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Sex Disparity in How Pain Sensitivity Influences Dry Eye Symptoms

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Purpose: Women have a higher dry eye disease prevalence compared with men, although only relatively minor differences in the ocular surface have been observed. Interestingly, a sex difference in pain sensitivity is known, and recent research suggests that pain sensitivity is associated with dry eye symptoms. This study attempts to discern whether the association between pain sensitivity and dry eye symptoms varies between women and men.

Methods: In this prospective cross-sectional study, subjects were seen for one visit where they were asked to fill out a set of questionnaires consisting of the Pain Sensitivity Questionnaire, Ocular Surface Disease Index (OSDI), and other dry eye questionnaires. This was followed by an ocular surface assessment on both eyes.

Results: Two hundred eighty-seven subjects (194 women, 93 men) completed the study. Intersex differences in the ocular surface were noted. Even after accounting for these differences, an interaction effect between sex and Pain Sensitivity Questionnaire-minor score on dry eye symptoms was observed, with only women noting increased symptoms on the OSDI ($P < 0.005$) and other dry eye questionnaires (P values ranging from 0.01 to <0.005) with greater pain sensitivity. After controlling for other variables, women with the highest pain sensitivity had a 17-point higher OSDI score and greater symptoms, as reported by all the other dry questionnaires compared with their male counterparts.

Conclusions: The role of pain sensitivity on dry eye symptoms appears to vary between women and men. This difference provides insight into why women have a significantly higher dry eye disease prevalence than men.

Key Words: pain sensitivity, sex, dry eye disease, symptoms, ocular surface

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Evidence suggests that sex is an important risk factor for dry eye disease (DED) because studies have found that women have a 16% to 300% greater prevalence of DED compared with men.[1,2] Women are also more apt to be affected by it, reporting a greater reduction in quality of life and encountering more issues with anxiety and depression related to their DED.[3] It is hypothesized that a major cause for the disparity in DED prevalence is attributed to the effects of sex hormones observed, primarily in vitro, on the ocular surface.[1,4] Estrogen is known to promote inflammatory processes and inhibit lipogenesis.[1] Androgen, which is found in higher levels in men, and testosterone are associated with preventing atrophy of the meibomian and lacrimal glands.[1,4] Therefore, it is surprising that most clinical studies have found no or relatively minor differences in the ocular surface between women and men.[5–7] Given the poor association between signs and symptoms of DED, it seems unlikely that a relatively minor sex difference in the ocular surface could satisfactorily explain the significant disparity in DED.[8]

In trying to formulate an alternate hypothesis to explain this disparity, it appears worthwhile to draw on insights from other chronic pain conditions that are more common in women, such as migraine and fibromyalgia.[9–11] Although there is a complex interaction of factors responsible for why these conditions are more common in women, there has been a focus on the fact that women are likely more pain sensitive than men as a potentially important cause.[9–11] The sex difference in pain sensitivity is of particular interest because of the results of recent studies, which have shown that greater pain sensitivity is associated with higher levels of dry eye symptoms and ocular surface discomfort.[12–14] It should be noted that the cohorts in these studies primarily consisted of women, and it is unknown whether there is a sex-specific difference in how pain sensitivity influences symptoms.[12,14]

To answer this question, a prospective cross-sectional study was conducted that included a thorough assessment of the ocular surface and used the Pain Sensitivity Questionnaire (PSQ) to quantify pain sensitivity.[15,16] The aim of the study was to determine whether pain sensitivity influences dry eye symptoms differently between women and men, while accounting for any significant intersex differences in subject characteristics and ocular surface parameters. The results of this study may offer insight on whether a sex difference in pain sensitivity could, in part, explain the disparity in DED prevalence.

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MATERIAL AND METHODS

Study Population

For this prospective cross-sectional study, subjects were recruited during a 2-year period from the University of California, Berkeley, and the surrounding community for a one-visit assessment. The study cohort consisted of a diverse set of individuals, which approximated the population makeup of the city of Berkeley, CA. Subjects were excluded if they chose not to discontinue contact lens wear, makeup, artificial tears, or facial lotion use for at least 24 hours before their visit. They were also excluded if they presented with evidence of active ocular infection or acute inflammatory event (eg, uveitis). This study attempted to recruit a broad population, so no exclusion criteria were set based on dry eye or contact lens wear status. To ensure there was no ascertainment or selection bias of dry eye subjects, no mention of DED, ocular discomfort, or any related terms were included in the subject recruitment material. Subjects were defined as noncontact lens wearers if they had never worn contact lenses or had discontinued contact lens wear more than 1 year before study participation. Because studies have found marked differences between Asians and non-Asians in DED prevalence and pain sensitivity, the subjects were asked about their ethnicity.[17] Individuals were considered to be Asian if they were of Chinese, Taiwanese, Japanese, Vietnamese, or Korean descent, or a mixture of these ethnicities. Individuals were considered to be non-Asian if they were of any other ethnicity (eg, European white, Latin American, African, or Spanish descent, or a mixture thereof). Written informed consent, with a complete description of the goals, risks, benefits and procedures of the study, was obtained from all participants. This study followed the tenets of the Declaration of Helsinki and was approved by the University of California, Berkeley, Committee for Protection of Human Subjects.

Study Protocol

The subjects were administered a battery of questionnaires composed of the Ocular Surface Disease Index (OSDI), Berkeley Dry Eye Flow Chart (DEFC), Standardized Patient Evaluation of Eye Dryness (SPEED), and 100-point visual analog rating scales for average daily comfort (0 = "poor comfort, intolerable," 100 = "excellent comfort") and average daily dryness (0 = "no sensation of dryness whatsoever," 100 = "extremely dry, intolerable").[18] Although there is a significant overlap of symptom assessment in dry eye between the questionnaires, they were included because they likely provide different dimensions and insights on the symptoms experienced by the subjects.[19] The subjects were also asked to complete the PSQ, which has been validated in normal and chronic pain populations and in ocular surface research.[12,15,16] Investigators were masked to the results of these questionnaires.

A comprehensive set of ocular surface assessments was performed on both eyes, with the test order selected from the least to the most invasive procedure; the grading criteria used for assessments in this study are described in more detail in Table 1. Subjects' tear film lipid layer thickness was measured using the LipiView interferometer (TearScience Inc, Morrisville, NC). Tear meniscus height was then assessed with the Oculus Keratograph 5M (Oculus Optikgeräte GmbH, Wetziar, Germany). The noninvasive tear breakup test (NITBUT) was conducted 3 times for each eye using the Medmont E300 corneal topographer (Medmont International Pty Ltd, Victoria, Australia), alternating between eyes, with a 30-second break between each measurement, and an endpoint consisting of the first visible disruption noted on the placido mires.

The subjects were then examined with a slit lamp (SL120; Carl Zeiss Meditec Inc, Jena, Germany) with white light only. One microliter of 2% sodium fluorescein was then applied to each eye using an adjustable-volume micropipette (Eppendorf, Hamburg, Germany).[20] Corneal staining was assessed under cobalt blue illumination and viewed through a 530-nm yellow barrier filter. Corneal staining type, depth, and extent were evaluated using the Cornea and Contact Lens Research Unit grading scale.[21]

One drop of 1% Lissamine Green (Leiter's Compounding Pharmacy, San Jose, CA) was then applied, and conjunctival staining was graded using the Sjogren International Collaborative Clinical Alliance grading scale.[22] Infrared meibography was then conducted on the upper and lower eyelid using the Oculus Keratograph 5M. In the final test, tear production was measured using Schirmer Strip Test 1 (without anesthesia).

Statistical Methods

The PSQ provides 3 values: the overall pain sensitivity score (PSQ-total) and scores for sensitivity to minor (PSQ-min) and moderate (PSQ-mod) pain situations. The PSQ provides a score that rates pain sensitivity on a scale of 0 to 10, with a higher score associated with greater pain sensitivity. Our previous study determined that the PSQ-min score most accurately reflected the influence of pain sensitivity on dry eye questionnaires.[12]

Data were analyzed with the R statistical package (version 3.3.2; R foundation for Statistical Computing, Vienna, Austria). Aggregate values (ie, summation of values from all grading zones) for corneal and conjunctival staining were used for analysis. The use of aggregate values in statistical modeling

TABLE 1. Grading Criteria for Ocular Surface Assessments Used in the Study

Assessment	Grading Criteria
Blepharitis	0: Clear eyelid margin 1: Occasional fragment (scurf), 1–5 collarettes 2: Few fragments, 6–20 collarettes 3: Many fragments, 21–40 collarettes 4. Clumps/strands, >40 collarettes
Corneal staining type[21]	0: Absent 1: Micropunctate 2: Macropunctate 3: Coalescent macropunctate 4: Patch
Conjunctival staining[22]	0: 0–9 dots 1: 10–32 dots 2: 33–100 dots 3: >100 dots

TABLE 2. Mean, SD, and Range for Subject and Ocular Surface Characteristics Between Men and Women, and *P* Value From Comparing the 2 groups

	Men (n = 93)	Women (n = 194)	*P*
Age	Mean (SD): 30 (15) yrs Range: 18–66 yrs	Mean (SD): 27 (12) yrs Range: 18–71 yrs	0.07
Ethnicity	38% Asian/62% non-Asian	47% Asian/53% non-Asian	**0.03**
Contact lens wear status	32% contact lens wearers/68% noncontact lens wearers	55% contact lens Wearers/45% noncontact lens wearers	**<0.005**
PSQ-min score	Mean (SD): 2.5 (1.2) Range: 0.3–5.7	Mean (SD): 2.8 (1.5) Range: 0.3–7.6	**0.02**
OSDI score	Mean (SD): 12 (13) Range: 0–70	Mean (SD): 14 (14) Range: 0–71	0.20
DEFC score	Mean (SD): 2.1 (1.4) Range: 1.0–5.0	Mean (SD): 2.7 (1.5) Range: 1.0–5.0	**<0.005**
SPEED score	Mean (SD): 6 (5) Range: 0–20	Mean (SD): 7 (5) Range: 0–22	0.19
Average daily comfort	Mean (SD): 78 (21) Range: 15–100	Mean (SD): 77 (22) Range: 3–100	0.54
Average daily dryness	Mean (SD): 21 (21) Range: 0–100	Mean (SD): 28 (26) Range: 0–96	**<0.005**
Average tear film lipid layer thickness	Mean (SD): 60 (19) nm Range: 24–100 nm	Mean (SD): 64 (20) nm Range: 21–100 nm	**0.02**
Blepharitis	Mean (SD): 1.3 (1.4) Range: 0.0–6.0	Mean (SD): 1.2 (1.4) Range: 0.0–6.0	0.22
Corneal staining type (aggregate)	Mean (SD): 0.7 (1.1) Range: 0.0–9.0	Mean (SD): 1.1 (1.5) Range: 0.0–10.0	**<0.005**
Conjunctival staining (aggregate)	Mean (SD): 1.2 (1.8) Range: 0.0–7.0	Mean (SD): 1.7 (2.1) Range: 0.0–12.0	**<0.005**
Noninvasive tear breakup time	Mean (SD): 13.2 (12.0) s Range: 0–95.2 s	Mean (SD): 11.4 (12.2) Range: 1.6–110.0 s	**0.01**
Schirmer strip	Mean (SD): 18 (10) mm Range: 0–35 mm	Mean (SD): 17 (10) mm Range: 0–35 mm	0.46
Tear meniscus height	Mean (SD): 0.27 (0.10) mm Range: 0.12–0.81 mm	Mean (SD): 0.25 (0.08) mm Range: 0.09–0.71 mm	**<0.005**

Bolded values indicate statistical significance, $P < 0.05$.

was decided a priori to minimize the possibility of type 1 error and because our previous studies have noted no-to-minimal benefits in sectorial analysis.[23]

The first set of statistical analysis was conducted to identify significant intersex differences in subject characteristics and ocular surface parameters, and was assessed using Student's *t* test, comparison of 2 proportions testing using Z-test or linear mixed effects model, when appropriate. The second analysis was to determine whether pain sensitivity and sex were significantly associated with dry eye symptoms. To accomplish this, a thorough exploratory and descriptive preliminary analysis was conducted by assessing bivariate plots to examine for significant associations between explanatory and outcome variables. Because the primary focus for the analysis was to determine the role of pain sensitivity on dry eye symptoms in men and women, the *primary* explanatory variables of interest were PSQ-min score, sex, and their interaction effect (PSQ-min score:sex). Because subject characteristics and the ocular surface parameters have been associated with dry eye symptoms, significant intersex differences noted during the first analysis were considered *secondary* explanatory variables and included in final multivariate models to control for their potential confounding effects on dry eye symptoms. It should be noted that although these significant intersex differences were identified using multiple Student *t* tests, a *P* value adjustment was not used because these *t* tests were not intended to reject a null hypothesis, but rather to facilitate the development of the most parsimonious multivariate models.

The possible explanatory variables were PSQ-min score, sex, their interaction effect (PSQ-min score:sex), and significant intersex differences in subject characteristics and ocular surface parameters. The decision to only use statistically significant intersex differences in subject characteristic and the ocular surface parameters in multivariate modeling was based on 2 reasons, the analysis was primarily meant to determine the role of pain sensitivity on dry eye symptoms between men and women but included other statistically significant intersex differences to control for their potential confounding effects and to maintain a principle of parsimony

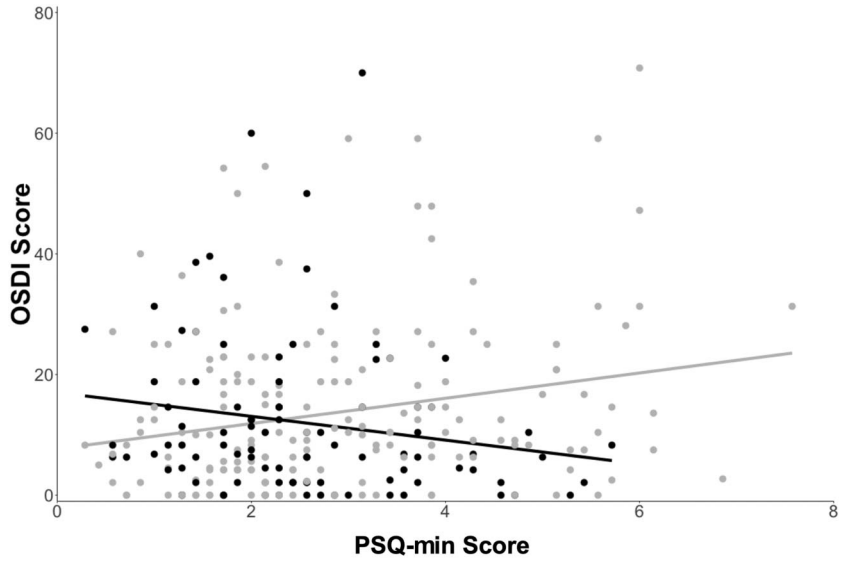

FIGURE 1. Scatter plot showing the association between the Pain Sensitivity Questionnaire (PSQ-min) score and Ocular Surface Disease Index (OSDI) scores in women (gray points/line) and in men (black points/lines).

during modeling. The outcome variables were responses to the dry eye questionnaires. Linear mixed-effects models were used to account for potential within-subject correlations related to measurements performed on both eyes. On examining residual plots, the NITBUT was natural log-transformed to better approximate normality to meet key assumptions for statistical modeling. In all statistical tests and models, the results with $P \leq 0.05$ were considered statistically significant. Significant intersex differences in subject characteristics and ocular surface parameters were included in all models to control for their possible confounding effects because they have been shown to be associated with dry eye

TABLE 3. Final Multivariate Model Showing the Association of PSQ-min Score, Sex, Interaction Term (PSQ-min Score:Sex), and Significant Intersex Differences in Subject and Ocular Surface Characteristics With Questionnaire Response, With Coefficients Also Listed

	OSDI	DEFC	SPEED	Average Daily Comfort	Average Daily Dryness
Intercept	**19.8**	**1.9**	**6.9**	**67.1**	**18.1**
	***P* < 0.005**	***P* < 0.005**	***P* < 0.005**	***P* < 0.005**	***P* < 0.005**
PSQ-min score	**−1.8**	−0.08	−0.3	**2.7**	−0.5
	***P* = 0.03**	*P* = 0.34	*P* = 0.08	***P* = 0.04**	*P* = 0.18
Sex	**−8.9**	−0.1	−0.2	**13.2**	−1.2
	***P* < 0.005**	*P* = 0.49	*P* = 0.06	***P* < 0.005**	*P* = 0.14
PSQ-min score:sex	**3.7**	**0.1**	**0.3**	**−4.8**	**1.6**
	***P* < 0.005**	***P* = 0.01**	***P* = 0.03**	***P* < 0.005**	***P* = 0.01**
ln (NITBUT)	**−2.0**	**−0.2**	**−1.2**	**4.6**	**−5.7**
	***P* = 0.02**	***P* < 0.005**	***P* < 0.005**	***P* < 0.005**	***P* < 0.005**
Tear film lipid layer thickness	0.01	0.0001	−0.01	0.02	−0.03
	P = 0.71	*P* = 0.95	*P* = 0.39	*P* = 0.70	*P* = 0.54
Tear meniscus height	3.7	0.8	4.4	−15.1	**35.6**
	P = 0.57	*P* = 0.20	*P* = 0.06	*P* = 0.14	***P* < 0.005**
Ethnicity	−1.0	0.03	−0.8	0.7	0.89
	P = 0.39	*P* = 0.81	*P* = 0.07	*P* = 0.72	*P* = 0.67
Conjunctival staining	**0.7**	**0.05**	**0.3**	**−1.2**	**1.8**
	***P* = 0.02**	***P* = 0.05**	***P* = 0.02**	***P* = 0.01**	***P* < 0.005**
Corneal staining type (aggregate)	0.1	0.06	−0.2	**−1.3**	0.80
	P = 0.82	*P* = 0.14	*P* = 0.24	***P* = 0.04**	*P* = 0.28
Contact lens wear status	−1.6	**1.2**	0.4	0.6	**4.6**
	P = 0.18	***P* < 0.005**	*P* = 0.30	*P* = 0.76	***P* = 0.03**

Bolded values indicate statistical significance, $P < 0.05$. The arbitrary reference groups for sex, ethnicity, and contact lens wear status were men, non-Asians, and noncontact lens wearers, respectively.

symptoms.[24] Previous studies have extensively assessed the disparity in dry eye symptoms between men and women because of an intersex difference in the ocular surface. Therefore, to minimize redundancy, this analysis focused only on assessing the possible effects of sex on the relationship between pain sensitivity and dry eye symptoms.

RESULTS

Subject Characteristics

Two hundred eighty-seven subjects completed the study (194 women, 93 men), providing 574 eyes for analysis. The study cohort had a mean (SD) age of 28 (13) years with a range of 18 to 71 years. The mean (SD) PSQ-min score was 2.7 with a range of 0.3 to 7.6. There were 127 subjects of Asian descent and 160 subjects of non-Asian descent, and there were 139 contact lens wearers and 148 noncontact lens wearers. Among the study cohort, 1 subject had cataract surgery, 3 subjects had refractive surgery, 2 subjects had strabismus surgery, 3 subjects had laser retinal treatment associated with retinal hole/detachment, and 5 subjects had lid surgery. None of the subjects had been diagnosed or treated for glaucoma. Table 2 shows that women, when compared with men, were more likely to be Asian (47% vs. 38%, respectively; $P = 0.03$), wear contact lenses (55% vs. 32%, respectively; $P < 0.005$), report more dryness on the visual analog scale (28% vs. 21%, respectively; $P < 0.005$), have a greater DEFC (2.7 vs. 2.1, respectively; $P < 0.005$) and PSQ-min score (2.8 vs. 2.5, respectively; $P = 0.02$), and were borderline younger (27 vs. 30 years old, respectively; $P = 0.07$). For the ocular surface parameters, women had a thicker tear lipid layer (64 vs. 60 nm, respectively; $P = 0.02$), lower NITBUT (11.4 vs. 13.2 seconds, respectively; $P = 0.01$), shorter tear meniscus height (0.25 vs. 0.27 mm, respectively; $P < 0.005$), and greater corneal (1.1 vs. 0.7, respectively; $P < 0.005$) and conjunctival (1.7 vs. 1.2, respectively; $P < 0.005$) staining. Although corneal staining type, depth, and extent were evaluated, only staining type was reported and used in statistical analyses because of the significant multicollinearity between type, depth, and extent,[21] and additional analysis (not shown) did not find significant differences in modeling when using corneal staining type, depth, or extent. No difference was noted for meibomian gland expression quality ($P = 0.45$) and quantity ($P = 0.97$) scores and Schirmer tear test ($P = 0.46$). Women had a larger range of PSQ-min scores (0.3–7.6) compared with men (0.3–5.7).

Multivariate Modeling

During preliminary analysis for multivariate modeling, evidence of an interaction effect between PSQ-min score and sex on questionnaire response was noted on bivariate plots (Figs. 1 and 2). In multivariate modeling (Table 3), even after accounting for confounding effects of significant intersex differences in the ocular surface, the main effects, PSQ-min score, and sex were both significantly associated with the OSDI ($P = 0.03$ and <0.005, respectively) and average daily comfort ($P = 0.04$ and <0.005, respectively); they were not associated with the DEFC ($P = 0.34$ and 0.49, respectively), SPEED ($P = 0.08$ and 0.06, respectively), and average daily dryness ($P = 0.18$ and 0.14, respectively). The interaction term of the PSQ-min score and sex variables was significantly associated with the OSDI ($P < 0.005$), DEFC ($P = 0.01$), SPEED ($P < 0.005$), average daily comfort ($P < 0.005$), and average daily dryness ($P < 0.005$). This meant that in women, greater pain sensitivity was associated with increased dry eye symptoms on all questionnaires. In men, greater pain sensitivity was either not associated with dry eye symptoms on the DEFC ($P = 0.49$), SPEED ($P = 0.06$), and average daily dryness ($P = 0.14$) or associated with decreased dry eye symptoms on the OSDI ($P < 0.005$) and average daily comfort ($P < 0.005$). After controlling for the other variables, the maximum effect sizes in the models were observed at the highest PSQ-min scores, where women with the greatest pain sensitivity (PSQ-min score of 7.6) were estimated to have greater dry eye symptoms by 17 points on the OSDI, 1 point on the DEFC, 2 points on the SPEED, 20 points on average daily comfort, and 13 points on average daily dryness when compared with men with the greatest pain sensitivity (PSQ-min score of 5.7).

DISCUSSION

The findings from this study suggest that there is a difference in how pain sensitivity influences dry eye symptoms between women and men. It was noted that in women, greater pain sensitivity was found to be associated with increased dry eye symptoms, whereas in men, depending on the questionnaire, greater pain sensitivity was either not associated with dry eye symptoms or associated with decreased dry eye symptoms. It is important to note that these associations (with a clinically meaningful effect size) were noted with all questionnaires administered and were still observed even after accounting for significant intersex differences in ocular surface and demographics.[25]

To date, it is difficult to determine whether men truly have no change or decreased symptoms associated with greater pain sensitivity because most studies on this topic consisted of cohorts that were predominantly women.[12,14] The higher proportion of women to men found in this study reflects the general recruitment pool that subjects were drawn upon. The only study that examined this in men was by Galor et al,[13] who found that increased pain sensitivity was associated with greater symptoms of dry eye. It should be noted that their cohort was significantly older (mean age of 60 years), with a majority of subjects having a mental illness and taking psychiatric medications, whereas our study consisted of a younger and healthy cohort. The stark contrast in cohorts between the 2 studies makes it difficult to directly compare findings because age, mental illness, and psychiatric medications have all been linked to increased pain sensitivity.[26,27] However, because of our large sample size, the fact that we accounted for confounding effects of significant intersex differences in ocular surface and demographics, along with the strength and consistency observed in our results among all the dry eye questionnaires, argues that there is likely

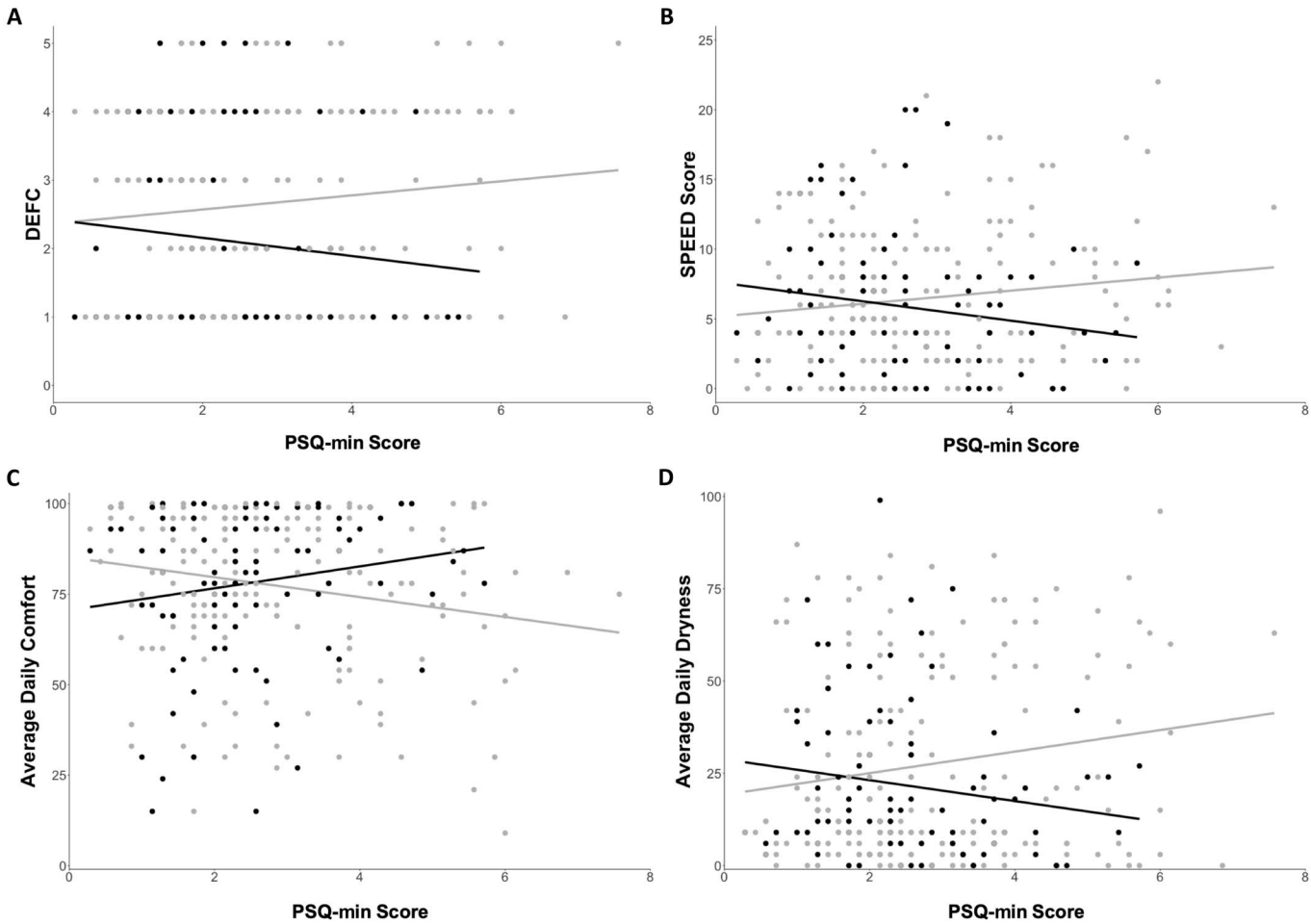

FIGURE 2. Scatter plot showing the association between Pain Sensitivity Questionnaire (PSQ-min) score and (A) UC Berkeley DEFC, (B) SPEED, (C) average daily comfort, and (D) average daily dryness in women (gray points/line) and in men (black points/lines). Higher DEFC, SPEED, and average daily dryness scores are associated with greater dry eye symptoms; higher average daily comfort score is associated with fewer dry eye symptoms.

a difference in how pain sensitivity influences dry eye symptom between women and men, but additional work will be needed to better define this difference. If, as our study suggests, greater pain sensitivity is found to be more strongly associated with higher dry eye symptoms in women, it could help explain why Vehof et al[28] found that women had a significantly lower correlation coefficient in the association between signs and symptoms of DED compared with men ($r = 0.11$ vs. $r = 0.33$, respectively). Pain sensitivity could potentially be a more significant confounder in the association between signs and symptoms for women compared with men.

Although a difference in the ocular surface likely exists between women and men, there is currently limited evidence to suggest that it explains the disparity in DED prevalence in a significant way.[5–7,29] The findings from this study suggest that pain sensitivity could potentially play a role in the disparity, which may be linked to the difference in the pain-signaling pathway between men and women. Sex hormones are thought to play a role because estrogen receptors have been found on corneal nociceptors.[30] Estrogens are also proinflammatory factors, and a consequence of increased inflammation is a diminishment in the stimuli threshold needed for nociceptor activation.[10,11] Finally, there is evidence to suggest that the diffuse noxious inhibitory control, which is an endogenous nociceptor modulator that inhibits painful stimuli, is less efficacious in women.[9] The diffuse noxious inhibitory control is important because it has been linked with the risk of developing chronic pain conditions, with low efficacy associated with fibromyalgia and temporomandibular joint disorder.[31] If a sex difference exists in either the nociceptors or their modulation, it may be of interest because symptoms of DED are thought to manifest from the activation of corneal nociceptors through ocular surface cooling and increased tear film osmolarity.[32]

Because pain is mediated by many factors, it is also important to consider the role sociocultural factors, which were not extensively assessed in this study, had in influencing the results.[33] At this point, it is difficult to determine whether the findings are due to underlying sex-specific differences in pain-

processing pathways, sociocultural factors, or a combination of these 2. Additional investigation would offer further insight on the role of pain sensitivity in DED and potentially into other chronic pain conditions that are more common in women. In some ways, DED may provide an ideal platform for understanding the sex difference in pain sensitivity because of the extensive testing procedures already developed to assess DED and because of corneal transparency, which allows for nerve imaging.

A limitation of this study is that although there are conflicting reports on whether a woman's pain sensitivity is influenced by the phase of the menstrual cycle, it would have been ideal to know the phase of cycle for each nonmenopausal female subject at the time of the study.[34] The study also primarily consisted of young and healthy subjects, so it is difficult to know whether the results are applicable to a broader population, and a study using a more diverse population is warranted. Nevertheless, having a largely young and healthy population minimizes the possibility that allodynia or hyperalgesia from nociceptor sensitization influenced the results, owing to the extended time it takes to develop.[35,36] In addition, compared with an older population, there is a lower risk of increased pain sensitivity from systemic diseases and medications.[27] Finally, although pain sensitivity is thought to be an important component of pain perception, considering other components of pain perception such as pain threshold, pain catastrophizing, and response to different types of induced pain stimuli (heat, cold and mechanical) through quantitative sensory testing would have provided a more comprehensive understanding on how pain influences the symptoms of DED.[15,37]

Unlike conditions such as hypertension where treatment success is defined by the reduction in blood pressure, success with DED is primarily dictated by symptom improvement.[38] Therefore, it is interesting to note that pain sensitivity has been shown to influence the perception of symptom improvement after medical treatment.[39] Tangentially, our findings pose a question on whether we should also view symptom improvement after dry eye treatment differently between sexes because pain relief provided by opioids has been shown to differ between women and men.[40] This could potentially have important implications during phase 3 clinical trials for DED treatments because it may be difficult to truly evaluate symptom improvement without considering the effect of sex and pain sensitivity on symptomology and may explain the high failure rate in dry eye clinical trials.[12,41] However, because much is still not understood regarding pain sensitivity and DED, further study is needed to elucidate how we should factor pain sensitivity in the diagnosis, monitoring, and treatment of DED.

This study suggests that pain sensitivity, as measured with the PSQ-min, influences dry eye symptoms differently between women and men. In women, greater pain sensitivity was associated with increased dry eye symptoms, whereas in men, greater pain sensitivity was either not associated with symptoms or associated with decreased symptoms. The results provide an additional explanation for why women have a significantly higher prevalence of DED than men.

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