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The relationship between dry eye and sleep quality

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ABSTRACT

Purpose: Sleep is an important determinant of health and quality of life. This study aimed to clarify the association between dry eye and sleep quality using a large population-based cohort.
Methods: 71,761 participants (19–94 yrs, 59.4% female) from the Lifelines cohort in the Netherlands were assessed for dry eye using the Women's Health Study Dry Eye Questionnaire. Sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI). Logistic regression was used to examine the relationship between poor sleep quality (PSQI score >5) and dry eye, while correcting for age, sex, BMI, education, income, and 51 possible confounding comorbidities, including autoimmune diseases and psychiatric disorders.
Results: Overall, 8.9% of participants had dry eye. Of these, 36.4% had poor sleep quality compared to 24.8% of controls (OR 1.52 (95%CI 1.44–1.60), P < 0.0001, corrected for age and sex). After correcting for all comorbidities, dry eye was still associated with poor sleep (OR 1.20 (95%CI 1.11–1.28), P < 0.0001). This relationship was seen across all ages and sexes. Patients with dry eye scored worse on all subcomponents of the PSQI. Almost one-in-two (44.9%) persons with dry eye symptoms "often" or "constantly" had poor sleep quality. This proportion was similar to participants with sleep apnea and osteoarthritis. Additionally, increasing symptom frequency was tied to increased prevalence of poor sleep quality.
Conclusions: All components of sleep quality were significantly reduced in participants with dry eye, even after correcting for comorbidities. These results indicate the substantial impact of dry eye on patients' lives, especially for those with frequent symptoms.

1. Introduction

Dry eye disease (DED) is a multifactorial disease affecting the ocular surface and tear film. DED affects millions of people worldwide, with prevalence estimates ranging from 5% to 50% across populations [1]. Dry eye causes a major financial burden to patients and society through both the direct cost of treatment and indirect cost of lost productivity at work [2]. The ocular symptoms of DED include pain, blurred vision, light sensitivity, and ocular burning. Patients with DED experience a reduced quality of life, with limited participation in both work and social life, and problems with everyday activities such as reading, watching television, and driving [2–5].

Sleep is an important factor for well-being and general health. Poor quality and short duration of sleep have been shown to reduce quality of life [6,7], and have been linked to an increased risk of stroke, cardiovascular events, and all-cause mortality [8]. Recent studies on sleep and DED have indicated that patients with DED have poorer sleep [9–17], and that patients with sleep disorders are more likely to have DED [18–20]. However, most of these studies were small or done in the setting of an eye clinic, where selection bias could affect results. To date, only a few, relatively small, population-based studies have been performed, in which limited sets of covariables were corrected for [9,10]. As DED is highly associated with numerous other disorders, these results could be confounded by these conditions that negatively impact sleep

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quality as well. In addition, no population-based study concerning sleep quality and DED has been conducted in a sample of European ancestry to date.

This study had several objectives. First, we aimed to determine the association between dry eye and sleep quality in a Northern European population, correcting for a large number of possible confounding factors. Second, we sought to investigate the impact of age and sex on this association through stratified analysis. Third, we planned to assess the strength of the association between dry eye and sleep quality through direct comparison to other chronic conditions known to reduce quality of sleep. Finally, we explored the effect of increasing frequency of dry eye symptoms on the likelihood of having poor sleep quality.

2. Methods

2.1. Lifelines cohort and participants

Lifelines is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviours of 167,729 persons living in the North of The Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioural, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics [21]. Participants, almost exclusively of European ancestry, were included via general practitioners or self-enrollment between 2006 and 2013 and will be followed for at least 30 years. The cohort is described in detail elsewhere [22]. The study protocol was approved by the medical ethics committee of the University Medical Center Groningen, was carried out in accordance with the Declaration of Helsinki, and all participants provided written informed consent. For the current study, we aimed to include at least 54,605 participants of this cohort to be able to detect an odds ratio of 1.1 for poor sleep quality in dry eye patients with a power of 80%, with an alpha of 0.05, and an estimated prevalence of dry eye of 10% [23] and of poor sleep quality of 25% [24].

2.2. Assessment of dry eye

No gold standard for a diagnosis of DED exists [25]. The most widely used dry eye questionnaire in population-based studies is the self-reported Women's Health Study (WHS) dry eye questionnaire [1, 26]. This short, three-question survey has been validated against a standardized clinical exam [27] and showed similar sensitivity and specificity as a 16-item instrument [26]. For this study, participants completed this questionnaire during the period 2014 to 2018. The questionnaire includes two symptom questions [1]: "How often do your eyes feel dry (not wet enough)?" and [2] "How often do your eyes feel irritated?" (both with possible answers: 0 never, 1 sometimes, 2 often, or 3 constantly), and a third question about a previous clinical diagnosis of dry eye [3]: "Have you ever been diagnosed (by a clinician) as having dry eye syndrome?" (with possible answers: yes or no). A subject is considered as having dry eye if there is the presence of both dryness and irritation either 'constantly' or 'often' and/or a report of a previous diagnosis of dry eye [26]. This definition was used as the primary outcome variable of our analysis and is further regarded as 'dry eye.' We also examined highly symptomatic dry eye and a past clinical diagnosis of dry eye disease separately as secondary outcomes. Patients reporting either 'constant' or 'often' symptoms of both ocular irritation and dryness (questions 1 and 2) are from here referred to as having 'highly symptomatic dry eye'.

2.3. Assessment of sleep quality

All participants completed the validated Pittsburgh Sleep Quality Index (PSQI) during the period 2011 to 2015. The PSQI, developed in 1988 by Buysse et al. [28], is the most often used validated questionnaire for assessing sleep quality in both clinical and research settings [29]. This self-reported questionnaire assesses the average sleep quality over the last month. It consists of 19 questions in seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction [28]. The scores in each of these seven domains, each on a 0–3 scale, are summed to generate a global score, with a possible range of 0–21 [28]. A global score >5 was used as the cut-off to distinguish between good sleepers (≤5) and poor sleepers (>5). This cut-off has been found to have a high sensitivity and specificity across studies [28–30].

2.4. Assessment of possible confounding factors

All participants completed repeated questionnaires from baseline to 2018 that included questions about the presence of a broad range of disorders using the question: "Could you indicate which of the following disorders you have or have had?" Subjects responded to each condition on the predefined list in addition to reporting any other disorders using free text. Using this information, 118 dichotomous variables were created for the occurrence of a broad range of diagnoses contemporaneous with the dry eye questionnaire. Of these 118 disorders and traits, 54 were independently associated with DED, see Vehof et al. [23]. Of these 54 possible confounding factors, we tested whether they were also associated with poor sleep quality ($P < 0.20$). This resulted in a total of 51 factors that were correlated with both DED and poor sleep quality and were corrected for in this study. These factors were contact lens use, macular degeneration, glaucoma/ocular hypertension, allergic conjunctivitis, laser refractive surgery, eye surgery (any other), rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, thyroid disease, Crohn's disease, sarcoidosis, depression, "burnout", autistic disorder, chronic fatigue syndrome, carpal tunnel syndrome, spasticity, migraine, asthma, eczema, hay fever, allergy (any), acne, psoriasis, rosacea, lichen planus, anemia, diabetes, hypertension, atherosclerosis, arrhythmia, liver cirrhosis, chronic cystitis, stomach ulcer, osteoporosis, incontinency, sinusitis, irritable bowel syndrome, fibromyalgia, intervertebral disc herniation, repetitive strain injury, back pain, osteoarthritis, sleep apnea, attention deficit hyperactivity disorder (ADHD), eating disorder, chronic obstructive pulmonary disease (COPD), vitamin B12 deficiency, gallstones, and costochondral junction syndrome. The three factors not related with poor sleep quality were Graves' disease, keratoconus, and Bell's palsy. Other variables corrected for in this study were age, sex, body mass index (BMI), educational level (completion of higher vocational or university education diploma or not), and net monthly household income (<1500 Euro per month, 1500–2500 Euro per month, or >2500 Euro per month).

2.5. Statistics

The characteristics of the study population were evaluated using descriptive statistics. Logistic regression models were used to assess the relationship between poor sleep quality (PSQI score >5 as the dependent variable) and dry eye ('dry eye' (WHS definition), clinical diagnosis of dry eye, and 'highly symptomatic dry eye' as the independent variables). Results were corrected for (i) age and sex, and (ii) age, sex, BMI, education, income, and 51 comorbidities associated with both DED and poor sleep quality. This was regarded as the main analysis. In addition, to investigate which components of sleep quality are most affected, we performed the same analysis for the seven components of the PSQI separately. The main analysis was also stratified by age in decades and sex. To examine any significant effect of age and sex on the relationship between sleep quality and dry eye, interaction terms 'age*dry eye' and 'sex*dry eye' were tested for significance in the multivariable models. A p-value lower than 0.05 was regarded as statistically significant in all analyses above. Additionally, we plotted the odds ratio of having poor sleep quality for highly symptomatic dry eye against the odds ratio of

having poor sleep quality for other chronic disorders in this population, all corrected for age and sex. This approach provided a clearer idea of how much dry eye patients suffer from poor quality of sleep compared to patients with other disorders. We also explored the effect of increasing frequency of ocular dryness and irritation on the prevalence of poor sleep quality and plotted this graphically. Statistical significance was tested by using logistic regression with symptom frequency as the independent, ordinal outcome variable, corrected for age and sex. Finally, due to the probable bidirectional association between sleep quality and dry eye, we also assessed the odds of having dry eye (dependent variable), given a poor sleep quality (independent variable), using a similar approach as the main analysis above.

3. Results

Table 1 describes the characteristics of the study population (n = 71,761). A total of 8.9% of participants were classified as having dry eye, as defined by the WHS dry eye questionnaire. Highly symptomatic dry eye was found in 1.8% of participants, and 8.4% of participants had a past clinical diagnosis of dry eye disease. As nearly all (93.6%) participants included in the primary outcome variable, 'dry eye,' had a past clinical diagnosis of dry eye, the results of the secondary outcome variable 'past clinical diagnosis of dry eye' is only presented in the supplemental material (Supplemental Tables 1 and 2), due to the close overlap with the primary outcome variable 'dry eye.' Poor sleep quality was common in our cohort, affecting approximately 1 in 4 participants (25.9%).

Table 2 presents the relationship between dry eye and sleep quality. In dry eye patients, poor sleep quality was much more prevalent than in controls (36.4% versus 24.8%, OR 1.52 (95%CI 1.44–1.60), corrected for age and sex only, P < 0.0001). Almost 1 in 2 (44.9%) of those with highly symptomatic dry eye had poor sleep quality (OR 2.06 (95%CI 1.85–2.30), corrected for age and sex only, P < 0.0001).

Conversely, participants with poor sleep quality were fifty percent more likely to have dry eye than those without poor sleep quality (WHS definition OR 1.49 (95%CI 1.41–1.58), corrected for age and sex only). Poor sleep quality particularly increased the risk of having highly symptomatic dry eye (OR 2.01 (95%CI 1.84–2.30)), compared to a clinical diagnosis (OR 1.45 (95%CI 1.37–1.54)).

Table 2 further demonstrates the association between dry eye and different components of sleep quality. It reveals that dry eye patients have worse scores than controls on all components of the PSQI (all P < 0.0001, corrected for age and sex). Daytime dysfunction and sleep disturbances were particularly prevalent in dry eye patients as compared to controls. As expected, after correcting for an additional 51 comorbidities of dry eye, all these odds ratios were reduced, but dry eye (primary outcome variable) was still associated with lower sleep quality on all seven components. Only the use of sleep medication was not clearly associated with highly symptomatic dry eye after correction for these comorbidities, which include disorders that are associated with increased use of sleep medication such as depression, sleep apnea syndrome, chronic fatigue syndrome, and osteoarthritis [31–36].

The age and sex stratified analysis is shown in Table 3. Poor sleep quality in dry eye patients is present in both young and old, and men and women. Poor sleep quality was more prevalent in patients with DED with increasing age (P-value interaction term 'age*dry eye' = 0.005). However, this increase with increasing age was no longer present after correction for possible confounding factors (P-value interaction term 'age*dry eye' = 0.20), indicating that at later age dry eye is increasingly associated with other comorbidities that also affect sleep. No clear differences in the effect of dry eye on sleep quality were found between men and women (P-value interaction term 'sex*dry eye' = 0.32).

Fig. 1 shows the odds of having poor sleep quality for participants with highly symptomatic dry eye as compared to other chronic disorders (corrected for age and sex only). These figures show participants with highly symptomatic dry eye have rates of poor sleep quality similar to conditions such as sleep apnea syndrome and osteoarthritis, and higher rates than conditions such as rheumatoid arthritis, Crohn's disease, and migraine.

Fig. 2 shows the prevalence of poor sleep quality in participants with increasing frequency of dry eye symptoms. The prevalence of poor sleep quality sharply rose with increasing dry eye symptoms, more than double in those experiencing symptoms 'often' or 'constantly' compared to those 'never' experiencing ocular dryness or irritation. This elevated risk with increasing dry eye symptom frequency was highly significant (P < 0.0001 for both dryness and irritation, corrected for age and sex).

Table 1
Characteristics of the study population.

	All participants (n = 71,761)
Age, yrs (mean (sd))	50.2 (12.3) (range 19–94)
Female sex	59.4%
BMI (mean (sd))	26.1 (4.2)
Higher education	30.3%
Household net monthly income	
Lower than 1500 Euro	13.2%
Between 1500 and 2500 Euro	27.5%
Higher than 2500 Euro	45.6%
Preferred not to answer	13.7%
PSQI score (mean (sd)) (0–21)	3.8 (2.5)
Poor sleep quality (PSQI>5)	25.9% (n = 18,563)
Dry eye (WHS definition)	8.9% (n = 6414)
Clinical diagnosis of dry eye	8.4% (n = 6002)
Highly symptomatic dry eye[a]	1.8% (n = 1320)

[a] Both irritation and dryness of the eyes either 'often' or 'constantly'. PSQI = Pittsburgh Sleep Quality Index, WHS = Women's Health Study Dry Eye Questionnaire.

4. Discussion

This large, population-based study found sleep quality to be substantially reduced in dry eye patients of all demographics. It further revealed that this relationship is partly explained by coexisting comorbidities such as autoimmune diseases, psychiatric disorders, and chronic pain syndromes. However, after correction for these comorbidities, dry eye was still found to be strongly associated with reduced sleep quality in this Northern European population. Patients with dry eye were one and a half times more likely to be poor sleepers, with worse outcome in all components of the PSQI. Furthermore, this is the first study to show that the relationship between poor sleep quality and dry eye is present in all segments of the population, affecting adults of all ages and sexes. Additionally, patients with highly symptomatic dry eye had a sleep quality comparable to that of patients with sleep apnea syndrome or osteoarthritis. This direct comparison of the reduced quality of sleep in participants with highly symptomatic dry eye to chronic conditions well-known to cause poor sleep quality [37,38] may emphasize the clinical value of this association and help increase awareness of dry eye disease as a serious disorder affecting many aspects of life. Highly symptomatic dry eye was more strongly associated with sleep quality than just a clinical diagnosis of dry eye, and similarly there was a clear increase in prevalence of poor quality of sleep with increasing frequency of ocular dryness and irritation.

Past studies investigating the directionality of the association between poor sleep quality and dry eye have shown that the relationship is likely to be complex and bidirectional. One study examining the effect of sleep deprivation on symptoms of dry eye in healthy adult subjects showed noticeable changes in tear film break-up time, tear osmolarity, and reduced tear secretion after one night of sleep deprivation [39]. Similar results have also been found in mice, where sleep deprivation reduced tear secretion and increased corneal epithelial cell defects. The corneal fluorescein staining scores worsened daily over the ten days period of sleep deprivation [40]. Following 14 days of rest, these changes mostly returned to normal [40]. On the other hand, not

Table 2
Association between sleep quality (all components of the PSQI) and dry eye.

PSQI component	Prevalence in controls (no WHS definition dry eye) (n = 65,347)	Prevalence in WHS definition dry eye (n = 6414)	Prevalence in highly symptomatic dry eye[a] (n = 1320)	Dry eye (WHS definition)				Highly symptomatic dry eye[a]			
				Corrected for age and sex only		Corrected for age, sex, BMI, education, income and 51 comorbidities of dry eye		Corrected for age and sex only		Corrected for age, sex, BMI, education, income and 51 comorbidities of dry eye	
				OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Global score: Overall poor quality of sleep (PSQI score >5)	24.8%	36.4%	44.9%	1.52 (1.44–1.60)	<0.0001	1.20 (1.11–1.28)	<0.0001	2.06 (1.85–2.30)	<0.001	1.37 (1.22–1.55)	<0.001
1. Subjective sleep quality ('bad' versus 'good')	11.8%	18.4%	24.4%	1.49 (1.39–1.60)	<0.0001	1.20 (1.12–1.29)	<0.0001	2.04 (1.80–2.32)	<0.001	1.41 (1.23–1.62)	<0.001
2. Suboptimal sleep latency (>2 versus≤2)	14.5%	21.4%	25.7%	1.35 (1.27–1.44)	<0.0001	1.17 (1.09–1.25)	<0.0001	1.64 (1.45–1.86)	<0.001	1.26 (1.10–1.44)	<0.001
3. Suboptimal sleep duration (≤6 h versus >6 h)	3.9%	6.1%	7.7%	1.42 (1.27–1.59)	<0.0001	1.17 (1.04–1.32)	0.009	1.77 (1.44–2.17)	<0.001	1.31 (1.06–1.63)	0.01
4. Poor habitual sleep efficiency (<75% vs≥75%)	13.6%	18.7%	23.0%	1.31 (1.22–1.40)	<0.0001	1.13 (1.04–1.21)	0.002	1.63 (1.42–1.86)	<0.0001	1.25 (1.09–1.44)	0.002
5. Sleep disturbances (>9 vs≤9)	12.2%	22.0%	29.1%	1.64 (1.54–1.76)	<0.0001	1.21 (1.12–1.30)	<0.0001	2.24 (1.98–2.53)	<0.001	1.36 (1.18–1.56)	<0.001
6. Use of sleep medication (yes versus no)	10.0%	16.4%	18.8%	1.44 (1.34–1.54)	<0.0001	1.12 (1.03–1.21)	0.007	1.59 (1.38–1.83)	<0.001	1.01 (0.86–1.17)	0.94
7. Daytime dysfunction (>2 versus≤2)	8.9%	14.2%	22.7%	1.71 (1.58–1.84)	<0.0001	1.23 (1.13–1.34)	<0.0001	2.95 (2.59–3.36)	<0.001	1.81 (1.56–2.09)	<0.001

[a] Both irritation and dryness of the eyes either 'often' or 'constantly'. PSQI = Pittsburgh Sleep Quality Index, WHS = Women's Health Study Dry Eye Questionnaire, BMI = Body Mass Index, CI = confidence interval, OR = odds ratio.

Table 3
Association between sleep quality and dry eye, stratified by age decade and sex.

		Prevalence			Dry eye (WHS definition)			Highly symptomatic dry eye[b]		
Age decade	n	Dry eye (WHS definition)	Dry eye with frequent symptoms	Poor sleep quality[a]	OR of poor sleep quality	95% CI	P-value	OR of poor sleep quality	95% CI	P-value
20-30	4504	6.8%	1.5%	26.4%	1.39	1.08–1.78	0.01	2.13	1.30–3.49	0.003
30-40	10,329	7.2%	1.2%	24.5%	1.43	1.21–1.68	<0.0001	2.20	1.53–3.16	<0.0001
40-50	18,992	7.3%	1.7%	22.3%	1.48	1.31–1.67	<0.0001	2.39	1.88–2.98	<0.0001
50-60	22,953	9.2%	2.0%	27.9%	1.46	1.33–1.61	<0.0001	1.98	1.64–2.40	<0.0001
60-70	11,316	11.9%	2.4%	27.8%	1.60	1.42–1.81	<0.0001	1.84	1.43–2.36	<0.0001
70+	3667	13.7%	3.1%	29.0%	1.52	1.24–1.86	<0.0001	1.71	1.16–2.53	0.007
Sex										
Male	29,153	4.9%	0.9%	18.9%	1.65	1.46–1.86	<0.0001	2.08	1.60–2.71	<0.0001
Female	42,608	11.7%	2.6%	30.6%	1.46	1.38–1.56	<0.0001	2.01	1.78–2.26	<0.0001

PSQI = Pittsburgh Sleep Quality Index. WHS = Women's Health Study Dry Eye Questionnaire. CI = confidence interval. OR = odds ratio.
[a] Poor sleep quality was defined as a PSQI score >5.
[b] Both irritation and dryness of the eyes either 'often' or 'constantly'.

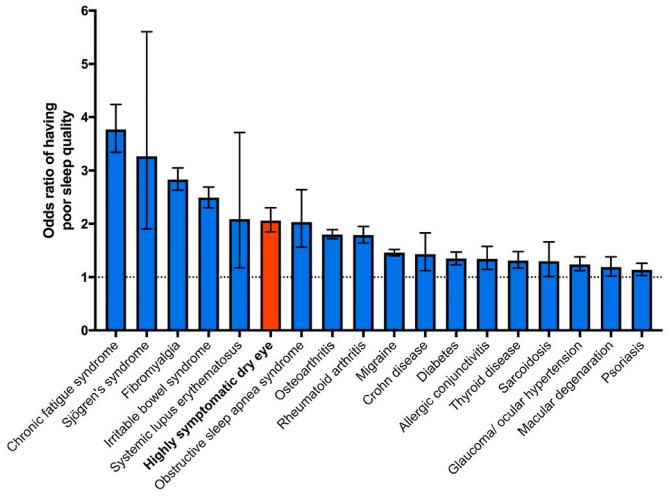

Fig. 1. Odds ratio of having poor sleep quality (PSQI score>5): Comparison of dry eye with frequent symptoms (both irritation and dryness of the eyes either 'often' or 'constantly') with various other chronic disorders. Odds ratio of having poor sleep quality, corrected for age and sex only, calculated separately for each disorder. The error bars represent 95% confidence intervals.

surprisingly, dry eye also leads to lower sleep quality. Ayaki et al. showed that topical treatment of dry eye significantly improved sleep quality in newly diagnosed DED patients [15]. However, the same improvement was not found in established DED patients [15]. In a different study, Ayaki et al. showed that patients with DED had worse sleep quality than patients with other ocular surface diseases, such as allergic conjunctivitis or chronic conjunctivitis [16].

This study is the first population-based study examining the relationship between sleep quality and dry eye using validated questionnaires in a non-Asian population. Due to the large sample size and resulting power of this study, we were able to test the strength of this association in each decades of adult life, in both men and women. There have been several population-based studies conducted in Asia. In one such study from Korea (n = 15,878), short sleep duration (<5 h per night) was associated with a significant 20% higher risk of having DED compared to optimal sleep duration (6–8 h) [41]. This study only looked at duration of sleep, not at other important elements of sleep quality, and did not adjust for medical comorbidities [41]. In a smaller population-based study (n = 2830) conducted in China, Yu et al. found that patients with dry eye were more likely to have sleep dysfunction than the normal population. They used the PSQI and the Ocular Surface Disease Index (OSDI) to assess dry eye symptoms and found an association between total OSDI score and six out of the seven components of the PSQI. Only the use of sleep medication was not found to be significantly linked to total OSDI score. This study excluded patients with comorbidities such as thyroid, psychiatric, and neurological disease, but only corrected for a limited set of other confounding factors [9]. In a population-based study conducted in Singapore (n = 3303), Lim et al. found that daytime sleepiness, clinical insomnia, and short sleep duration (less than 5 h) were associated with dry eye, even after adjusting for socioeconomic and a limited number of medical factors [10]. The results of our study are in agreement with the findings of these previous studies conducted in Asia, but are unique in being able the show the strength of

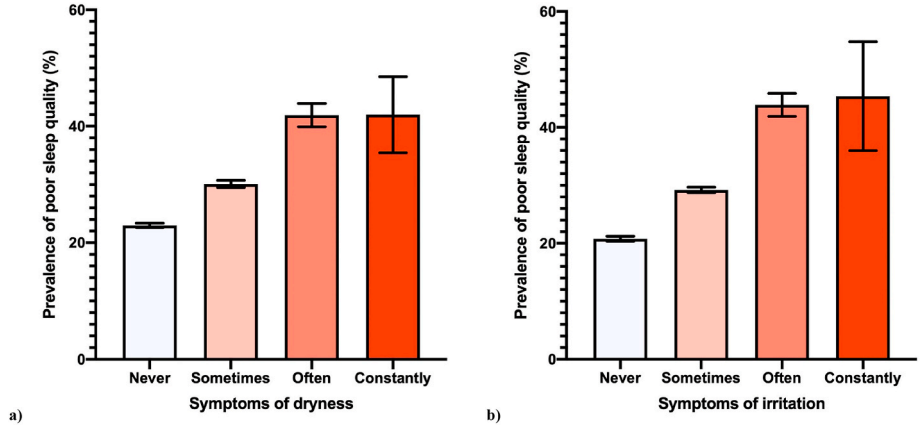

Fig. 2. The prevalence of poor sleep quality (PSQI score>5) for each frequency level of dry eye symptoms: a) symptoms of dryness b) symptoms of irritation. Error bars present 95% confidence intervals.

the relationship between sleep and dry eye, even when taking into account 118 possible confounding medical comorbidities. For example, both poor sleep quality and dry eye have independently been tied to depression and chronic pain syndromes; therefore, adjusting for these medical comorbidities is crucial [6,42–44]. Our results also add that the association between poor sleep quality and dry eye is present across all age groups and sexes. Our findings also show that the link between dry eye and poor sleep quality is not isolated to Asian populations, but may present a global issue.

Strikingly, this study showed that nearly one in two patients with highly symptomatic dry eye had poor sleep quality, which was comparable to chronic disorders such as osteoarthritis and obstructive sleep apnea syndrome. This highlights the impact of DED on a patient's life, but also the need for holistic thinking when treating a patient with DED. It is important to address comorbid conditions of dry eye, such as depression and poor sleep quality [12]. As these conditions are thought to exacerbate one another and contribute to the overall burden of disease, they should be assessed, especially in patients with highly symptomatic dry eye, and whenever possible, treatment options should be considered.

This study has several limitations. First, due to the cross-sectional assessment of dry eye and sleep quality it is impossible to determine causation. To better understand the direction and strength of association, we have corrected for comorbidities and traits associated with dry eye. This approach, however, does not guarantee detection of a causative association, as confounding factors might have been missed and the participants were not followed over time. It is also possible that our adjustments result in over-correction because we cannot disentangle the relationships between sleep quality, comorbidities, and dry eye. It is similarly possible that poor sleep quality might cause several of the comorbidities accounted for rather than resulting from them. Another limitation was that the assessments of sleep quality and dry eye were not conducted at the same time, and that the participants were not tested for signs of dry eye at enrollment in this study. As dry eye is well-known for the discordance between signs and symptoms [1,45], the measurement of clinical signs of dry eye could have provided valuable additional information, as a proportion of cases may not be discovered by symptom questions alone. Several neurosensory and psychosocial factors have been found to impact both the experienced symptom burden of dry eye [44,46,47] and aspects of sleep quality and sleep disturbances [48–50]. These mechanisms may confound the true causal relationship between sleep and dry eye. This study only corrected for the presence of recognized diagnoses such as depression, not for underlying neurosensory and psychological endophenotypes. Furthermore, the WHS questionnaire inquired about the presence of a clinical dry eye diagnosis, past or present, and could therefore include former cases that have been diagnosed in the past and treated with good effect. The true association between poor sleep quality and dry eye might, therefore, be even more pronounced if the assessment of both was conducted at the same time. This is indeed confirmed by our result that patients with current, frequent symptoms of dry eye showed poorer quality of sleep.

There are many strengths of this study exploring the complexity of the relationship between sleep and dry eye. First, the large sample size allowed for novel analyses across age and sex, which underscored the ubiquity of this association. Second, the use of validated questionnaires to assess both dry eye and sleep quality provided reliable and robust data on both outcome variables. Third, in addition to correcting for socioeconomic factors such as income and education, we also took into account 118 possible confounding factors, and corrected for 51 medical comorbidities associated with both dry eye and sleep quality. As several of these conditions are well-established causes of reduced sleep quality, it is vital to adequately account for these factors in epidemiological studies, which has not been done in past studies. Finally, the extensive data on concurrent medical conditions allowed for a novel, direct comparison of the sleep quality in dry eye versus other chronic systemic and eye conditions, showing the clinical relevance of these findings. Combined, these strengths have allowed us to draw new and more reliable conclusions about the association between sleep and dry eye. However, future studies that determine the causality of the link between dry eye and sleep quality are necessary. To develop a clearer idea of the effect of sleep quality on dry eye signs and symptoms, larger, prospective studies focusing on sleep deprivation and dry eye parameters are required. In addition to this, future large-scale epidemiology studies using GWAS outcomes and Mendelian randomization techniques can further clarify the directionality of this association.

5. Conclusion

Poor sleep quality is a serious problem in patients with dry eye. Almost one in two patients with highly symptomatic dry eye are poor sleepers, comparable to that of patients with osteoarthritis or obstructive sleep apnea syndrome. Dry eye is associated with worse outcomes in all quantitative and qualitative aspects of sleep, and this relationship is present in all ages and sexes. This is clinically relevant as poor sleep is linked to severe comorbidities including cardiovascular events and all-cause mortality. Therefore, clinicians should be aware of this relationship and ask about their patients' sleep, especially in highly symptomatic patients. Further prospective studies are needed to determine the directionality of this association and whether sleep hygiene interventions could alleviate dry eye and similarly whether intensive dry eye alleviation strategies could improve sleep quality.

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Appendix A. Supplementary data

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