

# Associations between dry eye disease and sleep quality: a cross-sectional analysis

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## ABSTRACT

**Background/aims** To investigate relationships between dry eye (DE) disease and sleep quality, with a focus on which aspects of sleep most closely relate to DE.

**Methods** 141 veterans (mean age: 56±5) seen at the Miami Veterans Affairs eye clinic filled out questionnaires to quantify the severity of DE symptoms (5-Item Dry Eye Questionnaire (DEQ-5) and Ocular Surface Disease Index (OSDI)) and ocular pain (Numerical Rating Scale (NRS) and Neuropathic Pain Symptom Inventory modified for the Eye (NPSI-E)). All individuals also underwent an ocular surface examination. Aspects of sleep quality were assessed using the Pittsburgh Sleep Quality Index (PSQI). DE metrics were examined by PSQI scores and subscores.

**Results** Most participants (76%) reported mild or greater DE symptoms (DEQ-5 ≥6). Overall, ocular symptoms were more related to sleep metrics than signs. The strongest DE symptom association was between the OSDI and sleep disturbances (PSQI subscore 5,  $r=0.49$ ,  $p<0.0005$ ). For DE signs, ocular surface inflammation and meibum quality were related to subjective sleep quality (PSQI subscore 1,  $r=0.29$ ,  $p=0.03$ , for both). On linear regression analyses, most ocular symptom questionnaires remained associated with sleep disturbances (PSQI subscore 5: NRS ( $r=0.52$ ,  $p<0.0005$ ), DEQ-5 ( $r=0.36$ ,  $p<0.0005$ ), and OSDI ( $r=0.31$ ,  $p<0.0005$ )). For DE signs, ocular surface inflammation and meibum quality remained associated with subjective sleep quality ( $r=0.26$ ,  $p=0.01$ ;  $r=0.46$ ,  $p<0.0005$ , respectively).

**Conclusion** DE symptom and ocular pain intensity were closely related to sleep metrics, most strongly to sleep disturbances. Relationships were weaker for DE signs, with subjective sleep quality relating to inflammation and meibum quality.

## INTRODUCTION

Dry eye (DE) disease is a multifactorial condition with symptoms that include pain and visual disturbances and signs that include tear instability, decreased tear production and epithelial disruption, to name a few.<sup>1</sup> DE symptoms have an impact on the quality of life as they affect work productivity, physical well-being and mental health, placing a significant burden on both individuals and the broader society.<sup>2</sup> Many factors have been linked to various aspects of DE, including demographics (eg, older age, female sex and

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Current research suggests a relationship between dry eye disease and sleep. However, there is a research gap on which components of ocular surface disease are most related to aspects of sleep.

## WHAT THIS STUDY ADDS

⇒ This study adds a unique perspective on the relationship between DE and sleep by examining how specific components of sleep relate to DE symptoms and ocular exam findings.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study sheds light on how clinicians can holistically approach DE management by discussing sleep problems and recommending appropriate referrals, as necessary. This strategy has the potential to translate into a beneficial effect on patient outcomes.

Asian race), medication use (eg, antihistamines and antihypertensives), environmental exposures (eg, air pollution and sunlight), comorbidities (eg, Sjögren's syndrome (SS) and migraine), hormonal status and surgery.<sup>3</sup> In addition, mental health disorders (eg, depression and anxiety) and sleep disturbances have also been found at higher frequencies in individuals with DE compared with controls.<sup>4</sup>

With respect to sleep, a meta-analysis of 19 articles reported that individuals with DE (variably defined) experienced significantly poorer sleep quality, spent less time asleep and had more sleep disturbances than controls.<sup>5</sup> Sleep disturbances have also been examined in subgroups of individuals with DE. For example, one meta-analysis reported that individuals with primary SS had more sleep disturbances and night awakenings compared with controls.<sup>6</sup>

Other studies have examined the link between DE symptoms and sleep. A study using data from the Singapore Malay Eye

Study-2 (n=1191) and the Singapore Indian Eye Study-2 (n=2112) assessed relationships between DE symptoms (questions regarding 'feeling of dryness', 'grittiness', 'burning sensation', 'redness', 'crusting of lashes' and 'eyelids getting stuck') and different sleep parameters. The presence of DE symptoms was defined as a positive response to any symptom that occurred monthly. Multiple dimensions of sleep quality were likewise assessed including excessive sleepiness (score of  $\geq 11$  out of 24 on the Epworth Sleepiness Scale), high risk for sleep apnoea (score of  $\geq 5$  out of 8 on the STOP-Bang Questionnaire), insomnia (score of  $\geq 15$  out of 28 on the Insomnia Severity Index, ISI) and  $< 5$  hours of sleep. On multivariable analyses, excessive sleepiness (OR=1.77, 95% CI 1.15 to 2.71), risk of sleep apnoea (OR=2.66, 95% CI 1.53 to 4.61), insomnia (OR=3.68, 95% CI 2.17 to 6.26) and  $< 5$  hours of sleep (OR=1.73, 95% CI 1.17 to 2.57) all increased the risk of reporting DE symptoms.<sup>7</sup> Similar findings were noted in our prior cross-sectional study of 187 South Florida veterans where DE symptoms (based on the 5-Item Dry Eye Questionnaire, DEQ-5) were positively associated with insomnia severity (ISI) ( $r=0.43$ ,  $p<0.01$ ).<sup>8</sup>

DE signs, on the other hand, appear to have less of an association with sleep. In our study, DE signs did not relate to insomnia, with the exception of eyelid vascularity which displayed a negative association ( $r=-0.21$ ,  $p<0.01$ ).<sup>8</sup> The noted relationships between DE and sleep disturbances require further examination given a knowledge gap with regard to which components of DE most closely relate to aspects of sleep. To bridge this knowledge gap, we examined relationships between ocular surface symptoms (both pain and non-pain related) and signs with different aspects of sleep quality, assessed with the Pittsburgh Sleep Quality Index (PSQI).<sup>9</sup> Understanding relationships between DE and facets of sleep can aid in the development of holistic interventions that address the specific components of sleep quality affected in an individual, potentially leading to better outcomes and improved quality of life.

## METHODS

### Study population

We performed a cross-sectional study of 141 veterans who served during the Gulf War era and who were seen in an eye clinic at the Miami Veterans Affairs (VA) Medical Center between November 2018 and July 2023. Inclusion criteria included normal external anatomy (eg, eyelids, conjunctiva and cornea). Exclusion criteria included the use of any eye drops beyond artificial tears, eye conditions that could impact DE testing (eg, history of glaucoma, retinal surgery, pterygium and corneal oedema) and any medical conditions that would make study procedures difficult (eg, neurological and mental health disorders that would preclude filling out questionnaires independently). Informed consent was obtained from all the patients who participated in the study. The study was approved by the Miami VA Institutional Review Board.

The study was conducted in accordance with the principles of the Declaration of Helsinki and complied with the requirements of the US Health Insurance Portability and Accountability Act.

### Data collection

Data on demographics, comorbidities, medications and medical and ocular diagnoses were collected from all individuals. Mental health status was assessed using the Patient Health Questionnaire (PHQ-9) for depression,<sup>10</sup> the PTSD Checklist – Military Version (PCL-M) for post-traumatic stress disorder (PTSD)<sup>11</sup> and the Modified Fatigue Impact Scale (MFIS) for fatigue.<sup>12</sup>

### Sleep quality assessment

Sleep quality was assessed using the PSQI, a self-administered questionnaire that assesses sleep quality. The PSQI consists of 19 individual items that provide 7 component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction. Subjective sleep quality is an individual's assessment of their overall sleep quality. Sleep latency is the amount of time it takes for an individual to fall asleep after deciding to go to sleep. It indicates how easily someone can transition from being awake to asleep. Sleep duration is the actual amount of time an individual sleeps during the night. Habitual sleep efficiency is the ratio of the total sleep time to the total amount of time spent in bed. Sleep disturbances include waking up in the middle of the night or early morning, needing to get up to use the bathroom, having trouble breathing comfortably, coughing, snoring loudly, feeling too cold or too hot, having bad dreams and experiencing pain. The use of sleeping medications indicates whether an individual takes any medications to help them sleep. Daytime dysfunction assesses how an individual's sleep affects them during the day, including difficulty staying awake while driving, eating meals, engaging in social activities and having enough enthusiasm to get things done. The global PSQI score is equal to the sum of the scores of its seven components, with a range of 0–21; higher scores indicate worse sleep quality. The PSQI's simplicity, ease of administration and high validity make it a great sleep quality assessment tool to use for our study.<sup>9</sup>

### Ocular surface examination

#### Ocular symptoms

All individuals filled out standardised questionnaires regarding ocular symptoms. DE symptoms were measured using the Ocular Surface Disease Index (OSDI, range 0–100) and DEQ-5 (range 0–22). Both questionnaires have been validated in DE and measure different aspects of symptoms including pain (OSDI, soreness and grittiness, and DEQ-5, dryness and discomfort), visual disturbances (OSDI: poor vision and blurriness) and other aspects of disease (OSDI, environmental triggers, and DEQ-5, tearing). Thus, the total severity score of

each questionnaire is a composite of various symptom domains.<sup>13</sup> Individuals were further classified into DE symptom severity groups based on prior DEQ-5 cut-off values (none <6, mild-moderate 6–11, severe ≥12).<sup>14</sup>

To examine relationships between ocular pain and sleep, we chose two validated pain questionnaires. Ocular pain intensity was graded using a Numerical Rating Scale (NRS, range 0–10), an instrument often used as an endpoint in clinical trials.<sup>15</sup> NRS scores were acquired for ocular pain felt ‘right now’, ‘average over the last week’ and ‘worst over the last week’. Neuropathic features of pain were captured using the Neuropathic Pain Symptom Inventory modified and validated for eye (NPSI-E: total score, range 0–100, and subscore, range 0–10).<sup>16</sup>

Convergence insufficiency symptoms, which have been linked to DE symptoms in prior studies,<sup>17</sup> were evaluated using the Convergence Insufficiency Symptoms Survey (CISS, 0–60).<sup>18</sup> This combination of instruments provided a multidimensional assessment of symptoms which we correlated with various aspects of sleep quality.

### Ocular surface signs

DE signs were assessed by a provider that was masked to the clinical symptoms for each patient. DE signs included, in the order assessed, the following:

1. Eyelid laxity determined by rotation (0=0%–25%, 1=25%–50% and 2=50%–100%) and the snapback test (0=prompt snapback, 1=slowed return and 2=does not return fully until blinking).
2. Matrix metalloproteinase 9 (InflammaDry, Quidel, San Diego)<sup>19</sup> qualitatively graded as 0=none, 1=mild, 2=moderate and 3=severe.
3. Corneal sensation graded as 0=absent, 1=reduced, 2=normal and 3=increased.
4. Anterior blepharitis graded as 0=none, 1=mild, 2=moderate and 3=severe.
5. Conjunctivochalasis in the inferior nasal, medial and temporal region, graded as 0=none, 1=mild and 2=severe.
6. Tear stability via tear break-up time (TBUT), 5 µL of fluorescein placed and three measurements recorded and averaged.
7. Papillary conjunctivitis graded as 0=none, 1=mild and 2=severe.
8. Fluorescein corneal staining graded using the National Eye Institute scale,<sup>20</sup> graded in five areas on a scale of 0 to 3 and scores summed (total range of 0–15).
9. Pain intensity using a 0–10 NRS assessed before and 30s after application of 10 µL of proparacaine hydrochloride 0.5% (one drop in each eye).
10. Schirmer’s test at 5 min, measured in millimetres with anaesthesia for the measurement of basal tear secretion. We acknowledge that this test does not measure reflex tear secretion but was chosen for patient comfort.
11. Eyelid margin vascularity graded as 0=none, 1=mild, 2=moderate and 3=severe engorgement.

12. Meibum quality graded as 0=clear, 1=cloudy, 2=granular, 3=toothpaste and 4=no meibum extracted.<sup>21</sup>

### Data analysis

Statistical analyses were performed using SPSS 28.0 (IBM Corp, Armonk, NY). Descriptive statistics were used to summarise demographic and clinical data. The one-way analysis of variance test and the Pearson  $\chi^2$  test were used, as appropriate, to compare profiles between individuals with none, mild-moderate and severe DE symptoms (DEQ-5 cut-offs). Post hoc testing examined significant differences between each of the two groups. Pearson correlations were used to examine relationships between DE metrics and sleep parameters. Forward stepwise linear regression analyses were used to further examine these relationships, while adjusting for potential confounders (ie, demographics, medications and comorbidities). A p value of <0.05 was deemed significant for all measures. In this paper, we opted to give information on all variables being compared as opposed to correcting the p value (eg, Bonferroni) since the latter methodology has its own limitations.<sup>22</sup> Missing data points were minimal, and as such, no imputation strategies were implemented. With an n of 141, we had the power to detect medium effect sizes for correlations between DE metrics and the PSQI using the terminology of Cohen.<sup>23</sup>

### Patient and public involvement

Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

## RESULTS

### Study population

Our population consisted of 141 individuals with a mean age of 56±5 years, 123 (87%) self-identified as male, 77 (55%) as white and 51 (36%) as Hispanic. The majority (76%) of individuals reported mild or greater DE symptoms, defined by a DEQ-5 score ≥6. Overall, individuals with any DE symptoms were more likely to be smokers than individuals without symptoms. Mental health (PHQ-9, PCL-M) and fatigue (MFIS) scores were higher in individuals with DE symptoms (table 1). Not surprisingly, all ocular symptom scores (including pain-specific symptoms) were higher in individuals with DE symptoms (table 2). On the other hand, DE signs, except for anterior blepharitis, were equally distributed across DE symptom groups. All sleep quality (PSQI) scores were higher in individuals with DE symptoms, except for the use of sleeping medications (table 2).

### DE and sleep metrics correlations

Overall, ocular symptoms were more related to sleep quality metrics than signs. The strongest association for DE symptoms was between the OSDI and sleep disturbances (PSQI subscore 5:  $r=0.49$ ,  $p<0.0005$ ) (table 3). Associations between DE signs and sleep metrics were less robust, with ocular surface inflammation and meibum

**Table 1** Demographics, comorbidities and medications in the study population, grouped by dry eye (DE) symptom status

	No DE symptoms DEQ-5 <6 (n=33)	Mild-moderate DE symptoms DEQ-5 6–11 (n=62)	Severe DE symptoms DEQ-5 ≥12 (n=46)	P value
<b>Demographics</b>				
Age, mean±SD	56±5	56±5	56±4	0.88
Gender, male, % (n)	23% (28)	43% (53)	34% (42)	0.60
Race, white, % (n)	26% (20)	42% (32)	33% (25)	0.77
Ethnicity, Hispanic, % (n)	18% (9)	43% (22)	39% (20)	0.34
<b>Comorbidities, % (n)</b>				
BMI, mean±SD	10±0.7	10±0.4	10±0.5	0.23
Current smoker, % (n)	9% (2)	59% (13)*	32% (7)	0.02
Previous smoker, % (n)	8% (2)	64% (16)*	28% (7)	0.02
Hypertension	18% (10)	54% (30)	29% (16)	0.13
Hyperlipidaemia	14% (9)	53% (33)*	32% (20)	0.04
Diabetes mellitus	21% (5)	33% (8)	46% (11)	0.29
Sleep apnoea	20% (16)	44% (35)	36% (29)	0.37
CPAP use	25% (15)	46% (28)	30% (18)	0.74
<b>Ocular comorbidities, % (n)</b>				
Cataract surgery	20% (1)	40% (2)	40% (2)	0.93
Refractive surgery	36% (5)	21% (3)	43% (6)	0.20
<b>Mental health, mean±SD</b>				
Depression, PHQ-9 (range 1–27)	6±5	10±7*	13±7*	<0.0005
PTSD (range 17–85)	35±17	42±17	54±18*†	<0.0005
Fatigue, MFIS (range 0–84)	22±19	36 ± 22*	50±19*†	<0.0005
<b>Oral medications, % (n)</b>				
Antianxiety	23% (5)	55% (12)	23% (5)	0.44
Antidepressant	19% (7)	46% (17)	35% (13)	0.69
Antihistamine	28% (10)	50% (18)	22% (8)	0.29
Aspirin	24% (6)	56% (14)	20% (5)	0.26
Beta blocker	10% (2)	65% (13)	25% (5)	0.08
Fish oil	28% (9)	38% (12)	34% (11)	0.74
Multivitamin	26% (14)	33% (18)	42% (23)	0.09
NSAID	27% (15)	42% (23)	31% (17)	0.77
Statin	15% (9)	52% (31)	33% (20)	0.06

\*Significantly different ( $p < 0.05$ ) from no DE symptom group.

†Significantly different ( $p < 0.05$ ) from mild-moderate DE symptom group.

BMI, body mass index; CPAP, continuous positive airway pressure; MFIS, Modified Fatigue Impact Scale; n, number in each group; NSAID, non-steroidal anti-inflammatory drug; PHQ-9, Patient Health Questionnaire-9; PTSD, post-traumatic stress disorder.;

quality relating to subjective sleep quality (PSQI subscore 1:  $r = 0.29$ ,  $p = 0.03$ , for both).

### Multivariable models

Forward stepwise linear regression analyses controlling for demographics (age, gender and race), smoking status (previous and current), medication use (antidepressants, antianxiety and antihistamines), mental health (PHQ-9 and PTSD), fatigue (MFIS) and comorbidities (hypertension, hyperlipidaemia, diabetes and sleep apnoea) were

conducted. Of all sleep components, sleep disturbances (PSQI 5) remained significantly associated with most DE symptom and ocular pain metrics (DEQ-5, OSDI and NRS) (table 4). Additionally, ocular surface inflammation and meibum quality remained significantly associated with subjective sleep quality (PSQI 1).

### DISCUSSION

To conclude, we found that ocular symptom severity, captured both with DE and pain questionnaires, was

**Table 2** Dry eye (DE) and sleep metrics in the study population, grouped by DE symptom status

	No DE symptoms DEQ-5 <6 (n=33)	Mild-moderate DE symptoms DEQ-5 6–11 (n=62)	Severe DE symptoms DEQ-5 ≥12 (n=46)	P value
Ocular symptoms, mean±SD				
DEQ-5	2.5±2.0	8.5±1.8*	13.9±1.7*‡	<0.0005
OSDI	12.4±13.0	32.5±22.6*	48.2±18.4*‡	<0.0005
NRS (right now)	0.2±0.5	1.1±1.8*	3.7±3.0*‡	<0.0005
NRS (average of 1 week)	0.1±0.3	1.5±1.9*	4.1±2.5*‡	<0.0005
NRS (worst in 1 week)	0.2±0.6	1.7±2.2*	4.7±2.9*‡	<0.0005
NPSI-E	1.3±2.8	12.5±13.6*	29.4±18.8*‡	<0.0005
CISS	9.9±9.2	20.1±12.3*	28.9±12.0*‡	<0.0005
Ocular surface exam, mean±SD††				
Eyelid laxity upper	0.3±0.5	0.4±0.5	0.2±0.4	0.45
Eyelid laxity lower	0.2±0.4	0.3±0.5	0.2±0.4	0.55
Ocular surface inflammation	0.9±1.0	1.2±1.4	1.4±1.0	0.40
Corneal sensation, % (n)				
Reduced	25% (4)	44% (7)	31% (5)	0.60
Normal	25% (27)	45% (49)	30% (33)	
Increased	13% (2)	38% (6)	50% (8)	
Anterior blepharitis	0.7±0.9	0.5±0.6	0.8±0.8‡	0.08
Conjunctivochalasis	0.3±0.3	0.3±0.4	0.4±0.5	0.46
Tear break-up time	11.0±4.0	11.0±5.0	9.4±3.5	0.14
Papillary conjunctivitis	0.3±0.5	0.3±0.5	0.4±0.5	0.49
Corneal staining	1.4±2.1	1.0±1.8	1.9±2.6	0.10
Schirmer score	20.5±10.4	18.4±9.5	16.2±9.8	0.16
Eyelid vascularity	0.7±0.7	0.4±0.7	0.5±0.7	0.13
Meibum quality	0.7±0.8	0.9±1.0	1.1±1.2	0.28
Sleep symptoms, mean±SD				
PSQI global score	9.3±4.3	11.3±4.7	13.7±3.6*‡	<0.0005
PSQI 1: subjective sleep quality	1.3±0.8	1.9±0.9*	2.3±0.7*	<0.0005
PSQI 2: sleep latency	1.6±1.2	1.9±1.1	2.4±0.9*‡	<0.0005
PSQI 3: sleep duration	1.9±0.9	2.1±0.9	2.5±0.8*‡	0.01
PSQI 4: habitual sleep efficiency	0.8±1.1	1.3±1.3	1.5±1.2*	0.04
PSQI 5: sleep disturbances	1.4±0.7	1.7±0.8	2.2±0.6*‡	<0.0005
PSQI 6: use of sleeping medication	1.2±1.4	1.2±1.3	1.2±1.3	0.94
PSQI 7: daytime dysfunction	0.9±0.9	1.2±0.9	1.7±0.9*‡	<0.0005

\*Significantly different (p<0.05) from no DE symptom group.  
 †Signs from the more severely affected eye.  
 ‡Significantly different (p<0.05) from mild-moderate DE symptom group.  
 CISS, Convergence Insufficiency Symptoms Survey; DEQ-5, 5-Item Dry Eye Questionnaire; n, number in each group; NPSI-E, Neuropathic Pain Symptom Inventory modified for the Eye; NRS, Numerical Rating Scale; OSDI, Ocular Surface Disease Index; PSQI, Pittsburgh Sleep Quality Index.

related to all components of sleep quality, except for the use of sleep medication. Of all PSQI sleep components, sleep disturbances (eg, waking up in the middle of the night or early morning, needing to get up to use the bathroom, having trouble breathing comfortably, coughing, snoring loudly, feeling too cold or too hot, having bad

dreams and experiencing pain) were most closely related to DE symptoms (DEQ-5 and OSDI), ocular pain (NRS and NPSI-E) and convergence insufficiency (CISS). On the other hand, signs of tear and ocular surface dysfunction were less related to aspects of sleep. Of these, ocular surface inflammation and meibum quality were most

**Table 3** Pearson correlations (R) between dry eye (DE) disease and sleep metrics

	PSQI total	PSQI 1 subjective quality	PSQI 2 latency	PSQI 3 duration	PSQI 4 efficiency	PSQI 5 disturbance	PSQI 6 medication	PSQI 7 daytime dysfunction
<b>Ocular symptoms</b>								
DEQ-5	0.41*	0.43*	0.27*	0.27*	0.23*	0.44*	0.05	0.40*
OSDI	0.43*	0.47*	0.23*	0.26*	0.14	0.49*	0.13	0.37*
NRS (right now)	0.30*	0.34*	0.13	0.15	0.06	0.36*	0.12	0.30*
NRS (average of 1 week)	0.32*	0.36*	0.12	0.20*	0.14	0.41*	0.07	0.31*
NRS (worst in 1 week)	0.31*	0.34*	0.11	0.18*	0.10	0.45*	0.06	0.30*
NPSI-E	0.35*	0.37*	0.10	0.22*	0.03	0.44*	0.16	0.44*
CISS	0.48*	0.48*	0.21*	0.29*	0.13	0.51*	0.19*	0.56*
<b>Ocular surface exam†</b>								
Eyelid laxity upper	0.04	0.04	0.02	-0.09	0.06	-0.02	0.09	0.00
Eyelid laxity lower	0.04	0.05	0.03	-0.01	0.03	0.00	0.12	-0.04
Ocular surface inflammation	0.20*	0.29*	0.16	0.06	0.11	0.14	0.00	0.20*
Corneal sensation	0.19*	0.05	0.14	0.05	0.09	0.19	0.07	0.14
Anterior blepharitis	0.08	0.03	0.05	0.09	0.11	0.03	0.00	-0.01
Conjunctivochalasis	0.22*	0.14	0.07	0.18*	0.13	0.11	0.11	0.22*
Tear break-up time	-0.12	-0.03	-0.14	-0.07	-0.12	0.02	-0.12	0.08
Papillary conjunctivitis	-0.01	-0.04	-0.05	-0.09	0.01	0.01	0.07	-0.14
Corneal stain	0.09	0.07	-0.04	0.11	0.13	0.08	-0.01	0.00
Schirmer score	0.05	0.02	0.13	0.06	0.05	-0.04	-0.13	0.15
Vascularity	-0.05	-0.04	-0.12	-0.09	-0.01	0.03	0.06	-0.07
Meibum quality	0.17	0.29*	0.07	0.22*	0.03	0.00	0.09	0.07

\*Correlation is significant at the 0.05 level (two tailed).

†Measurement from more severely affected eye.

‡Green = positive correlation, red = negative correlation.

CISS, Convergence Insufficiency Symptoms Survey; DEQ-5, 5-Item Dry Eye Questionnaire; NPSI-E, Neuropathic Pain Symptom Inventory modified for the Eye; NRS, Numerical Rating Scale; OSDI, Ocular Surface Disease Index; PSQI, Pittsburgh Sleep Quality Index.

closely related to subjective sleep quality, which was an individual's assessment of their overall sleep quality.

Our findings share both similarities and differences compared with prior studies that have used the PSQI. In the China Hangzhou study (n=3070), the OSDI was used to assess DE symptoms, and a Chinese version of the PSQI was used to assess sleep quality. Patients were classified based on DE severity using OSDI scores: normal (score 0–12), mild (score 13–22), moderate (score 23–32) and severe (score 33–100). Similar to our results, mean PSQI global scores were higher in groups with worse DE symptoms (normal=4.7±2.8, mild=5.4±3.1, moderate=6.1±3.1 and severe=6.5±3.4, p<0.001). In contrast to our model, which identified sleep disturbances as the only sleep component related to OSDI, the Chinese study found broader relationships between DE symptoms and sleep. Specifically, the PSQI total scores and all subscores, with the exception of medication use, remained significantly related to DE symptoms after controlling for confounding variables ( $\beta=0.13$ , 95% CI 0.10 to 0.16, p<0.001).<sup>24</sup> Our

inclusion of mental health indices in the multivariable analysis may have contributed to the noted differences. A limitation of the Hangzhou study is that DE signs were not assessed, and as such, comparisons with our study are limited to symptoms only. Sleep quality has also been examined in a Japanese population (n=301) where mild DE was defined by symptoms and signs controlled by hyaluronate and severe DE by the need for additional medications. Individuals with severe DE had worse PSQI total scores (mean=6.4±3.3, p<0.05), sleep duration (PSQI 3: mean=1.5±0.8, p<0.05) and sleep efficacy (PSQI 4, mean=0.40±0.77, p<0.05) compared with the mild group. Similar to our study, no significant relationships were noted between DE signs (TBUT, Schirmer) and PSQI scores.<sup>25</sup> In the Netherlands, DE symptom presence (defined by the Women's Health Study Dry Eye Questionnaire)<sup>26</sup> and sleep quality (PSQI) were captured in 71 761 individuals (59% women). Similar to our study, DE symptom presence was related to sleep disturbances (PSQI 5: OR=2.24, 95% CI 1.98 to 2.53, p<0.001) and

**Table 4** Linear regression analysis between dry eye (DE) disease and sleep metrics

		Beta	P value
DE symptoms: DEQ-5	Depression: PHQ-9	0.37	<0.0005
	Sleep disturbances: PSQI 5	0.36	<0.0005
	Use of antidepressants	-0.22	0.01
DE symptoms: OSDI	Use of antihistamines	-0.20	0.02
	Depression: PHQ-9	0.46	<0.0005
	Sleep disturbances: PSQI 5	0.31	<0.0005
Ocular pain: NPSI-E	Use of antidepressants	-0.21	0.01
	Depression: PHQ-9	0.47	<0.0005
	Sleep disturbances: PSQI 5	0.23	0.02
Ocular pain: Now	Habitual sleep efficiency: PSQI 4	-0.19	0.03
	Sleep disturbances: PSQI 5	0.32	<0.0005
	Use of antianxiety	-0.15	0.10
Ocular pain: average over 1 week recall	Depression: PHQ-9	0.28	0.01
	Use of antidepressants	-0.20	0.04
	Sleep disturbances: PSQI 5	0.33	<0.0005
Ocular pain: worst over 1 week recall	Subjective sleep quality: PSQI 1	0.25	0.02
	Use of antianxiety	-0.18	0.04
	Sleep disturbances: PSQI 5	0.52	<0.0005
Ocular surface inflammation	Use of antianxiety	-0.24	0.01
	Use of antihistamines	0.27	0.01
Meibum quality	Subjective sleep quality: PSQI 1	0.26	0.01
	Subjective sleep quality: PSQI 1	0.46	<0.0005
Conjunctivochalasis	PTSD	-0.31	0.01
	Use of antianxiety	-0.27	<0.0005
	PSQI global score	0.27	0.01

DEQ-5, 5-Item Dry Eye Questionnaire; NPSI-E, Neuropathic Pain Symptom Inventory modified for the Eye; OSDI, Ocular Surface Disease Index; PHQ-9, Patient Health Questionnaire-9; PSQI, Pittsburgh Sleep Quality Index; PTSD, post-traumatic stress disorder.

daytime dysfunction (PSQI 7: OR=2.95, 95% CI 2.59 to 3.36,  $p<0.001$ ), when corrected for age and sex.<sup>27</sup> Taken together, these data suggest that sleep disorders are more related to ocular symptoms than signs, with sleep disturbances most closely relating to ocular symptoms across several populations.

Other investigators used different questionnaires to examine sleep quality. For example, the ISI has been used to examine relationships between ocular disease parameters and sleep. The ISI is a seven-item instrument measuring a patient's perception of his or her insomnia with a focus on aspects such as sleep onset, sleep maintenance, early morning awakenings, dissatisfaction with current sleep patterns, interference of sleep problems with daily functioning, noticeability of sleep problems by others and distress or worry caused by the sleep problem.<sup>28</sup> In our prior study, we found that ISI scores were related to DE symptoms (DEQ-5,  $r=0.43$ ,  $p<0.01$ ; OSDI,  $r=0.46$ ,  $p<0.01$ ) and ocular pain (NRS:  $r=0.39$ ,  $p<0.01$ ) but not with DE signs (including meibum quality), to a similar magnitude as found in the current study.<sup>8</sup> In another

recent study involving 1393 participants in China, those with DE symptoms, defined as a score of  $>12$  out of 100 on the OSDI, also had higher ISI scores (mean= $10.48\pm 7.27$ ,  $p=0.003$ ) compared with those without DE symptoms (mean= $3.57\pm 5.10$ ,  $p=0.003$ ).<sup>29</sup>

It is interesting to note that similar to prior reports,<sup>30</sup> DE signs were similarly distributed across our three DE symptom groups (none, mild-moderate and severe), highlighting the disconnect between symptoms and signs of disease. We hypothesise that this observation is driven by the reality that DE symptoms, specifically ocular pain, can arise from multiple sources, including nociceptive and neuropathic/nociplastic mechanisms. Nociceptive pain occurs as a result of the normal physiological response to mechanical, heat and chemical stimuli and can be driven by tear (eg, instability), ocular surface (eg, inflammation) and environmental (eg, air pollution) causes, to name a few.<sup>31</sup> Neuropathic and nociplastic pain, on the other hand, are driven by somatosensory system dysfunction, leading to changes in how sensory signals are processed both at the periphery and in the central



nervous system.<sup>32</sup> Patients with neuropathic/nociplastic pain may report feeling dryness (or another ocular pain complaint) despite having minimal abnormalities in tear and epithelial health. This may explain why sleep disturbances, which may also be impacted by central nervous system dysfunction, are more closely related to ocular symptoms rather than signs.

Based on our cross-sectional study design, we cannot comment on whether ocular symptoms lead to sleep abnormalities if sleep abnormalities lead to ocular symptoms or if shared contributors underlie both conditions. While the pathophysiological mechanisms that underlie the connection between ocular symptoms and sleep disturbances are unclear, several potential mechanisms have been proposed. One potential mechanism is that ocular pain itself may lead to a disruption in sleep. In fact, the PSQI has a specific question regarding experiencing pain as part of its sleep disturbance components. A second hypothesis is that the presence of distress from ocular symptoms may lead to poor sleep quality.<sup>25</sup> Prior studies have noted that ocular symptoms have a negative effect on feelings and daily activities, such as reading, driving, watching television and computer use.<sup>33–36</sup> Decreased quality of life may lead to chronic stress and anxiety with a negative impact on sleep.<sup>37</sup> A third hypothesis is that central nervous system abnormalities (eg, central sensitisation) that can be seen with a variety of conditions related to ocular symptoms (eg, fibromyalgia and migraine) underlie the noted associations. A fourth hypothesis is that individuals with poor sleep quality use electronics or read at night which may impact both ocular symptoms and sleep quality.<sup>34</sup> In total, more research is needed to understand potential mechanisms that underlie the noted associations and their directionality.

There are several limitations to our study that must be considered when evaluating our findings. First, as noted above, the cross-sectional nature of our study does not allow an evaluation of directionality. Second, our patient population consisted of US veterans, the majority of whom were men. As such, our results may not be generalisable to the broader public. Third, the subjective nature of self-reported sleep quality and ocular symptoms versus the objective capture of ocular findings may contribute to the noted differential relationships. Assessing sleep quality using objective metrics, such as with a formal sleep study, would have strengthened the study design. Fourth, there may have been unaccounted confounders (lifestyle, diet and physical activity) that impacted our findings. Fifth, while we chose not to apply Bonferroni adjustments given their tendency to address a universal null hypothesis and inflate type II errors, this decision could be viewed as a limitation. Specifically, it may increase the risk of type I errors (false positives), particularly in the context of multiple comparisons, potentially affecting the interpretation of our findings.<sup>22</sup> Finally, while minimal, missing data may have reduced our statistical power and induced bias in our results.

Despite these limitations, our study supports prior research that links DE to impaired sleep quality and highlights that the strongest association is with respect to ocular symptoms and sleep disturbances. Addressing sleep disturbances such as nocturia (the need to void more than one time during sleep), breathing issues (such as in the setting of obstructive sleep apnoea) and night-time waking may beneficially impact ocular symptoms, although this suggestion needs further study. Previous research has found that sleep quality can be improved using a variety of methods. In one Iranian study, 32 individuals with insomnia underwent 3 sessions of exercise therapy weekly for 12 weeks (three movements for the upper limbs and three movements for the lower limbs). Exercise therapy was found to improve sleep quality (mean PSQI preintervention versus postintervention: 13.94 vs 9.94,  $p=0.01$ ) compared with a control group that did not receive any interventions (14.56 vs 13.88,  $p=0.55$ ).<sup>38</sup> Given the availability of techniques that may improve sleep quality, it is important for eye care providers to consider a holistic approach in their management of DE although it is not yet known if improving sleep quality will impact DE status.

Conversely, treating DE may improve sleep quality. A Japanese study of 71 individuals with DE (defined by the Japanese Dry Eye Society)<sup>39,40</sup> found that treating DE with topical therapy improved sleep quality (PSQI). Interestingly, the effect was more pronounced in individuals with newly diagnosed DE (diagnosed at the time of study enrollment) compared with established DE (diagnosed prior to study enrollment) (35% vs 20%,  $p<0.05$ ). Additionally, improved sleep quality (PSQI) was correlated with reduced depression severity (Hospital Anxiety and Depression Scale score), again more so in individuals with newly diagnosed DE ( $r=0.5$ ,  $p<0.05$ ) compared with established DE ( $r=0.3$ ,  $p<0.05$ ).<sup>41</sup> As such, addressing both DE symptoms and sleep disturbances as early as they are identified may help reduce sleeping problems and improve mental health simultaneously.

**Correction notice** This article has been corrected since it was published. The name of the author has been corrected to 'Simran Mangwani-Mordani'.

**Contributors** MA, KC, SM and EVTL carried out the experiment and collected the data. MA performed the data analysis and interpretation of the results. MA wrote the manuscript with support from AG and KC. AG supervised the project and acted as the guarantor. All authors reviewed the results and approved the final version of the manuscript.

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**Competing interests** One of the authors (AG) is an editor for BMJ Ophthalmology.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.



**Patient consent for publication** Not applicable.

**Ethics approval** This study involved human participants and was approved by Miami Veteran Affairs Institutional Review Board: 3011.09 Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; internally peer reviewed.

**Data availability statement** Data are available upon reasonable request.

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#### REFERENCES

- Craig JP, Nichols KK, Akpek EK, *et al*. TFOS DEWS II definition and classification report. *Ocul Surf* 2017;15:276–83.
- Pouyeh B, Viteri E, Feuer W, *et al*. Impact of ocular surface symptoms on quality of life in a United States veterans affairs population. *Am J Ophthalmol* 2012;153:1061–66.
- Stapleton F, Alves M, Bunya VY, *et al*. TFOS DEWS II epidemiology report. *The Ocular Surface* 2017;15:334–65.
- Galor A, Britten-Jones AC, Feng Y, *et al*. TFOS lifestyle: impact of lifestyle challenges on the ocular surface. *Ocul Surf* 2023;28:262–303.
- Au NH, Mather R, To A, *et al*. Sleep outcomes associated with dry eye disease: a systematic review and meta-analysis. *Can J Ophthalmol* 2019;54:180–9.
- Hackett KL, Gotts ZM, Ellis J, *et al*. An investigation into the prevalence of sleep disturbances in primary Sjögren's syndrome: a systematic review of the literature. *Rheumatology (Oxford)* 2017;56:570–80.
- Lim EWL, Chee ML, Sabanayagam C, *et al*. Relationship between sleep and symptoms of tear dysfunction in Singapore Malays and Indians. *Invest Ophthalmol Vis Sci* 2019;60:1889–97.
- Galor A, Seiden BE, Park JJ, *et al*. The association of dry eye symptom severity and comorbid insomnia in US veterans. *Eye Contact Lens* 2018;44:S118–24.
- Buyse DJ, Reynolds CF 3rd, Monk TH, *et al*. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
- Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16:606–13.
- Wilkins KC, Lang AJ, Norman SB. Synthesis of the psychometric properties of the PTSD checklist (PCL) military, civilian, and specific versions. *Depress Anxiety* 2011;28:596–606.
- Amtmann D, Bamer AM, Noonan V, *et al*. Comparison of the psychometric properties of two fatigue scales in multiple sclerosis. *Rehabil Psychol* 2012;57:159–66.
- Schiffman RM, Christianson MD, Jacobsen G, *et al*. Reliability and validity of the ocular surface disease index. *Arch Ophthalmol* 2000;118:615–21.
- Chalmers RL, Begley CG, Caffery B. Validation of the 5-item dry eye questionnaire (DEQ-5): discrimination across self-assessed severity and aqueous tear deficient dry eye diagnoses. *Cont Lens Anterior Eye* 2010;33:55–60.
- Thong ISK, Jensen MP, Miró J, *et al*. The validity of pain intensity measures: what do the NRS, VAS, VRS, and FPS-R measure *Scand J Pain* 2018;18:99–107.
- Farhangi M, Feuer W, Galor A, *et al*. Modification of the neuropathic pain symptom inventory for use in eye pain (NPSI-eye). *Pain* 2019;160:1541–50.
- Rueff EM, King-Smith PE, Bailey MD. Can binocular vision disorders contribute to contact lens discomfort *Optom Vis Sci* 2015;92:e214–21.
- Rouse M, Borsting E, Mitchell GL, *et al*. Validity of the convergence insufficiency symptom survey: a Confirmatory study. *Optom Vis Sci* 2009;86:357–63.
- Lanza NL, Valenzuela F, Perez VL, *et al*. The matrix metalloproteinase 9 point-of-care test in dry eye. *Ocul Surf* 2016;14:189–95.
- Lemp MA. Report of the national eye Institute/industry workshop on clinical trials in dry eyes. *CLAO J* 1995;21:221–32.
- Bron AJ, Benjamin L, Snibson GR. Meibomian gland disease. classification and grading of lid changes. *Eye (Lond)* 1991;5 (Pt 4):395–411.
- Perneger TV. What's wrong with Bonferroni adjustments. *BMJ* 1998;316:1236–8.
- Cohen J. *Statistical Power Analysis for the Behavioral Sciences* 2nd ed. New Jersey: Lawrence Erlbaum Associates, 1988.
- Yu X, Guo H, Liu X, *et al*. Dry eye and sleep quality: a large community-based study in Hangzhou. *Sleep* 2019;42:zsz160.
- Ayaki M, Kawashima M, Negishi K, *et al*. Sleep and mood disorders in dry eye disease and allied irritating ocular diseases. *Sci Rep* 2016;6:22480.
- Gulati A, Sullivan R, Buring JE, *et al*. Validation and repeatability of a short questionnaire for dry eye syndrome. *Am J Ophthalmol* 2006;142:125–31.
- Magno MS, Utheim TP, Snieder H, *et al*. The relationship between dry eye and sleep quality. *Ocul Surf* 2021;20:13–9.
- Bastien CH, Vallières A, Morin CM. Validation of the insomnia severity index as an outcome measure for insomnia research. *Sleep Med* 2001;2:297–307.
- Qin G, Luan X, Chen J, *et al*. Effects of insomnia on symptomatic dry eye during COVID-19 in China: an online survey. *Medicine (Baltimore)* 2023;102:e35877.
- Galor A, Feuer W, Lee DJ, *et al*. Ocular surface parameters in older male veterans. *Invest Ophthalmol Vis Sci* 2013;54:1426–33.
- McMonnies CW. Why the symptoms and objective signs of dry eye disease may not correlate. *J Optom* 2021;14:3–10.
- Galor A, Levitt RC, Felix ER, *et al*. Neuropathic ocular pain: an important yet undervalued feature of dry eye. *Eye (Lond)* 2015;29:301–12.
- Uchino M, Schaumberg DA. Dry eye disease: impact on quality of life and vision. *Curr Ophthalmol Rep* 2013;1:51–7.
- Tong L, Waduthantri S, Wong TY, *et al*. Impact of symptomatic dry eye on vision-related daily activities: the Singapore Malay eye study. *Eye (Lond)* 2010;24:1486–91.
- Deschamps N, Ricaud X, Rabut G, *et al*. The impact of dry eye disease on visual performance while driving. *Am J Ophthalmol* 2013;156:184–9.
- Miljanović B, Dana R, Sullivan DA, *et al*. Impact of dry eye syndrome on vision-related quality of life. *Am J Ophthalmol* 2007;143:409–15.
- Han KS, Kim L, Shim I. Stress and sleep disorder. *Exp Neurobiol* 2012;21:141–50.
- Dadgostar H, Basharkhah A, Ghalehbandi MF, *et al*. An investigation on the effect of exercise on insomnia symptoms. *Int J Prev Med* 2023;14:16:16..
- Shimazaki J. Definition and diagnosis of dry eye 2006. *Atarashii Ganka* 2007;24:181–4.
- Uchino Y, Uchino M, Dogru M, *et al*. Changes in dry eye diagnostic status following implementation of revised Japanese dry eye diagnostic criteria. *Jpn J Ophthalmol* 2012;56:8–13.
- Ayaki M, Toda I, Tachi N, *et al*. Preliminary report of improved sleep quality in patients with dry eye disease after initiation of topical therapy. *Neuropsychiatr Dis Treat* 2016;12:329–37.

		Reporting Item	Page Number
<b>Title and abstract</b>			
Title	<a href="#">#1a</a>	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	<a href="#">#1b</a>	Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background / rationale	<a href="#">#2</a>	Explain the scientific background and rationale for the investigation being reported	3
Objectives	<a href="#">#3</a>	State specific objectives, including any prespecified hypotheses	3
<b>Methods</b>			
Study design	<a href="#">#4</a>	Present key elements of study design early in the paper	4
Setting	<a href="#">#5</a>	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Eligibility criteria	<a href="#">#6a</a>	Give the eligibility criteria, and the sources and methods of selection of participants.	4
	<a href="#">#7</a>	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Data sources / measurement	<a href="#">#8</a>	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	5
Bias	<a href="#">#9</a>	Describe any efforts to address potential sources of	4

		bias	
Study size	<a href="#">#10</a>	Explain how the study size was arrived at	n/a
Quantitative variables	<a href="#">#11</a>	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6
Statistical methods	<a href="#">#12a</a>	Describe all statistical methods, including those used to control for confounding	6
Statistical methods	<a href="#">#12b</a>	Describe any methods used to examine subgroups and interactions	6
Statistical methods	<a href="#">#12c</a>	Explain how missing data were addressed	6
Statistical methods	<a href="#">#12d</a>	If applicable, describe analytical methods taking account of sampling strategy	n/a
Statistical methods	<a href="#">#12e</a>	Describe any sensitivity analyses	n/a

## Results

Participants	<a href="#">#13a</a>	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	n/a patients were selected if they fulfilled the criteria and consented to being in study.
Participants	<a href="#">#13b</a>	Give reasons for non-participation at each stage	n/a
Participants	<a href="#">#13c</a>	Consider use of a flow diagram	n/a
Descriptive data	<a href="#">#14a</a>	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	6
Descriptive data	<a href="#">#14b</a>	Indicate number of participants with missing data for each variable of interest	6,7
Outcome data	<a href="#">#15</a>	Report numbers of outcome events or summary	6

		measures. Give information separately for exposed and unexposed groups if applicable.	
Main results	<a href="#">#16a</a>	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
Main results	<a href="#">#16b</a>	Report category boundaries when continuous variables were categorized	6
Main results	<a href="#">#16c</a>	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	<a href="#">#17</a>	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	8,9
<b>Discussion</b>			
Key results	<a href="#">#18</a>	Summarise key results with reference to study objectives	11
Limitations	<a href="#">#19</a>	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	13
Interpretation	<a href="#">#20</a>	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	12,13
Generalizability	<a href="#">#21</a>	Discuss the generalizability (external validity) of the study results	13
<b>Other Information</b>			
Funding	<a href="#">#22</a>	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	n/a

Notes: certain elements from the checklist were deemed not applicable to our specific study and were therefore omitted for relevance and clarity.