Relationship Between Sleep and Symptoms of Tear Dysfunction in Singapore Malays and Indians

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Purpose. The purpose of this study was to investigate the association between sleep (duration and quality) and symptoms of dry eye in Singapore Malay and Indian adults.

Methods. This was a prospective cross-sectional study. A total of 3303 subjects aged 40 years and above from two large population-based cohorts, the Singapore Malay Eye Study-2 (n = 1191, 2011–2013) and the Singapore Indian Eye Study-2 (n = 2112, 2013–2015), were included. The presence of symptoms of dry eye was defined as having at least one of six symptoms often or all the time. Sleep questionnaires included the Epworth Sleepiness Scale, Berlin Questionnaire, STOP-bang questionnaire, and Insomnia Severity Index. Poor sleep quality was defined as meeting the respective questionnaire thresholds. General health questionnaires (including sleep duration) and standardized ocular and systemic tests were also used.

Results. Of 3303 participants, 6.4% had excessive sleepiness, 20.5% had high risk for sleep apnea, 2.7% had clinical insomnia, and 7.8% had <5 hours of sleep. These sleep factors were associated with symptoms of dry eye. After adjusting for relevant demographic, medical, and social factors, the following were associated with higher odds of symptoms of dry eye: excessive sleepiness (Epworth Sleepiness Scale: odds ratio [OR] = 1.77 [1.15–2.71]), high risk of sleep apnea (Berlin Questionnaire: OR = 1.55 [1.17–2.07], STOP-Bang Questionnaire: OR = 2.66 [1.53–4.61]), clinical insomnia (Insomnia Severity Index: OR = 3.68 [2.17–6.26]) and <5 hours of sleep (OR = 1.73 [1.17–2.57], reference sleep duration 5–9 hours). Sleep apnea, insomnia, and sleep duration were each shown to be independently associated with symptoms of dry eye.

Conclusion. Short sleep duration and poor quality are both significantly and independently associated with symptoms of dry eye.

Keywords: dry eye syndrome, cross sectional study, population-based study, cohort study, sleep, insomnia, sleep apnea

Dry eye disease (DED) is a multifactorial disease of the ocular surface resulting in ocular discomfort, visual disturbance, and tear film instability.[1] It is a common ocular condition affecting 12.3% of the Singapore population.[2] It has been shown to adversely affect quality of life due to pain, inability to perform activities requiring sustained visual attention (such as reading and driving), and reduced productivity at work.[3] DED is a huge economic burden worldwide, with studies showing that the average annual cost of managing a patient with DED in the United States is USD $783. In 2008, the overall burden of DED for the US healthcare system was USD $3.84 billion.[4] In Singapore, the revenue for dry eye products in one pharmacy alone for the years 2008 and 2009 were USD $1,509,372.30 and USD $1,520,797.80, respectively. Total expenditure per patient visit for these products in 2008 and 2009 were USD $22.11 and USD $23.59, respectively.[5] Symptoms of dry eye such as ocular discomfort, fatigue, and visual disturbance are important manifestations of DED as they significantly affect quality of life and prompt many to seek medical treatment.[3]

Several risk factors of DED have previously been identified by the Beaver Dam Eye Study. Advanced age, female sex, positive arthritis history, positive smoking history, thyroid disease, gout history, and diabetes mellitus have been positively associated with DED, whereas caffeine intake and higher total to high-density lipoprotein cholesterol ratio have been negatively associated with DED.[6]

Sleep is important for both physical and mental health. Sleep insufficiency is associated with a number of chronic diseases such as coronary heart disease, hypertension, and diabetes mellitus.[7]

Recent studies have pointed to a possible relationship between sleep disturbances and dry eye. One general population-based study done in Korea showed that shorter sleep durations were associated with symptoms of dry eye.[8] However, this study used only a single question to determine sleep duration and a single question to evaluate symptoms of

dry eye. Because the relationship between sleep duration and systemic diseases is not linear,[9] it is important to explore quality of sleep in addition to duration. Two other studies, one on high school students in China and another on veterans in America,[10,11] found a positive association between poor sleep quality and symptoms of dry eye. A longitudinal study on veterans in America came to a similar conclusion after a 1-year follow-up.[12] A cross-sectional study on Japanese office workers also showed that poorer sleep quality was associated with a diagnosis of dry eye.[13] Ayaki et al. did a series of three studies on the association of sleep and mood disorders with DED patients and found a significantly higher prevalence of sleep and mood disorders in patients with dry eye.[13–15]

The relationship between sleep and dry eye is important because sleep disorders are an emerging public health issue.[16] In each of the published studies, only a single sleep questionnaire was reported (an unspecified questionnaire, the Pittsburgh Sleep Quality Index, or the Insomnia Severity Index). None of the studies investigated whether sleep apnea, insomnia, and sleep duration are independently associated with dry eye. Additionally, to the best of our knowledge, there are no studies investigating sleep quality and symptoms of dry eye in the Malay or Indian population. The aim of our study is to investigate the relationship between sleep (quality and duration) with symptoms of tear dysfunction in the Malay and Indian populations in Singapore.

Methods

Study Population

This study was based on cross-sectional data from Singapore Malay Eye Study-2 (SiMES-2) and Singapore Indian Eye Study-2 (SINDI-2), two large ongoing population-based cohorts in southwestern Singapore. Singapore is a relatively small equatorial island city (637.5 km^2) with a humid tropical nonseasonal climate with relatively minor monthly temperature fluctuation. The response rates for SiMES-2 and SINDI-2 were 72.1% and 75.5%, respectively. A total of 3303 (1191 Malays, 2112 Asian Indians) subjects from these two studies underwent standardized ocular and systemic tests and answered questionnaires (mean age, 63.5 ± 9.7 years; 52.5% women). All participants provided written informed consent. Our study complied with the tenets of the Declaration of Helsinki on human research and was prospectively reviewed and approved by the SingHealth Centralized Institutional Review Board.

SiMES-2 is a 6-year follow-up study of Singaporean Malay adults aged 46 to 85 years who attended the SiMES-1 clinical examinations in 2004 to 2006. The study design and methodology has been described in detail elsewhere.[17] SINDI-2 is a 6-year follow-up study of Asian Indian adults aged 46 to 86 years who participated in the baseline SINDI in 2007 to 2009. The protocol used in SINDI-2[18] was similar to that of SINDI baseline study. The study design and methodology has been described in detail elsewhere.[18,19]

Outcome Variables

All participants were given the sleep questionnaires, the dry eye questionnaire, and other general health questionnaires. The sleep questionnaires include the Epworth Sleepiness Scale (a measure of daytime sleepiness), the Berlin and STOP-Bang questionnaires (both measures of the risk of obstructive sleep apnea), the Insomnia Severity Index (a measure of insomnia severity),[20–23] and other questions related to sleep-disordered breathing such as previously diagnosed sleep conditions and sleep duration in hours (Fig. 1). Excessive sleepiness was defined as a score of ≥11 out of 24 in the Epworth scale.[24–26] A high risk of sleep apnea on the Berlin questionnaire was defined as a positive answer in at least two categories of questions.[23] On the STOP-Bang questionnaire, high risk of obstructive sleep apnea was defined as a score of 5 to 8, intermediate risk defined as a score of 3 to 4, and low risk defined as a score of 0 to 2.[21,27] Clinical insomnia was defined as a score of 15 to 28 on the Insomnia Severity Index,[20,28,29] and finally a short sleep duration was defined as <5 hours of sleep per day,[30,31] a long sleep duration >9 hours of sleep per day, and a normal sleep duration (reference category) from 5 to 9 hours of sleep per day.[30,32]

The dry eye questionnaire used was based on previous studies,[33–35] initially described in the Salisbury eye evaluation study.[35–37] It included questions of "feeling of dryness," "grittiness," "burning sensation," "redness," "crusting of lashes," and "eyelids getting stuck."[38] The answers were classified into categories never, rarely (at least once in 3 months), sometimes (at least once in a month), often (more than once a month but less than daily), and all the time (at least once daily). The presence of significant symptoms of dry eye was defined as a positive answer (often or all the time) in at least one of the questions.[35–37]

Other data obtained in these cohorts include demographic and socioeconomic status information, as well as systemic and ocular examinations. Details of these procedures have been described elsewhere.[17–19] These variables include age, sex, ethnicity, educational level, household income, housing type, occupation, history of comorbidities (diabetes mellitus, cardiovascular disease, hypertension, asthma, and anxiety/depression), current smoking status, random blood glucose, HbA1c, blood pressure, body mass index, current menstrual status, and medication history.

Statistical Methods

All statistical analyses were performed using STATA statistical software (Version 14.1; StataCorp, College Station, TX, USA). Characteristics of participants with and without symptoms of dry eye were compared using independent *t*-test or χ^2 test for continuous and categorical variables, respectively. Univariate logistic regression was performed to assess the association of demographic and clinical factors with prevalent symptoms of dry eye. The level of significance was at α of 0.05, but the actual *P* values were reported so that readers can perform adjustment for multiple testing if desired. Variables associated with symptoms of dry eye ($P < 0.05$) in univariate analysis were subsequently included in the multiple logistic regression models. Association of sleep quality with symptoms of dry eye was assessed using two multiple logistic regression models; the first model adjusting for age, sex, and ethnicity and the second model further adjusting for relevant covariates (cardiovascular disease, smoking, asthma history, history of anxiety/depression, and use of medications [antidepressants, anticonvulsants, and muscle relaxant medication]) associated with symptoms of dry eye in our univariate analysis. We further examined the consistency of the association between sleep and symptoms of dry eye within the Malay and Indian population separately by performing subgroup analysis stratified by ethnicity.

Results

Table 1 shows the characteristics of the study population and univariate analyses to investigate factors associated with symptoms of dry eye. Initially, there were 3469 participants (2198 Indians and 1271 Malays). However, 12 participants

PART E. OTHER SLEEP-RELATED QUESTIONS

Choose the BEST option for each question. Do not leave any blanks.

NO.	QUESTIONS	CODE	
1	Have you been told by a doctor that you have a sleeping disorder?	Yes……1 No……0 Don't know ……88	**Go to Q4** **Go to Q4**
2	What type of disorder was it?	Sleep apnea……1 Insomnia……2 Others……3 Specify:_____	
3	Have you or are you receiving treatments for it?	Yes……1 No……0	
4	Have any of your family members been told by a doctor that they have a sleeping disorder?	Yes……1 No……0 Don't know……88	**Go to Q6** **Go to Q6**
5	What type of disorder was it?	Sleep apnea ……1 Insomnia …… 2 Others……3 Specify:_____	
6	Have you been told by a doctor that you have a breathing disorder?	Yes……1 No……0 Don't know……88	**Go to Q8** **Go to Q8**
7	What type of disorder was it?	Asthma ……1 Chronic Obstructive Pulmonary Disease (COPD)……2 Other lung diseases ……3 Specify:_____	
8	What is the average number of hours of sleep you get every day?	Hours:	

Figure 1. Additional sleep questionnaire. This is the additional sleep questionnaire used in SiMES-2 and SINDI-2.

were excluded due to missing dry eye data and 154 were excluded due to missing data on covariates (age, sex, ethnicity, cardiovascular disease, asthma, anxiety/depression, smoking, and medication use [antidepressants, anticonvulsants, and muscle relaxant medication]). Of the remaining 3303 participants, 8.0% (265) had symptoms of dry eye. Of the 265 participants with symptoms of dry eye, 58.1% experienced eye dryness, 25.7% experienced a gritty or sandy sensation, 10.2% experienced a burning sensation, 25.0% experienced eye redness, 9.1% experienced crusting on the eye lashes, and 5.3% experienced their eyes getting stuck shut. Figure 2A shows the inverse cumulative frequency of participants with one or more symptoms of dry eye. The majority of these participants may have probable dry eye. Participants with symptoms of dry eye were more likely to be Indians, current smokers, and have a history of cardiovascular disease, asthma, and medication use (antidepressants, anticonvulsants, and muscle relaxant medication). Overall, 6.4% (211) of participants had excessive sleepiness, 20.5% (677) had high risk for sleep apnea (Berlin Questionnaire), 3.5% (115) had high risk for sleep apnea (STOP-Bang Questionnaire), 2.7% (88) had clinical insomnia, and 7.8% (256) had <5 hours of sleep per night.

In univariate analysis, patients with excessive sleepiness, a high risk of sleep apnea, clinical insomnia, or a short sleep duration were more likely to have symptoms of dry eye. The following were found to be associated with symptoms of dry eye: excessive sleepiness (Epworth Sleepiness Scale: odds ratio [OR] = 1.84; 95% confidence interval, 1.21–2.80), a high risk of sleep apnea (Berlin Questionnaire: OR = 1.60 [1.21–2.12]; STOP-Bang Questionnaire: OR = 2.72 [1.62–4.59]), clinical insomnia (Insomnia Severity Index: OR = 4.35 [2.65–7.12]), and short sleep duration <5 hours (OR = 2.04 [1.40–2.98]; Table 2). On a continuous scale, the total scores of the following questionnaires were also found to be significantly associated with symptoms of dry eye (Epworth Sleepiness Scale: OR = 1.06 [1.03–1.09]; STOP-Bang Questionnaire: OR = 1.26 [1.13–1.40]; Insomnia Severity Index: OR = 1.08 [1.05–1.11]). However, the number of hours of sleep between participants with and without symptoms of dry eye on a continuous scale was not significantly different (Tables 1, 2), likely due to the nonlinear relationship of sleep with dry eye.[9]

Univariate analyses were also performed to examine factors associated with poor sleep quality or duration (Supplementary Tables S1–S5). Many of the factors associated with poor sleep quality or duration were also associated with symptoms of dry eye, suggesting potential confounding bias in univariate analyses. These factors were adjusted for in multivariate analyses (Table 3).

Because several factors affecting symptoms of dry eye and sleep were in common, it is important to evaluate in multivariate analyses if these factors are confounding the above associations between sleep and symptoms of dry eye. Table 3 shows the adjusted OR of having symptoms of dry eye

Table 1. Demographic and Systemic Characteristics of Participants With and Without Symptoms of Dry Eye

Variables	Overall (N = 3303)	Dry Eye (n = 265)	No Dry Eye (n = 3038)	P†
Age (y ± SD)	63.32 ± 9.68	64.31 ± 10.09	63.24 ± 9.64	0.085
Sex				
Female (%)	52.53	47.17	53	0.069
Male (%)	47.47	52.83	47	
Ethnicity				
Malay (%)	36.06	28.68	36.7	0.009**
Indian (%)	63.94	71.32	63.3	
Highest education				
Primary or less (%)	57.22	52.45	57.64	0.102
Secondary or more (%)	42.78	47.55	42.36	
Income‡				
<$1000 (%)	53.09	54.65	52.95	0.291
$1000–$2000 (%)	22.19	18.22	22.54	
$2000–$3000 (%)	10	12.4	9.79	
≥$3000 (%)	14.72	14.73	14.72	
Housing type				
1–2 rooms (%)	9.65	7.98	9.79	0.37
3–4 rooms (%)	60.95	59.32	61.09	
≥5 rooms (%)	29.4	32.7	29.11	
Job				
Indoors (%)	96.78	98.28	96.65	0.179
Outdoors (%)	3.22	1.72	3.35	
Low socioeconomic status§ (%)	7.82	6.64	7.92	0.465
Current menstrual status (females only, n = 1735)				
Menopausal (%)	87.14	88	87.07	0.765
Nonmenopausal (%)	12.86	12	12.93	
Cardiovascular disease history, yes (%)	13.62	19.62	13.1	0.003**
Diabetes mellitus history, yes (%)	39.27	40.75	39.14	0.605
Current smoking (%)	14.08	20.75	13.5	0.001**
Random blood glucose (mmol/L ± SD)	7.32 ± 3.50	7.38 ± 3.20	7.31 ± 3.55	0.753
HbA1C (% ± SD)	6.40 ± 1.41	6.43 ± 1.32	6.39 ± 1.42	0.685
Systolic BP (mm Hg ± SD)	138.09 ± 19.41	137.24 ± 18.79	138.17 ± 19.47	0.457
Diastolic BP (mm Hg ± SD)	76.76 ± 9.86	75.97 ± 9.10	76.83 ± 9.93	0.174
BMI (kg/m^2 ± SD)	26.43 ± 4.77	26.48 ± 4.75	26.43 ± 4.77	0.863
BMI categories				
Underweight (BMI < 18.5) (%)	2.56	3.89	2.44	0.33
Normal (18.5 ≤ BMI < 25) (%)	38.73	35.02	39.05	
Overweight (25 ≤ BMI < 30) (%)	39.38	42.02	39.15	
Obese (BMI ≥ 30) (%)	19.33	19.07	19.36	
Hypertension, yes (%)	70.49	72.08	70.36	0.556
Asthma, yes (%)	6.24	9.81	5.92	0.012*
Anxiety/depression				
Not anxious or depressed (%)	66.64	67.92	66.52	0.144
Moderately anxious or depressed (%)	31.7	29.06	31.93	
Extremely anxious or depressed (%)	1.67	3.02	1.55	
Medications				
ACEI (%)	16.02	19.25	15.73	0.135
ARB (%)	9.93	11.32	9.81	0.43
Antidepressants (%)	1.06	3.02	0.89	0.001**
Antihistamines (%)	2.06	2.26	2.04	0.806
Anticonvulsants (%)	1.39	3.4	1.22	0.004**
Muscle relaxants (%)	0.7	2.26	0.56	0.001**
Epworth Sleepiness Scale Total Score				
Normal (%)	93.61	89.43	93.98	0.004**
Excessive sleepiness (%)	6.39	10.57	6.02	
Berlin Questionnaire Total Score				
Low risk (%)	79.5	71.7	80.18	0.001**
High risk (%)	20.5	28.3	19.82	
STOP-bang questionnaire Total Score				
Low (%)	62.1	52.45	62.94	<0.001***
Intermediate (%)	34.43	40.38	33.9	
High (%)	3.48	7.17	3.16	

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Table 1. Continued

Variables	Overall ($N = 3303$)	Dry Eye ($n = 265$)	No Dry Eye ($n = 3038$)	P†
Insomnia Severity Index Total Score				
Below threshold (%)	97.34	91.32	97.86	< 0.001***
Clinical insomnia (%)	2.66	8.68	2.14	
Hours of sleep				
Short: <5 hours (%)	7.75	13.58	7.24	0.001**
Normal: 5–9 hours (%)	90.1	83.4	90.68	
Long: >9 hours (%)	2.15	3.02	2.07	
Sleep hours (h)	6.40 ± 1.40	6.32 ± 1.60	6.40 ± 1.38	0.362

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; BMI, body mass index.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.
† P value was based on χ^2 or t-test for categorical and continuous variables, respectively.
‡ In Singapore dollars.
§ Primary or lower education, individual monthly income <SGD2000, and living in a one- to two-room HDB flat.

(dependent variable) with the sleep questionnaire outcomes as independent variables.

After adjustment for the various factors (age, sex, ethnicity, cardiovascular disease, current smoking status, asthma, anxiety/depression, and use of medications [antidepressants, anticonvulsants, and muscle relaxants]), excessive sleepiness was still associated with symptoms of dry eye (Epworth Sleepiness Scale: OR = 1.77 [1.15–2.71]); a high risk of sleep apnea was still significantly associated with symptoms of dry eye (Berlin Questionnaire: OR = 1.55 [1.17–2.07]; STOP-Bang Questionnaire: OR = 2.66 [1.53–4.61]); clinical insomnia was still associated with symptoms of dry eye (OR = 3.68 [2.17–6.26]); short sleep duration was still associated with symptoms of dry eye (OR = 1.73 [1.17–2.57]).

Figure 2B shows the prevalence of symptoms of dry eye and 95% confidence intervals for different sleep durations. It further reinforces that short sleep duration of <5 hours is associated with a higher prevalence of symptoms of dry eye. A logistic regression model adjusted for age showed that participants with <5 hours of sleep had higher odds of having symptoms of dry eye compared with the other three groups (5, 6–8, and >9 hours of sleep; data not shown).

Sleep duration and quality of sleep may potentially be independent factors affecting symptoms of dry eye. A patient who has insomnia and difficulty falling asleep may compensate by sleeping longer hours. We found that sleep apnea, insomnia, and sleep duration were each independently associated with symptoms of dry eye. When adjusted for sleep duration and insomnia in separate models, sleep apnea was still significantly associated with symptoms of dry eye. Similarly, both insomnia and sleep duration were significantly associated with DES when adjusted for sleep apnea (data not shown). Therefore, the quality and quantity of sleep are each associated with symptoms of dry eye independently. Insomnia and sleep duration were found to be highly correlated and were hence not able to be placed in the same logistic regression model as this violates the independent assumption and leads to collinearity and unreliable estimates.

The above analyses were repeated stratified by ethnicity (Malay or Indian populations), and similar conclusions were found (Supplementary Tables S6 and S7). However, in the Malay population, among the sleep parameters measured, only excessive sleepiness (Epworth Sleepiness Scale) was found to be significantly associated with symptoms of dry eye (OR = 3.45 [1.51–7.87]). In the Indian population, three sleep parameters were associated with symptoms of dry eye. These were sleep apnea (Berlin Questionnaire: OR = 1.55 [1.10–2.19]; STOP-Bang Questionnaire: OR = 2.70 [1.40–5.20]), clinical insomnia (OR = 4.11 [2.32–7.28]), and short sleep duration (OR = 1.82 [1.15–2.88]). The reduction in the number of significant sleep parameters may be related to decreased

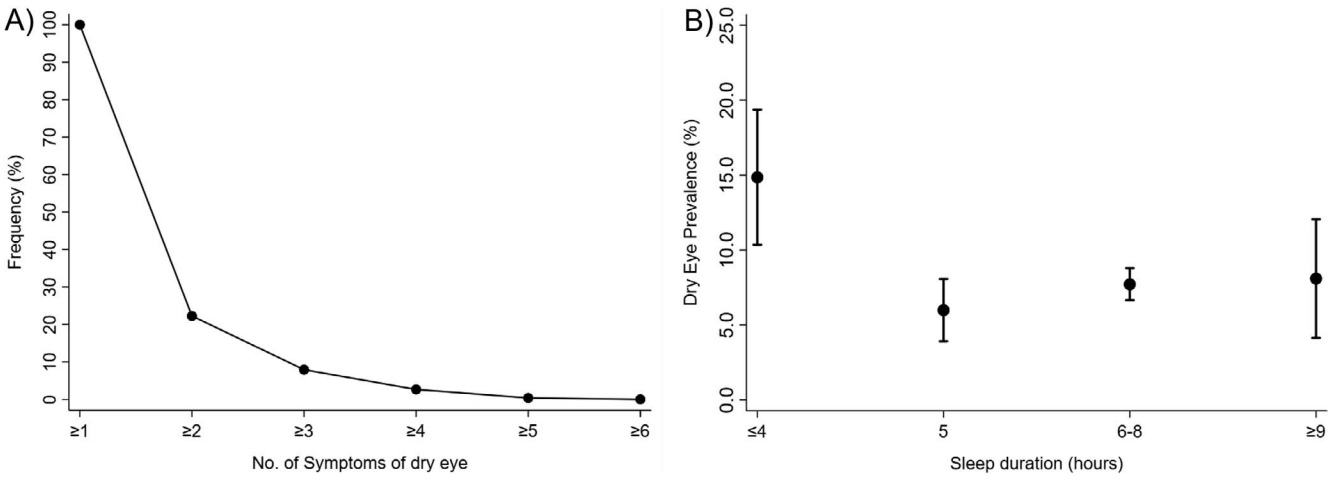

Figure 2. (**A**) Inverse cumulative frequency of the percentage of participants with one or more symptoms of dry eye. (**B**) Age-adjusted prevalence of symptoms of dry eye in various sleep duration categories. Patients with a nightly sleep duration of ≤4 hours had a higher prevalence of symptoms of dry eye compared with patients with a nightly sleep duration of 5 and 6 to 8 hours.

Table 2. Univariate Analysis Showing the Association of Demographic, Systemic, and Sleep Characteristics With Symptoms of Dry Eye

Variables	OR (95% Confidence Interval)
Age	1.01 (1.00–1.02)
Sex	
Female	0.79 (0.62–1.02)
Male	1
Ethnicity	
Malay	1
Indian	1.44 (1.09–1.90)**
Highest education	
Primary or less	1
Secondary or more	1.23 (0.96–1.59)
Income†	
<$1000	1
$1000–$2000	0.78 (0.56–1.10)
$2000–$3000	1.23 (0.82–1.84)
≥$3000	0.97 (0.67–1.41)
Housing type	
1–2 rooms	1
3–4 rooms	1.19 (0.74–1.91)
≥5 rooms	1.38 (0.84–2.26)
Low socioeconomic status‡	0.83 (0.50–1.38)
Cardiovascular disease history, yes	1.62 (1.17–2.23)**
Diabetes mellitus history, yes	1.07 (0.83–1.38)
Current smoking	1.68 (1.23–2.30)**
Random blood glucose	1.01 (0.97–1.04)
HbA1C	1.02 (0.93–1.11)
Systolic BP	1.00 (0.99–1.00)
Diastolic BP	0.99 (0.98–1.00)
BMI	1.00 (0.98–1.03)
BMI categories	
Underweight (BMI < 18.5)	1.77 (0.89–3.56)
Normal (18.5 ≤ BMI < 25)	1
Overweight (25 ≤ BMI < 30)	1.20 (0.89–1.60)
Obese (BMI ≥ 30)	1.10 (0.76–1.58)
Hypertension, yes	1.09 (0.82–1.44)
Asthma, yes	1.73 (1.12–2.66)*
Anxiety/ depression	
Not anxious or depressed	1
Moderately anxious or depressed	0.89 (0.68–1.18)
Extremely anxious or depressed	1.91 (0.89–4.11)
Medications	
ACEI	1.28 (0.93–1.76)
ARB	1.17 (0.79–1.75)
Antidepressants	3.47 (1.56–7.72)**
Antihistamines	1.11 (0.48–2.60)
Anticonvulsants	2.85 (1.36–5.97)**
Muscle relaxants	4.12 (1.61–10.53)**
Epworth Sleepiness Scale Total Score	
Normal	1
Excessive sleepiness	1.84 (1.21–2.80)**
Berlin Questionnaire Total Score	
Low risk	1
High risk	1.60 (1.21–2.12)**
STOP-bang questionnaire Total Score	
Low	1
Intermediate	1.43 (1.10–1.86)**
High	2.72 (1.62–4.59)***
Insomnia Severity Index Total Score	
Below threshold	1
Clinical insomnia	4.35 (2.65–7.12)***
Hours of sleep	
Short: <5 hours	2.04 (1.40–2.78)***
Normal: 5–9 hours	1
Long: >9 hours	1.58 (0.75–3.35)
Sleep hours	0.96 (0.88–1.05)

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; BMI, body mass index.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

† In Singapore dollars.

‡ Primary or lower education, individual monthly income <SGD2000, and living in a one- to two-room HDB flat.

statistical power from the drop in the sample size after stratification.

Discussion

Our results in a population of Singapore Malay and Indian people showed that poor sleep quality (sleep apnea and insomnia) and short sleep duration (<5 hours) were both significantly and independently associated with symptoms of dry eye. The associations are still significant after adjusting for potential confounding variables (age, sex, ethnicity, current smoking status, history of cardiovascular disease, asthma, anxiety/depression, or medication use [antidepressants, anticonvulsants, and muscle relaxant medication]).

Other studies support our results. Lee et al.[8] did a population-based survey with 15,878 subjects in Korea and concluded that shorter sleep durations are associated with symptoms of dry eye.[8] Further studies have been performed on a veteran eye clinic. Ong et al. performed a study on 120 US veterans and concluded that sleep apnea is an important risk factor for symptoms of dry eye,[12] whereas Galor et al. performed a cross-sectional study ($n = 16,862$) on US veterans and concluded that sleep apnea is a risk factor for DED.[10] Ayaki et al. did a series of three studies on eye clinic patients ($n =$ 700–1000) and concluded that sleep and mood disorders are associated with dry eye disease[13–15]; however, sleep results were not adjusted for the depression outcomes, and it is unclear if all the sleep effect is due to the presence of depression.

Results of studies in younger participants are consistent with our findings. Kawashima et al. performed a study on 672 Japanese office workers and concluded that poor sleep quality was associated with dry eye disease.[13] Zhang et al. performed a study on stratified-sampled senior high school students ($n =$ 1902) in China and concluded that poor sleep quality is a significant risk factor for dry eye.[11]

In an interventional study, Makateb et al. showed that occupational factors such as working in a night shift disrupted tear film stability and exacerbated symptoms of dry eye.[39] We did not specifically examine the nature of the work shifts in our sample.

Our findings differ from previous studies in that there are more men (52.7% of population) than women (47.3% of population) with symptoms of dry eye. However, this difference was not statistically significant ($P = 0.068$). Previous analyses of the SiMES-1 population showed significantly more males with symptoms of dry eye than females.[38] In other studies performed outside Singapore, however, there were significantly more women than men with symptoms of dry eye.[8,10,13,40–43] There have been a few studies in the literature

Table 3. Multiple Logistic Regression Analyses Showing Association of Sleep Parameters With Symptoms of Dry Eye

Sleep Parameters	*N*	Dry Eye Prevalence (%)	Age, Sex, Ethnicity Adjusted OR (95% CI)	Multivariable Adjusted OR† (95% CI)
Epworth Sleepiness Scale total score				
Normal	3092	7.66	1	1
Excessive sleepiness	211	13.27	1.78 (1.16–2.71)**	1.77 (1.15–2.71)**
Berlin Questionnaire total score				
Low risk	2626	7.24	1	1
High risk	677	11.08	1.59 (1.20–2.11)**	1.55 (1.17–2.07) **
STOP-Bang Questionnaire total score				
Low	2051	6.78	1	1
Intermediate	1137	9.41	1.34 (1.00–1.80)*	1.29 (0.96–1.73)
High	115	16.52	2.54 (1.47–4.38) **	2.66 (1.53–4.61) **
Insomnia Severity Index				
Below threshold	3215	7.53	1	1
Clinical insomnia	88	26.14	4.33 (2.63–7.14) ***	3.68 (2.17–6.26) ***
Hours of sleep				
Short (<5 hours)	256	14.06	2.00 (1.37–2.93)***	1.73 (1.17–2.57)**
Normal (5–9 hours)	2976	7.43	1	1
Long (>9 hours)	71	11.27	1.53 (0.72–3.25)	1.37 (0.63–2.95)

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

† Model adjusted for age, sex, ethnicity, cardiovascular disease, current smoking status, asthma, anxiety/depression, and use of medications (antidepressants, anticonvulsants, and muscle relaxants).

which report a statistically significant higher prevalence of symptoms of dry eye (Lee et al.)[44] and meibomian gland dysfunction (Viso et al.)[45] in males than females. Our prevalence of symptoms of dry eye (8.0%) is lower than that in several Asian studies (33.7% in a Taiwan study and 21% in a Beijing study).[33,46] This may be due to our unique population (Malays and Asian Indians on a small island).

Although it is currently uncertain exactly how sleep disorders cause dry eye, several potential mechanisms have been proposed. A possible mechanism is the effect of deranged hormones on dry eye. Sleep deprivation causes reduced androgen levels,[47,48] impaired circadian rhythms,[39] and high levels of stress hormones (norepinephrine and cortisol),[49,50] which could possibly decrease tear secretion. It has been postulated that androgens facilitate lacrimal and meibomian gland function,[51] and low androgen levels are thought to increase tear evaporation.[51] This is consistent with the findings that patients with androgen deficiency (congenital androgen insufficiency syndrome[52] or use of antiandrogen medication[53]) have increased symptoms of dry eye. Lacrimal secretion has been shown to follow a circadian rhythm, and as a result, sleep disturbances also may disrupt its regulation.[54] Poor sleep quality, mood disorders, and dry eye have previously been shown to be closely interlinked.[13–15] Sleep and mood disorders could potentially result in symptoms of dry eye as a consequence of hormonal changes such as serotonin, norepinephrine, and dopamine imbalances and disruption of the hypothalamic pituitary axis.

Another possible mechanism is autonomic nervous system dysfunction secondary to poor sleep. Sleep deprivation has been shown to decrease parasympathetic activity,[55] and loss of parasympathetic innervation can lead to rapid reduction in tear flow.[56] Sleep deprivation has been found to be associated with reduced brain-derived neurotrophic factor (BDNF), which could potentially predispose to dry eye.[57,58] A study has shown that a certain single nucleotide polymorphism in the *BDNF* gene was borderline associated with dry eye disease.[58] Finally, sleep deprivation has been shown to reduce tear secretion and increase tear instability,[59] resulting in raised tear osmolarity and dry eye.[1]

Our study is the first general adult population-based study on sleep and symptoms of dry eye outside Korea. It has a large age-stratified sampling frame in southwestern Singapore ($n = 3455$) and involves two unique Asian ethnic groups (Malays and Indians) that have never been evaluated for the relationship between sleep and symptoms of dry eye. Apart from duration of sleep, multiple sleep questionnaires (Epworth Sleepiness Scale, Berlin Questionnaire, STOP-bang Questionnaire, and Insomnia Severity Index) were used to assess sleep quality, which strengthened our results. Our study was also the first to look for an independent association of each of the sleep variables (sleep apnea, insomnia, and sleep duration) with symptoms of dry eye. A limitation of our study is that it is cross-sectional, and cause effect relationships are unable to be determined. As symptoms of dry eye predominantly occur or are aggravated at night,[1,60] it is possible that ocular discomfort secondary to dry eye prevents people from falling asleep. A brief eyelid examination was done to look for meibomitis, blepharitis, ectropion/entropion, ptosis, and lid tumors. However, ocular examination for signs specific to dry eye such as tear breakup time, Schirmer's test, fluorescein staining, and tear osmolarity were not performed. As a result, our findings may be more applicable to patients with symptoms of dry eye rather than a dry eye diagnosis. We also did not confirm the presence of sleep apnea and insomnia by objective clinical measurements.

The clinical significance of our results is that intervention to improve sleep quality and duration could potentially be useful in dry eye patients. Reduction of symptoms of dry eye may then allow improvement of overall quality of life. The current study adds to the existing literature on the importance of sleep intervention in chronic diseases. However, the evidence may need further evaluation in a randomized study. It may be interesting to extend our previous report on anxiety and depression and tear function[61] to a population-based study as well. It is also relevant to investigate whether specific tear neurotransmitter levels are biomarkers for sleep disorders and dry eye.[62]

In conclusion, our results in a population of Singapore Malay and Indian people show that poor sleep quality (sleep apnea and insomnia) and short sleep duration (<5 hours) were

significantly associated with symptoms of dry eye. The individual sleep variables (sleep apnea, insomnia, and short sleep duration) were also shown to be independently associated with symptoms of dry eye.

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