cooling rate, average tear-film lipid layer thickness, and PSQ score as potential explanatory variables. Linear mixed-effects modeling was used to account for potential within-subject correlations related to repeated measurements. Upon examining residual plots, the MIBP length was natural-log transformed to better approximate normality to meet key assumptions for statistical modeling. The results were reported after back-transformation. In all tests, results with $P \leq 0.05$ and $P \leq 0.10$ were considered statistically significant and borderline significant, respectively.

Univariate linear mixed-effects modeling identified explanatory variables that were associated with the outcome variable. Significant or borderline significant explanatory variables identified in univariate modeling were then examined by using multivariate linear mixed-effects modeling. A stepwise regression procedure with consideration of *F*-test *P* values and examination of residual and other diagnostic plots was used to determine accurate multivariate regression models.

RESULTS

Subject Characteristics

Forty-two subjects completed the study (36 females, 6 males), with a mean (SD) age of 23.2 (3.8) years and a range of 18 to 34 years. Table 1 shows the clinical measurements from the study cohort. There were 22 subjects of Asian descent and 20 subjects of non-Asian descent. Table 2 shows the measurements between Asians and non-Asians, with no interethnic difference noted in PSQ score ($P = 0.79$), OSDI score ($P = 0.96$), DEFC score ($P = 0.87$), CLDEQ-8 score ($P = 0.52$), ocular surface cooling rate ($P = 0.42$), NITBUT ($P = 0.78$), average tear-film lipid layer thickness ($P = 0.25$), tear meniscus height ($P = 0.12$), and years of contact lens wear ($P = 0.15$). Asians were found to have a longer MIBP (12.4 s vs. 9.2 s; $P = 0.02$), less exposed interpalpebral area (2.7 cm² vs. 2.9 cm²; $P = 0.04$), slightly older (24.5 years versus 21.6 years; $P = 0.02$), and had greater aggregate corneal staining type (0.8 vs. 0.1; $P = 0.01$), extent (0.5 vs. 0.1; $P = 0.04$), and depth (0.5 vs. 0.1; $P = 0.03$) as compared to non-Asians. Subjects were all contact lens wearers.

Univariate and Multivariate Modeling

In univariate modeling (Table 3), a longer MIBP was associated with a reduced ocular surface cooling rate ($P < 0.001$; Fig. 1), a

TABLE 1. Mean, Standard Deviation, and Range for Measurements in All Subjects

Test	Mean (SD)	Range
Age	23.1 (3.8) y	18–34 y
Years of contact lens wear	8.0 (3.9)	1–20
Corneal staining type (aggregate)	0.5 (1.3)	0.0–7.5
Corneal staining extent (aggregate)	0.3 (0.7)	0.0–3.5
Corneal staining depth (aggregate)	0.3 (0.7)	0.0–3.5
PSQ score	2.9 (1.4)	0.6–6.1
OSDI score	9.7 (8.8)	0.0–31.3
DEFC score	2.7 (1.4)	1.0–5.0
CLDEQ-8 score	10.8 (6.7)	1.0–25.0
Exposed interpalpebral area	2.8 (0.4) cm ²	2.0–3.6 cm ²
MIBP length	10.9 (8.7) s	2.3–57.9 s
Average tear-film lipid layer thickness	57 (17) nm	32–100 nm
Tear meniscus height	0.25 (0.08) mm	0.09–0.52 mm
NITBUT	10.8 (9.4) s	2.9–86.9 s
Ocular surface cooling rate	0.08 (0.06)°C/s	0.002°C/s–0.27°C/s

lower PSQ score ($P = 0.04$; Fig. 2), Asian ethnicity ($P = 0.02$; Fig. 3), and male sex ($P = 0.01$); it was borderline associated with a longer NITBUT ($P = 0.06$) and greater aggregate corneal staining depth ($P = 0.08$). No association was noted with age ($P = 0.35$), years of contact lens wear ($P = 0.34$), aggregate corneal staining type ($P = 0.15$), aggregate corneal staining extent ($P = 0.19$), tear meniscus height ($P = 0.64$), average tear-film lipid layer thickness ($P = 0.61$), exposed interpalpebral area ($P = 0.67$), OSDI score ($P = 0.26$), DEFC score ($P = 0.72$), and CLDEQ-8 score ($P = 0.60$). Interaction terms were considered but none were found to be significant.

In multivariate modeling (Table 4), a longer MIBP was associated with a reduced ocular surface cooling rate ($P < 0.001$), a lower PSQ score ($P = 0.04$), and Asian ethnicity ($P = 0.003$). No association was noted with aggregate corneal staining depth ($P = 0.72$), NITBUT ($P = 0.21$), and sex ($P = 0.22$). Based on the model, there would be an estimated 8.7-second increase in the MIBP length when comparing the lowest (0.002°C/s) to the highest (0.27°C/s) ocular surface cooling rate. In addition, there would be an estimated 3.6-second increase in the MIBP length when comparing the lowest PSQ score (0.6) to the highest PSQ score (6.1). Supplementary Video S1 shows an example of how MIBP length varied between two subjects (Subject EP: 4 s versus Subject JF: 13 s) even though they had the same ocular surface cooling rate (0.03°C/s), which may have been influenced by their PSQ score (Subject EP: 5.6 versus Subject JF: 1.3). Asians were able to refrain from blinking for an additional 3.1 seconds as compared to non-Asians.

DISCUSSION

Research on ocular discomfort related to dry eye has primarily focused on understanding how conditions on the ocular surface (e.g., ocular surface cooling, tear hyperosmolarity) influence the level of discomfort experienced.^{12,26–28} Advances in technology will improve the accuracy of measuring ocular surface conditions, but it would be unsurprising if a weak-to-moderate correlation between measurements and dry eye symptoms is still observed. There are similar parallels to when clinical tests measuring skin conductance²⁹ and cytokine levels³⁰ were hailed as potential gold standards for measuring

TABLE 2. Mean, Standard Deviation, and Range for Clinical Measurements of Asian and Non-Asian Subjects, and *P* Values From Comparing the Two Groups

	Asian (<i>n</i> = 22)	Non-Asian (<i>n</i> = 20)	<i>P</i> Value
Age	Mean (SD): 24.5 (4.3) y Range: 19–34 y	Mean (SD): 21.6 (2.6) y Range: 18–27 y	0.02
Years of contact lens wear	Mean (SD): 8.8 (4.9) Range: 1–20	Mean (SD): 7.1 (2.2) Range: 4–11	0.15
Corneal staining type (aggregate)	Mean (SD): 0.8 (1.7) Range: 0.0–7.5	Mean (SD): 0.1 (0.3) Range: 0.0–1.0	0.01
Corneal staining extent (aggregate)	Mean (SD): 0.5 (0.9) Range: 0.0–3.5	Mean (SD): 0.1 (0.4) Range: 0.0–2.0	0.04
Corneal staining depth (aggregate)	Mean (SD): 0.5 (0.9) Range: 0.0–3.5	Mean (SD): 0.1 (0.3) Range: 0.0–1.0	0.03
PSQ score	Mean (SD): 2.9 (1.3) Range: 0.7–5.6	Mean (SD): 2.8 (1.4) Range: 0.6–6.1	0.79
OSDI score	Mean (SD): 9.7 (9.3) Range: 0.0–31.3	Mean (SD): 9.6 (8.2) Range: 0–31.3	0.96
DEFC score	Mean (SD): 2.8 (1.4) Range: 1.0–5.0	Mean (SD): 2.7 (1.5) Range: 1.0–5.0	0.87
CLDEQ-8 score	Mean (SD): 10.1 (6.1) Range: 1.0–22.0	Mean (SD): 11.5 (7.1) Range: 1.0–25.0	0.52
Ocular surface cooling rate	Mean (SD): 0.08 (0.06)°C/s Range: 0.006°C/s–0.27°C/s	Mean (SD): 0.09 (0.06)°C/s Range: 0.002°C/s–0.26°C/s	0.42
NITBUT	Mean (SD): 10.6 (9.9) s Range: 2.9–87.0 s	Mean (SD): 11.1 (9.0) s Range: 4.0–48.6 s	0.78
Average tear-film lipid layer thickness	Mean (SD): 55 (15) nm Range: 34–100 nm	Mean (SD): 59 (18) nm Range: 32–100 nm	0.25
Tear meniscus height	Mean (SD): 0.24 (0.07) mm Range: 0.12–0.44 mm	Mean (SD): 0.27 (0.09) mm Range: 0.09–0.52 mm	0.12
MIBP length	Mean (SD): 12.4 (9.0) s Range: 3.3–57.1 s	Mean (SD): 9.2 (8.2) s Range: 2.3–57.9 s	0.02
Exposed interpalpebral area	Mean (SD): 2.7 (0.3) cm ² Range: 2.0–3.3 cm ²	Mean (SD): 2.9 (0.4) cm ² Range: 2.1–3.6 cm ²	0.04

pain because they objectively assess physiological markers for pain. Tellingly, these tests were never readily adopted by clinics and have been relegated to niche use.^{31,32}

Nevertheless, although the development of new diagnostic technology is important, the results from the study argue that it may also be important to understand how intrinsic factors such as pain sensitivity, ethnicity, and sex influence the relationship between signs and symptoms of dry eye. When assessing the

multivariate model, ocular surface cooling rate had the greatest estimated effect size on the MIBP length, which is not surprising as ocular surface cooling represents a noxious stimulus on the ocular surface.³³ Of interest, although PSQ is unrelated to ocular surface conditions and is considered an intrinsic factor of a subject's characteristic, it had a relatively large effect size on MIBP length, as the maximum effect size for the PSQ on MIBP length of 3.6 s represents nearly a third of the

TABLE 3. Separate Univariate Models Showing the Association Between Natural-Log-Transformed MIBP Length and Explanatory Variables

Explanatory Variable	Intercept	Coefficient	<i>P</i> Value
Ocular surface cooling rate	2.68	−4.84 (per 1°C/s)	<0.001
PSQ score	2.59	−0.10 (per unit on the PSQ score)	<0.05
Ethnicity: Asian	2.12	0.34	0.02
Sex: Female	2.72	−0.50	0.01
NITBUT	2.09	0.01 (per s of NITBUT)	0.06
Age			0.35
Years of contact lens wear			0.34
Corneal staining type (aggregate)			0.15
Corneal staining extent (aggregate)			0.19
Corneal staining depth (aggregate)	2.25	0.12	0.08
Tear meniscus height			0.64
Average tear-film lipid layer thickness			0.61
Exposed interpalpebral area			0.67
OSDI score			0.26
DEFC score			0.72
CLDEQ-8 score			0.60

The arbitrary reference groups for ethnicity and sex were Asian and female, respectively.

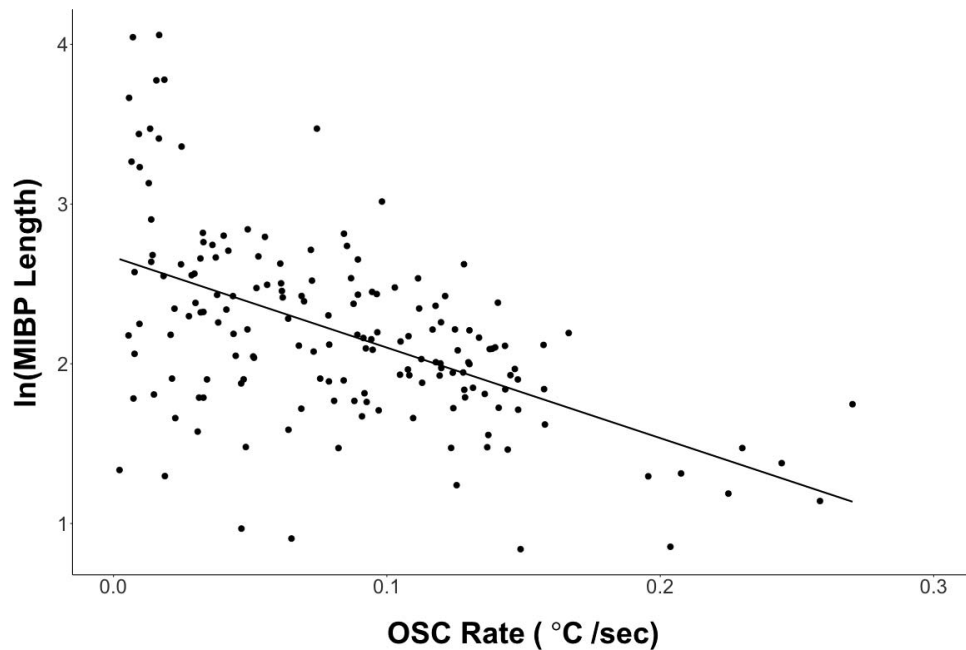


FIGURE 1. Scatter plot showing the association between ocular surface cooling (OSC) rate and natural-log-transformed maximum interblink period (lnMIBP) length ($P < 0.001$). Each subject provided a total of four data points in the scatter plot.

mean MIBP length of 10.8 s. This agrees with studies that have found similar trends in other areas of the body^{20,21} and supports our previous work in which the PSQ has been found to influence OSDI by up to 9 points and up to 31 points on a 100-point visual analog scale for comfort and dryness, respectively.⁹ It should be noted that Kaido et al.³⁴ have found that greater corneal sensitivity to pain is associated with increased dry eye symptomology. Although greater corneal sensitivity to pain is a byproduct of dry eye, it is possible that baseline corneal sensitivity to pain (unaffected by contact lens wear or dry eye) is associated with an individual's pain sensitivity, and further study is warranted on this topic.^{20,21,34}

In addition to pain sensitivity, ethnicity was another intrinsic factor associated with MIBP length, with Asians having a longer MIBP than non-Asians. Although ocular surface parameters and symptoms play a mediating role in when blinks occur, there was only a minor interethnic difference in corneal staining, which has been previously noted, and no differences in dry eye symptoms.^{10,11,16,23,35,36} Therefore, the interethnic difference in MIBP length appears to be primarily mediated by ethnicity as an intrinsic attribute.

First, it may be related to distinct differences in eyelid anatomy between the two groups, with Asians having a smaller vertical palpebral aperture, more oblique palpebral fissure, and

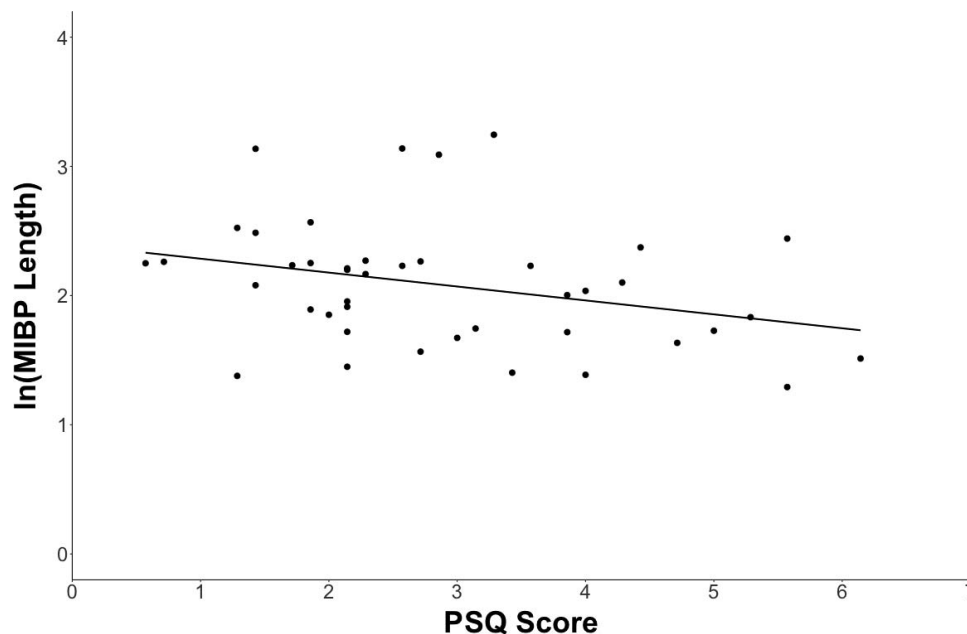


FIGURE 2. Scatter plot showing the association noted between the PSQ score and lnMIBP length ($P = 0.04$). Each point represents the average MIBP length (from four measurements) for each subject.

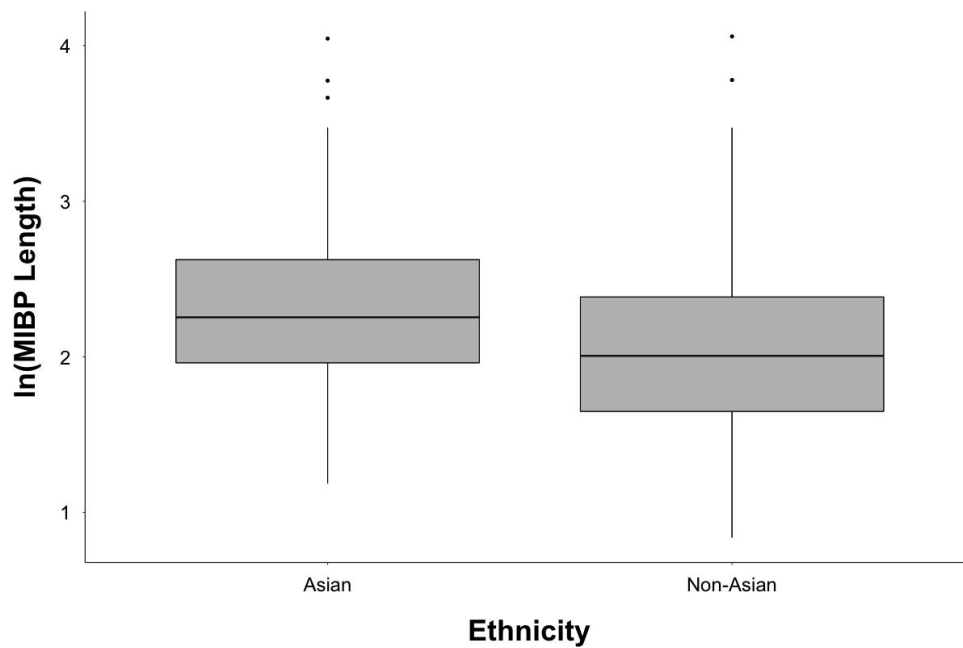


FIGURE 3. Box plot comparing the lnMIBP length between Asians and non-Asians ($P = 0.02$).

greater herniation of orbital fat in the eyelids.³⁷ This causes a smaller surface area of the eye to be exposed to tear-film evaporation, which assuming a similar tear film, would allow Asians more time to refrain from blinking before they experience ocular discomfort.³⁸ In this study, Asian subjects were found to have a smaller exposed interpalpebral area than non-Asian subjects; however, the difference in the exposed area was small (<10%). More important, the exposed interpalpebral area was not found to be associated with the MIBP length in both univariate and multivariate models, possibly owing to a small range of interpalpebral area obtained in this cohort. Further studies are warranted to improve our understanding about the relationship among exposed interpalpebral area, MIBP, ocular surface cooling, and comfort.

Second, the previous reports of greater tear-film instability^{39,40} and corneal staining in Asians compared to non-Asians²³ may suggest that Asians are continually exposed to a higher frequency and greater magnitude of noxious stimuli on the ocular surface.^{23,41,42} It is possible that Asians might adapt to a greater proclivity for noxious stimuli by decreasing corneal nociceptor sensitivity as a compensatory mechanism.⁴³ Evidence to support this reasoning is seen in the study of Tran et al.,²³ where dryness symptoms are associated with the severity of corneal staining in non-Asians, but not in Asians. However, owing to the relatively small sample size and makeup of the study cohort, it is impossible to make any conclusive statements on the role of ethnicity on dry eye symptoms and further research is needed. It should be noted that Asians have twice the prevalence of dry eye, compared to non-Asians, and although ocular surface differences have been found to differ between these two groups, it does not seem pronounced enough to explain the significant disparity in dry eye.^{18,19,44}

In addition to pain sensitivity and ethnicity, there was evidence in the univariate model to suggest that sex may be another intrinsic factor that influenced the MIBP length. It is difficult to draw any conclusions regarding sex owing to the small number of males in the study cohort. However, there is significant research that has demonstrated that males and females process pain differently.^{20,45-47} This may offer an insight on why females have a significantly higher dry eye prevalence rate, are more apt to be affected by dry eye in their everyday lives with a greater likelihood of seeking dry eye treatment than males, even though studies have not necessarily found a pronounced ocular surface difference.^{2,5,48-50} The role of hormones likely plays a key reason in the disparity in dry eye prevalence rates, but the difference in pain perception between males and females should be considered as a possible mediating factor.^{51,52}

The results from this study provide evidence to suggest that pain sensitivity and other intrinsic factors play a role in how ocular discomfort is perceived. A limitation of the study was that the cohort was composed of young and healthy subjects, so it is difficult to know if the same association is seen in older individuals. Nevertheless, one benefit of having a younger cohort is that it is unlikely that any subjects had corneal allodynia or hyperalgesia from nociceptor sensitization, owing to the extended period of time it takes to develop.^{53,54} It should also be noted that the subjects were all contact lens wearers; studies suggest that contact lens wear may influence corneal sensation.⁵⁵ In addition, studies suggest that contact lens wearers perceive ocular discomfort and dryness differently than non-contact lens wearers, so the results found in this study may not hold true in non-contact lens wearers and further investigation is warranted for different subgroups.^{56,57} Ultimately, a large cross-sectional study is needed to determine

TABLE 4. Multivariate Model Showing the Association Between the Natural-Log-Transformed MIBP Length and Significant Explanatory Variables, With Coefficients From the Model Also Listed

Outcome	Intercept	Ocular Surface Cooling Rate	PSQ Score	Ethnicity: Asian
ln(MIBP length)	2.74	-4.63 ($P < 0.001$)	-0.077 ($P = 0.04$)	0.31 ($P = 0.003$)

the exact role that pain sensitivity has on the relationship between signs and symptoms of dry eye. If pain sensitivity is found to play an important role, then it may require a paradigm shift in how dry eye is diagnosed and treated.

Acknowledgments

Supported by Roberta Smith Research Fund (MCL); Clinical Research Center Unrestricted Fund (MCL).

Disclosure: **W. Li**, None; **M.C. Lin**, None

References

- Chao W, Belmonte C, Benitez Del Castillo JM, et al. Report of the inaugural meeting of the TFOS i2 = initiating innovation series: targeting the unmet need for dry eye treatment. *Ocul Surf*. 2016;14:264-316.
- Nichols KK, Nichols JJ, Mitchell GL. The lack of association between signs and symptoms in patients with dry eye disease. *Cornea*. 2004;23:762-770.
- Mizuno Y, Yamada M, Miyake Y. Association between clinical diagnostic tests and health-related quality of life surveys in patients with dry eye syndrome. *Jpn J Ophthalmol*. 2010;54:259-265.
- Labbé A, Wang YX, Jie Y, Baudouin C, Jonas JB, Xu L. Dry eye disease, dry eye symptoms and depression: the Beijing Eye Study. *Br J Ophthalmol*. 2013;97:1399-1403.
- Sullivan BD, Crews LA, Messmer EM, et al. Correlations between commonly used objective signs and symptoms for the diagnosis of dry eye disease: clinical implications. *Acta Ophthalmol*. 2014;92:161-166.
- Karpecki PM. Why dry eye trials often fail. *Rev Optom*. 2013;1:50-56.
- Tan E, Lim Y, Teo Y, Goh R, Law H, Sia AT. Ethnic differences in pain perception and patient-controlled analgesia usage for postoperative pain. *J Pain*. 2008;9:849-855.
- Kil HK, Kim WO, Chung W, Kim GH, Seo H, Hong J. Preoperative anxiety and pain sensitivity are independent predictors of propofol and sevoflurane requirements in general anaesthesia. *Br J Anaesth*. 2012;108:119-125.
- Li W, Graham A, Lin M. Understanding ocular discomfort and dryness using the Pain Sensitivity Questionnaire. *PLoS One*. 2016;11:e0154753.
- Wu Z, Begley CG, Situ P, Simpson T, Liu H. The effects of mild ocular surface stimulation and concentration on spontaneous blink parameters. *Curr Eye Res*. 2014;39:9-20.
- Begley C, Himebaugh N. Tear breakup dynamics: a technique for quantifying tear film instability. *Optom Vis Sci*. 2006;83:15-21.
- Li WY, Graham AD, Lin MC. Ocular surface cooling corresponds to tear film thinning and breakup. *Optom Vis Sci*. 2015;92:248-256.
- Liu H, Begley C, Chen M, et al. A link between tear instability and hyperosmolarity in dry eye. *Invest Ophthalmol Vis Sci*. 2009;50:3671-3679.
- Parra A, Gonzalez-Gonzalez O, Gallar J, Belmonte C. Tear fluid hyperosmolarity increases nerve impulse activity of cold thermoreceptor endings of the cornea. *Pain*. 2014;155:1481-1491.
- Hirata H, Rosenblatt MI. Hyperosmolar tears enhance cooling sensitivity of the corneal nerves in rats: possible neural basis for cold-induced dry eye pain. *Invest Ophthalmol Vis Sci*. 2014;55:5821-5833.
- Nakamori K, Odawara M, Nakajima T, Mizutani T, Tsubota K. Blinking is controlled primarily by ocular surface conditions. *Am J Ophthalmol*. 1997;124:24-30.
- Green CR, Anderson KO, Baker TA, et al. The unequal burden of pain: confronting racial and ethnic disparities in pain. *Pain Med*. 2003;4:277-294.
- Jie Y, Xu L, Wu YY, Jonas JB. Prevalence of dry eye among adult Chinese in the Beijing Eye Study. *Eye (Lond)*. 2009;23:688-693.
- Gayton JL. Etiology, prevalence, and treatment of dry eye disease. *Clin Ophthalmol*. 2009;3:405-412.
- Ruscheweyh R, Marziniak M, Stumpfenhorst F, Reinholz J, Knecht S. Pain sensitivity can be assessed by self-rating: development and validation of the Pain Sensitivity Questionnaire. *Pain*. 2009;146:65-74.
- Ruscheweyh R, Verneuer B, Dany K, et al. Validation of the Pain Sensitivity Questionnaire in chronic pain patients. *Pain*. 2012;153:1210-1218.
- Chalmers RL, Begley CG, Moody K, Hickson-Curran SB. Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8) and opinion of contact lens performance. *Optom Vis Sci*. 2012;89:1435-1442.
- Tran N, Graham AD, Lin MC. Ethnic differences in dry eye symptoms: effects of corneal staining and length of contact lens wear. *Cont Lens Anterior Eye*. 2013;36:281-288.
- Tan J-H, Ng E, Rajendra Acharya U, Chee C. Infrared thermography on ocular surface temperature: a review. *Infrared Phys Technol*. 2009;52:97-108.
- Koushan K, Skibell BC, Harvey JT, Jankowski HK, Deangelis DD, Oestreicher JH. Digital photography as a novel technique of measuring ocular surface dimensions. *Orbit*. 2008;27:259-265.
- Messmer EM, Bulgen M, Kampik A. Hyperosmolarity of the tear film in dry eye syndrome. *Dev Ophthalmol*. 2010;45:129-138.
- Yoon D, Gadaria-Rathod N, Oh C, Asbell PA. Precision and accuracy of TearLab osmometer in measuring osmolarity of salt solutions. *Curr Eye Res*. 2014;39:1247-1250.
- Potvin R, Makari S, Rapuano CJ. Tear film osmolarity and dry eye disease: a review of the literature. *Clin Ophthalmol*. 2015;9:2039-2047.
- Pereira-da-Silva L, Virella D, Monteiro I, et al. Skin conductance indices discriminate nociceptive responses to acute stimuli from different heel prick procedures in infants. *J Matern Fetal Neonatal Med*. 2012;25:796-801.
- Nagahiro I, Andou A, Aoe M, Sano Y, Date H, Shimizu N. Pulmonary function, postoperative pain, and serum cytokine level after lobectomy: a comparison of VATS and conventional procedure. *Ann Thorac Surg*. 2001;72:362-365.
- Younger J, McCue R, Mackey S. Pain outcomes: a brief review of instruments and techniques. *Curr Pain Headache Rep*. 2009;13:39-43.
- Mao J. Translational pain research: achievements and challenges. *J Pain*. 2009;10:1001-1011.
- Begley C, Simpson T, Liu H, et al. Quantitative analysis of tear film fluorescence and discomfort during tear film instability and thinning. *Invest Ophthalmol Vis Sci*. 2013;54:2645-2653.
- Kaido M, Kawashima M, Ishida R, Tsubota K. Relationship of corneal pain sensitivity with dry eye symptoms in dry eye with short tear break-up time. *Invest Ophthalmol Vis Sci*. 2016;57:914-919.
- Li WY, Hsiao C, Graham AD, Lin MC. Corneal epithelial permeability: ethnic differences between Asians and non-Asians. *Cont Lens Anterior Eye*. 2013;36:215-218.
- Chan SM, Svitova TE, Lin MC. Accounting for ethnicity-related differences in ocular surface integrity as a step toward understanding contact lens discomfort. *Eye Contact Lens*. 2017;43:23-31.
- Carter SR, Seiff SR, Grant PE, Vigneron DB. The Asian lower eyelid: a comparative anatomic study using high-resolution

- magnetic resonance imaging. *Ophthalmol Plast Reconstr Surg*. 1998;14:227-234.
38. Cho P, Sheng C, Chan C, Lee R, Tam J. Baseline blink rates and the effect of visual task difficulty and position of gaze. *Curr Eye Res*. 2000;20:64-70.
 39. Lam SM, Tong L, Yong SS, et al. Meibum lipid composition in Asians with dry eye disease. *PLoS One*. 2011;6:e24339.
 40. Svitova TE, Lin MC. Racial variations in interfacial behavior of lipids extracted from worn soft contact lenses. *Optom Vis Sci*. 2013;90:1361-1369.
 41. Yeh TN, Graham AD, Lin MC. Relationships among tear film stability, osmolarity, and dryness symptoms. *Optom Vis Sci*. 2015;92:e264-e272.
 42. Albietsz JM, Lenton LM, McLennan SG. Dry eye after LASIK: comparison of outcomes for Asian and Caucasian eyes. *Clin Exp Optom*. 2005;88:89-96.
 43. Linte RM, Ciobanu C, Reid G, Babes A. Desensitization of cold- and menthol-sensitive rat dorsal root ganglion neurones by inflammatory mediators. *Exp Brain Res*. 2007;178:89-98.
 44. Waduthantri S, Yong SS, Tan CH, et al. Cost of dry eye treatment in an Asian clinic setting. *PLoS One*. 2012;7:e37711.
 45. Miller C, Newton SE. Pain perception and expression: the influence of gender, personal self-efficacy, and lifespan socialization. *Pain Manag Nurs*. 2006;7:148-152.
 46. Greenspan JD, Craft RM, LeResche L, et al. Studying sex and gender differences in pain and analgesia: a consensus report. *Pain*. 2007;132(suppl):S26-S45.
 47. Hsieh AY, Tripp DA, Ji L, Sullivan MJL. Comparisons of catastrophizing, pain attitudes, and cold-pressor pain experience between Chinese and European Canadian young adults. *J Pain*. 2010;11:1187-1194.
 48. Liu NN, Liu J, Liu J, Sun YZ. Prevalence of and risk factors for dry eye symptom in mainland China: a systematic review and meta-analysis. *J Ophthalmol*. 2014;2014:748654.
 49. DEWS The epidemiology of dry eye disease. *Ocul Surf*. 2007;5:93-107.
 50. Schaumberg DA, Uchino M, Christen WG, Semba RD, Buring JE, Li JZ. Patient reported differences in dry eye disease between men and women: impact, management, and patient satisfaction. *PLoS One*. 2013;8:e76121.
 51. Maïssa C, Guillon M. Tear film dynamics and lipid layer characteristics—effect of age and gender. *Cont Lens Anterior Eye*. 2010;33:176-182.
 52. Versura P, Fresina M, Campos EC. Ocular surface changes over the menstrual cycle in women with and without dry eye. *Gynecol Endocrinol*. 2007;23:385-390.
 53. Weyer AD, Zappia KJ, Garrison SR, O'Hara CL, Dodge AK, Stucky CL. Nociceptor sensitization depends on age and pain chronicity. *eNeuro*. 2016;3:ENEURO.0115-15.2015.
 54. Gold MS, Gebhart GF. Nociceptor sensitization in pain pathogenesis. *Nat Med*. 2010;16:1248-1257.
 55. Murphy PJ, Patel S, Marshall J. The effect of long-term, daily contact lens wear on corneal sensitivity. *Cornea*. 2001;20:264-269.
 56. Chalmers RL, Begley CG. Dryness symptoms among an unselected clinical population with and without contact lens wear. *Cont Lens Anterior Eye*. 2006;29:25-30.
 57. Dumbleton KA, Guillon M, Theodoratos P, Patel T. Diurnal variation in comfort in contact lens. *Optom Vis Sci*. 2016;93:820-827.