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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.

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.

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.[1] 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.[2] Many factors have been linked to various aspects of DE, including demographics (eg, older age, female sex and 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.[3] 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.[4]

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.[5] 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.[6]

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 ≥11 out of 24 on the Epworth Sleepiness Scale), high risk for sleep apnoea (score of ≥5 out of 8 on the STOP-Bang Questionnaire), insomnia (score of ≥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.[7] 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).[8]

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).[8] 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).[9] 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,[10] the PTSD Checklist – Military Version (PCL-M) for post-traumatic stress disorder (PTSD)[11] and the Modified Fatigue Impact Scale (MFIS) for fatigue.[12]

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.[9]

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.[13] 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).[14]

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.[15] 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).[16]

Convergence insufficiency symptoms, which have been linked to DE symptoms in prior studies,[17] were evaluated using the Convergence Insufficiency Symptoms Survey (CISS, 0–60).[18] 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)[19] 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,[20] 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 30 s 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.[21]

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 X^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.[22] 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.[23]

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
Demographics				
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
Comorbidities, % (n)				
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
Ocular comorbidities, % (n)				
Cataract surgery	20% (1)	40% (2)	40% (2)	0.93
Refractive surgery	36% (5)	21% (3)	43% (6)	0.20
Mental health, mean±SD				
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
Oral medications, % (n)				
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
Ocular symptoms								
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*
Ocular surface exam†								
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 (β=0.13, 95% CI 0.10 to 0.16, p<0.001).[24] 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.[25] In the Netherlands, DE symptom presence (defined by the Women's Health Study Dry Eye Questionnaire)[26] 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
	Use of antihistamines	−0.20	0.02
DE symptoms: OSDI	Depression: PHQ-9	0.46	<0.0005
	Sleep disturbances: PSQI 5	0.31	<0.0005
	Use of antidepressants	−0.21	0.01
Ocular pain: NPSI-E	Depression: PHQ-9	0.47	<0.0005
	Sleep disturbances: PSQI 5	0.23	0.02
	Habitual sleep efficiency: PSQI 4	−0.19	0.03
Ocular pain: Now	Sleep disturbances: PSQI 5	0.32	<0.0005
	Use of antianxiety	−0.15	0.10
	Depression: PHQ-9	0.28	0.01
	Use of antidepressants	−0.20	0.04
Ocular pain: average over 1 week recall	Sleep disturbances: PSQI 5	0.33	<0.0005
	Subjective sleep quality: PSQI 1	0.25	0.02
	Use of antianxiety	−0.18	0.04
Ocular pain: worst over 1 week recall	Sleep disturbances: PSQI 5	0.52	<0.0005
	Use of antianxiety	−0.24	0.01
Ocular surface inflammation	Use of antihistamines	0.27	0.01
	Subjective sleep quality: PSQI 1	0.26	0.01
Meibum quality	Subjective sleep quality: PSQI 1	0.46	<0.0005
	PTSD	−0.31	0.01
Conjunctivochalasis	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.[27] 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.[28] 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.[8] 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±7.27, p=0.003) compared with those without DE symptoms (mean=3.57±5.10, p=0.003).[29]

It is interesting to note that similar to prior reports,[30] 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.[31] 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.[32] 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.[25] 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.[33–36] Decreased quality of life may lead to chronic stress and anxiety with a negative impact on sleep.[37] 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) underly 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.[34] 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.[22] 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 nighttime 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).[38] 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)[39 40] 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).[41] 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'.

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