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A multi-institutional cohort study on risk of sleep disorders in dry eyes patients using TriNetX

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To explore the relationship between DED and sleep disorders and examine the impact of DED's duration on sleep disorders. This multi-institutional, retrospective cohort study used the TriNetX database. We recruited participants with and without DED diagnosis from 2004 to 2023. Dry eye patients were propensity-matched to individuals from our non-DED cohort (1:1 ratio) based on variables such as age (every 5 year), sex, ethnicity, race, and relevant comorbidities. The Cox proportional hazards regression model was utilized to assess the impact of variables on sleep disorder risk, reporting hazard ratios (HRs) with 95% confidence intervals (CI). Kaplan-Meier survival analysis and log-rank tests were applied to estimate the cumulative incidence of sleep disorder. A total of 688,413 DED adult patients (64.91% female; mean age at index 56.96 ± 15.93) and 688,413 propensity-matched non-DED comparators (64.92% female; mean age at index 56.96 ± 15.93) were recruited. Our analysis showed an overall increased risk of uveitis among DED patients at 5-year time points (HR = 1.04) and all-year (19 years) follow-up durations (HR = 1.03). We observed a higher risk of sleep apnea in DED individuals irrespective of follow-up intervals. Further analyses revealed this increased risk specifically in those diagnosed with Sjögren syndrome (HR = 1.22). This study highlights the significant link between sleep disorders and DED, emphasizing the role of sleep apnea in DED patients. Aqueous-deficient DED has a more pronounced impact on sleep disturbances compared to evaporative DED, while the influence of DED on non-physiological insomnia may be overstated.

Keywords TriNetX, Dry eye disease, Sleep disorders, Sleep apnea, Retrospective, Propensity score matched

Abbreviations

DED	Dry eye disease
SMD	Standardized mean difference
HRs	Hazard ratios
CI	Confidence interval
KCS	Keratoconjunctivitis sicca
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
HCOs	Healthcare organizations
EMEA	Europe, the Middle East, and Africa
HIPPA	Health Insurance Portability and Accountability Act

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STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
OSA	Obstructive sleep apnea
PSQI	Pittsburgh Sleep Quality Index
HADS	Hospital Anxiety and Depression Scale
CPAP	Continuous positive airway pressure
MGD	Meibomian gland dysfunction

Dry eye disease (DED) is a condition that affects the preocular tear film, resulting from damage to the ocular surface and characterized by symptoms of ocular discomfort. It is also known as keratoconjunctivitis sicca (KCS), sicca syndrome, keratitis sicca, dry eye syndrome (DES), xerophthalmia, dysfunctional tear syndrome, ocular surface disease, or simply dry eyes[1]. The prevalence of this condition ranges from 5 to 50%, with rates potentially reaching up to 75% in individuals over the age of 40, and women being disproportionately affected. In contrast, only 2.7% of younger adults aged 18 to 45 years are likely to develop DED[2]. The economic burden of DED is significant, with annual costs estimated between $687 and $1,267, depending on disease severity, contributing to an overall economic impact of approximately $3.8 billion in the United States[2,3]. These costs encompass expenses related to prescription medications, over-the-counter products, and the placement of punctal plugs[4].

The Tear Film & Ocular Surface Society characterized dry eye as a multifactorial disorder of the ocular surface, characterized by a loss of homeostasis in the tear film and accompanied by ocular symptoms[5]. This condition is associated with inflammation of the ocular surface, hyperosmolarity of the tear film, and neurosensory abnormalities[5,6]. Recent findings indicate that dry eye is an inflammatory disease that shares several characteristics with autoimmune disorders. The pathogenesis of DED may be attributed to stress on the ocular surface, including infection, environmental factors, endogenous stress, genetic factors, and antigens[7,8].

Sleep disorders have been found to have a positive correlation with both the incidence and severity of dry eye, with various risk factors associated with sleep disorders also linked to dry eye conditions[9,10]. Investigating the relationship between sleep disorders and dry eye is crucial for understanding the onset, progression, and management of dry eye conditions. Our research, utilizing the TriNetX database—a comprehensive resource—aims to explore this relationship and examine the impact of the duration of DED on sleep disorders.

Materials and methods

Data source and study design

This multi-institutional retrospective cohort study utilized the TriNetX analytics platform. This federated, international health research platform contains up to 100 million de-identified patient records from 77 healthcare organizations (HCOs) across nine countries. These organizations are part of regional collaborative networks, including those from the United States, Europe, the Middle East, and Africa (EMEA), Latin America, and the Asia-Pacific regions. Specifically, our study primarily utilized the U.S. research network within TriNetX. Furthermore, TriNetX platform strictly adheres to all the standards outlined in Section § 164.514 (b) (1) of the Health Insurance Portability and Accountability Act (HIPAA), as well as ISO 27001:2013. Any output from TriNetX platform can only be presented as aggregate counts and statistical summaries in de-identified formats.

The study adhered to the principles outlined in the Declaration of Helsinki. This study was approved by the Institutional Review Board of the Chung Shan Medical University Hospital Research Ethics Committee (CS2 - 21176). This research followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Study population selection, primary outcomes and measures

The progress of our cohort construction is illustrated in Fig. 1. The study period spanned from 2004 to 2023. The dry eye cohort comprised individuals over 20 years old diagnosed with DED. The index event for this dry eye cohort was established based on an encounter diagnosis derived from the date of the initial assignment of the related diagnostic codes listed below (Table S1):

1) DES (ICD- 10-CM: H04.12),
2) KCS, not specified as Sjögren's (ICD- 10-CM: H16.22),
3) Neurotrophic KCS (ICD- 10-CM: H16.23),
4) Ophthalmia nodosa (ICD- 10-CM: H16.24),
5) Conjunctival xerosis, unspecified (ICD- 10-CM: H11.14),
6) Sjögren syndrome (ICD- 10-CM: M35.0),
7) Meibomian gland dysfunction of eyelid (ICD- 10-CM: H02.88).

Regarding the exclusion criteria, patients with a pre-existing diagnosis before the end date were excluded (Table S2): (1) Other congenital malformations of respiratory system (ICD- 10-CM: G47.411), (2) Narcolepsy with cataplexy (ICD- 10-CM: A15–A19), (3) Smith-Magenis syndrome (ICD- 10-CM: Q93.88), (4) Angelman syndrome (ICD- 10-CM: Q93.51), (5) Huntington's disease (ICD- 10-CM: G10), (6) Schizophrenia (ICD-10-CM: F20), (7) Parkinson's disease (ICD- 10-CM: G20), (8) Pregnant (ICD- 10-CM: Z33), (9) Restless legs syndrome (ICD- 10-CM: G25.81), (10) Periodic limb movement disorder (ICD- 10-CM: G47.61), 11) ADHD (ICD- 10-CM: F90), 12) Sleep-related bruxism (ICD- 10-CM: G47.63), 13) Nocturnal muscle cramps (ICD- 10-CM: G47.62), 14) Sleep terrors (ICD- 10-CM: F51.4), 15) Lewy bodies (ICD- 10-CM: G31.83), 16) Alzheimer's (ICD- 10-CM: G30), 17) Dementia (ICD- 10-CM: F01-F03), 18) Sleep Enuresis (ICD- 10-CM: N39.44), 19) Disorders of thyroid gland (ICD- 10-CM: E00-E07), 20) Depressive disorders (ICD- 10-CM: F32, F33), 21) Anxiety disorders (ICD- 10-CM: F41), and 22) Drug-induced dry eye (RxNorm: 6064, OMOP5179229, 134615).

The non-dry eye cohort was randomly sampled from the TriNetX database of patients who did not meet our inclusion criteria and had no dry eye diagnosis. The index date for the non-dry eye cohort was derived from the

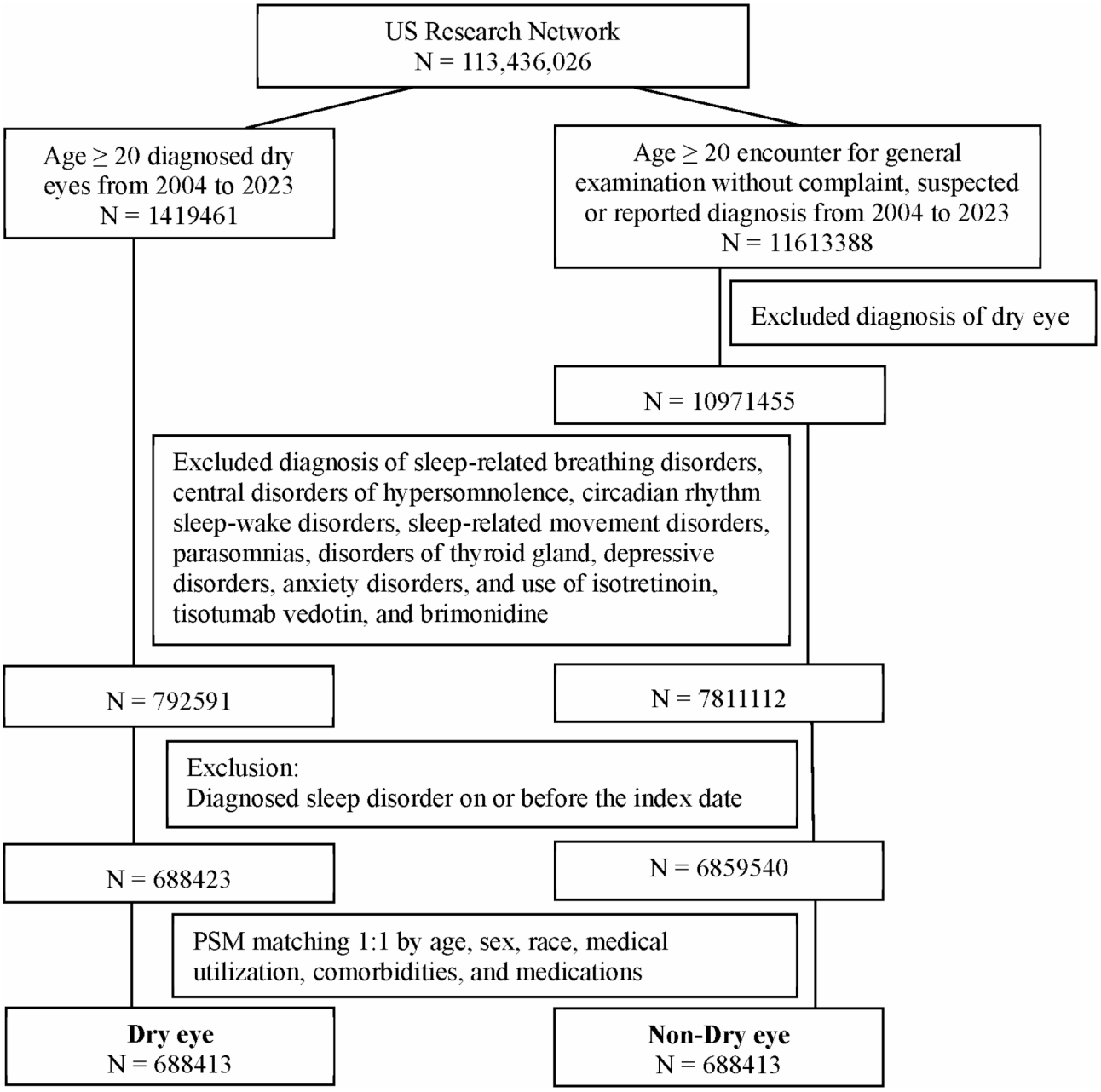

Fig. 1. Flow-chart of patient selection.

first healthcare visit for a general examination without complaints, suspected conditions, or reported diagnoses (ICD- 10-CM: Z00) between 2004 and 2023.

Baseline demographics and comorbidities were obtained one year before the index date. Baseline demographics of interest included sex, age, ethnicity, race, setting of medical utilization. Our propensity score matching was created using a 1:1 ratio, in which dry eye patients were propensity-matched to individuals from our non-dry eye cohort based on variables such as age (every 5 year), sex, ethnicity, race, and relevant comorbidities and medication usage (Table S3).

This study's primary outcome of interest was the first-time encounter diagnosis of ICD- 10 code of sleep disorders after the index date, including sleep disorders (G47), insomnia not due to a substance or known physiological condition (F51.0), other sleep disorders not due to a substance or known physiological (F51.8), and unspecified sleep disorder not due to a substance or known physiological condition (F51.9). We stratified the risk of developing sleep disorders at specific follow-up intervals of 1 year, 2 years, and 5 years, as well as across the entire follow-up duration (19 years). Furthermore, we categorized dry eye conditions into Sjögren syndrome (M35.0) and Meibomian gland dysfunction of the eyelid (H02.88) based on their underlying disease mechanisms: aqueous tear-deficient dry eye and evaporative dry eye[5,11]. Stratified analyses were performed to

evaluate the hazard ratios associated with the risk of sleep disorders, taking into account variables such as sex, age, ethnicity, race, and specific medical comorbidities.

Statistical analyses

The standardized mean differences (SMD) were used to assess the equality of distribution among our baseline variables of interest. Well-matched variables were defined as achieving an SMD value of less than 0.1. The Cox proportional hazards regression analysis was also employed to analyze the effect of different variables on the risk of sleep disorders among the matched cohorts, with their respective 95% confidence intervals (95% CI) and HRs being reported. The Kaplan-Meier survival statistics and the associated log-rank test were also used to calculate the incidence of sleep disorders. Achieving a two-sided p-value of less than 0.05 was defined as statistical significance. All analyses were conducted on the TriNetX online platform, which utilizes R version 4.0.2 as its underlying statistical software, alongside Java version 11.0.16 and Python version 3.7.

Results

Demographic characteristics of the study population

A detailed description of the demographic characteristics of the two cohorts was provided in Table 1. After conducting propensity score matching, the control cohort consisted of 688,413 individuals, while the study cohort included 688,413 individuals (Fig. 1). The gender distribution was equal in both cohorts (SMD < 0.001 for female and male). The mean age at index of both dry-eye group and comparison group were 56.96 (± 15.93). No statistical significance existed in the demographics of ethnicity, race, medical utilization, and comorbidities (SMD < 0.1).

Cox regression analysis on risk of sleep disorder development

The primary outcome of this study was the risk of developing sleep disorders among the dry eye group compared to the non-dry eye group. The risk of developing sleep disorders was assessed at specific follow-up intervals of 1 year, 2 years, and 5 years, as well as across all durations following the index date (Table 2; Fig. 2).

At the 1-year time point following the index date, adult patients (aged over 20 years) with dry eye were associated with no overall increased risk of developing sleep disorders (HR [95% CI] = 0.99 [0.97–1.01]) (Fig. 2). Further stratification revealed an increased risk was particularly evident for developing sleep apnea (G47.3) (HR = 1.06 [1.03–1.09]). Conversely, a lower risk of developing insomnia (G47.0) was observed in the dry eye cohort compared to the non-dry eye cohort (HR = 0.94 [0.92–0.97]). For other types of sleep disorders, adult patients with dry eye showed a lower risk of developing insomnia not due to a substance or known physiological condition (F51.0) (HR = 0.93 [0.88–0.99]), whereas those with dry eye demonstrated a positive association with other sleep disorders not due to a substance or known physiological condition (F51.8) (HR = 1.39 [1.08–1.80]). However, no significant association was found in dry eye patients developing unspecified sleep disorders not due to a substance or known physiological condition (F51.9) (HR = 0.71 [0.39–1.29]).

At the 2-year follow-up, patients with dry eye did not exhibit an overall increased risk of developing sleep disorders compared to the non-dry eye cohort (HR = 1.01 [0.99–1.02]) (Fig. 2). When examining specific categories of sleep disorders, the risk was slightly elevated for general sleep disorders (G47) (HR = 1.02 [1.01–1.04]), reaching statistical significance. In contrast, the risk of insomnia (G47.0) was slightly lower in the dry eye group (HR = 0.97 [0.95–1.00]); however, this association did not reach statistical significance. A significantly increased risk was observed for sleep apnea (G47.3) in the dry eye cohort (HR = 1.10 [1.07–1.12]). Further, dry eye patients had a significantly lower risk of developing insomnia not due to a substance or known physiological condition (F51.0) (HR = 0.95 [0.91–0.99]). However, they showed a markedly higher risk of developing other sleep disorders not due to a substance or known physiological condition (F51.8) (HR = 1.87 [1.50–2.32]). Although an increased risk was also observed for unspecified sleep disorders not due to a substance or known physiological condition (F51.9), the association did not reach statistical significance (HR = 1.57 [0.96–2.57]).

At the 5-year follow-up, patients with dry eye demonstrated an overall increased risk of developing sleep disorders compared to the non-dry eye cohort (HR = 1.04 [1.02–1.05]) (Fig. 2). The risk was significantly elevated for several specific categories of sleep disorders, including general sleep disorders (G47) (HR = 1.05 [1.04–1.06]), insomnia (G47.0) (HR = 1.03 [1.01–1.05]), and sleep apnea (G47.3) (HR = 1.10 [1.09–1.12]). Dry eye patients also exhibited a markedly higher risk of developing other sleep disorders not due to a substance or known physiological condition (F51.8) (HR = 1.70 [1.46–1.98]) and unspecified sleep disorders not due to a substance or known physiological condition (F51.9) (HR = 1.70 [1.21–2.39]). In contrast, no significant association was found between dry eye and insomnia not due to a substance or known physiological condition (F51.0) (HR = 1.01 [0.98–1.04]).

Over the entire follow-up duration, patients with dry eye exhibited an overall increased risk of developing sleep disorders compared to the non-dry eye cohort (HR = 1.03 [1.02–1.04]) (Fig. 2). The risk was significantly higher for general sleep disorders (G47) (HR = 1.04 [1.03–1.05]), insomnia (G47.0) (HR = 1.02 [1.004–1.03]), and sleep apnea (G47.3) (HR = 1.11 [1.10–1.13]). Dry eye patients also had a significantly elevated risk of developing insomnia not due to a substance or known physiological condition (F51.0) (HR = 1.04 [1.01–1.06]), other sleep disorders not due to a substance or known physiological condition (F51.8) (HR = 1.59 [1.41–1.79]), and unspecified sleep disorders not due to a substance or known physiological condition (F51.9) (HR = 1.43 [1.10–1.85]).

Risk of sleep disorder among different subtypes of dry eye

We further divided dry eye disease (DED) into two subtypes based on underlying mechanisms: Sjögren syndrome (M35.0) and meibomian gland dysfunction of the eyelid (H02.88) (Table 3; Fig. 3). Among patients diagnosed with dry eye associated with Sjögren syndrome, we observed an increased risk of developing various types of

	Before PSM			After PSM		
	Dry eye *N* = 688,423	Non-Dry eye *N* = 6,859,540	SMD	Dry eye *N* = 688,413	Non-Dry eye *N* = 688,413	SMD
Age at Index	56.96 ± 15.93	45.67 ± 16.88	0.688	56.96 ± 15.93	56.96 ± 15.93	< 0.001
Sex						
Female	446,864 (64.91)	3,348,222 (48.81)	0.329	446,854 (64.91)	446,884 (64.92)	< 0.001
Male	222,223 (32.28)	3,105,173 (45.27)	0.269	222,223 (32.28)	222,212 (32.28)	< 0.001
Unknown Gender	19,336 (2.81)	406,145 (5.92)	0.153	19,336 (2.81)	19,317 (2.81)	< 0.001
Ethnicity						
Not Hispanic or Latino	515,179 (74.84)	4,376,014 (63.80)	0.241	515,179 (74.84)	515,215 (74.84)	< 0.001
Hispanic or Latino	60,007 (8.72)	423,201 (6.17)	0.097	59,997 (8.72)	59,965 (8.71)	< 0.001
Unknown Ethnicity	113,237 (16.45)	2,060,325 (30.04)	0.326	113,237 (16.45)	113,233 (16.45)	< 0.001
Race						
White	395,795 (57.49)	4,080,780 (59.49)	0.041	395,795 (57.49)	395,796 (57.49)	< 0.001
Black or African American	109,827 (15.95)	916,706 (13.36)	0.073	109,827 (15.95)	121,902 (17.71)	0.047
Asian	43,476 (6.32)	320,140 (4.67)	0.072	43,475 (6.32)	37,684 (5.47)	0.036
American Indian or Alaska Native	2820 (0.41)	21,348 (0.31)	0.016	2819 (0.41)	2866 (0.42)	0.001
Native Hawaiian or Other Pacific Islander	6901 (1.00)	33,299 (0.49)	0.060	6901 (1.00)	6910 (1.00)	< 0.001
Other Race	41,044 (5.96)	324,147 (4.73)	0.055	41,038 (5.96)	34,826 (5.06)	0.040
Unknown Race	88,560 (12.86)	1,163,120 (16.96)	0.115	88,558 (12.86)	88,429 (12.85)	0.001
Medical utilization						
Ambulatory	410,655 (59.65)	2,960,312 (43.16)	0.335	410,645 (59.65)	410,653 (59.65)	< 0.001
Emergency	53,164 (7.72)	370,613 (5.40)	0.094	53,161 (7.72)	45,848 (6.66)	0.041
Inpatient Encounter	51,989 (7.55)	315,733 (4.60)	0.124	51,988 (7.55)	49,807 (7.24)	0.012
Comorbidities						
Hypertensive diseases	129,898 (18.87)	764,495 (11.15)	0.218	129,894 (18.87)	147,595 (21.44)	0.064
Hyperlipidemia	111,986 (16.27)	615,349 (8.97)	0.221	111,985 (16.27)	116,398 (16.91)	0.017
Diabetes mellitus	65,693 (9.54)	300,364 (4.38)	0.204	65,690 (9.54)	58,818 (8.54)	0.035
Overweight and obesity	28,215 (4.10)	200,881 (2.93)	0.064	28,215 (4.10)	30,178 (4.38)	0.014
Ischemic heart diseases	25,763 (3.74)	159,690 (2.33)	0.083	25,763 (3.74)	31,020 (4.51)	0.038
Heart failure	8289 (1.20)	58,243 (0.85)	0.035	8289 (1.20)	12,706 (1.85)	0.052
Tobacco use	4343 (0.63)	46,631 (0.68)	0.006	4341 (0.63)	6565 (0.95)	0.036
Alcohol related disorders	3617 (0.53)	34,411 (0.50)	0.003	3617 (0.53)	3969 (0.58)	0.007
Rheumatoid arthritis with rheumatoid factor	3655 (0.53)	5975 (0.09)	0.080	3655 (0.53)	1302 (0.19)	0.057
Other rheumatoid arthritis	10,575 (1.54)	20,452 (0.30)	0.130	10,575 (1.54)	4224 (0.61)	0.090
Chronic obstructive pulmonary disease	9386 (1.36)	60,279 (0.88)	0.046	9385 (1.36)	12,274 (1.78)	0.034
Chronic fatigue, unspecified	2061 (0.30)	7690 (0.11)	0.041	2061 (0.30)	1131 (0.16)	0.028
Chronic pain, not elsewhere classified	26,369 (3.83)	109,241 (1.59)	0.138	26,368 (3.83)	17,362 (2.52)	0.075
Medications						
Hypnotics and sedatives	51,479 (7.48)	245,752 (3.58)	0.171	51,478 (7.48)	38,058 (5.53)	0.079
Benzodiazepine derivatives	24,423 (3.55)	129,163 (1.88)	0.103	24,423 (3.55)	17,760 (2.58)	0.056
Anticholinergics	11,830 (1.72)	78,575 (1.15)	0.048	11,830 (1.72)	13,574 (1.97)	0.019

Table 1. Demographic characteristics of dry eye and non-dry eye. SMD: Standardized mean difference.

sleep disorders, including overall sleep disorders (HR = 1.22 [1.20–1.25]), general sleep disorders (G47) (HR = 1.26 [1.23–1.29]), insomnia (G47.0) (HR = 1.16 [1.12–1.21]), sleep apnea (G47.3) (HR = 1.41 [1.37–1.46]), insomnia not due to a substance or known physiological condition (F51.0) (HR = 1.10 [1.04–1.17]), and other sleep disorders not due to a substance or known physiological condition (F51.8) (HR = 1.89 [1.42–2.52]). The risk for unspecified sleep disorders not due to a substance or known physiological condition (F51.9) was also elevated, although not statistically significant (HR = 1.59 [0.87–2.92]).

Conversely, patients with dry eye attributed to meibomian gland dysfunction of the eyelid did not exhibit significant associations with most types of sleep disorders. The overall risk of sleep disorders in this group was not elevated (HR = 0.98 [0.95–1.01]), and there was no significant association with general sleep disorders (HR = 0.99 [0.96–1.02]) or insomnia (HR = 0.91 [0.87–0.95]). A modest but statistically significant increase was observed in the risk of sleep apnea (HR = 1.10 [1.06–1.14]), while the associations for insomnia not due to a substance or known physiological condition (HR = 1.04 [0.97–1.12]) and unspecified sleep disorders (HR = 0.64 [0.27–1.51]) were not significant. However, a significantly elevated risk was found for other sleep disorders not due to a substance or known physiological condition (HR = 1.68 [1.14–2.47]).

	No. of event		
	Dry eye (*N* = 688413)	Non-Dry eye (*N* = 688413)	HR (95% C.I.)
All duration			
Sleep disorder (G47, F51.0, F51.8, F51.9)	91,026	97,677	1.03 (1.02–1.04)
G47 Sleep disorders	85,461	90,753	1.04 (1.03–1.05)
G47.0 Insomnia	37,517	40,777	1.02 (1.004–1.03)
G47.3 Sleep apnea	47,902	47,802	1.11 (1.10–1.13)
F51.0 Insomnia not due to a substance or known physiological condition	13,695	14,999	1.04 (1.01–1.06)
F51.8 Other sleep disorders not due to a substance or known physiological condition	657	459	1.59 (1.41–1.79)
F51.9 Sleep disorder not due to a substance or known physiological condition, unspecified	130	101	1.43 (1.10–1.85)
1-yr follow-up duration			
Sleep disorder (G47, F51.0, F51.8, F51.9)	23,608	24,407	0.99 (0.97–1.01)
G47 Sleep disorders	22,130	22,581	1.00 (0.98–1.02)
G47.0 Insomnia	8341	9043	0.94 (0.92–0.97)
G47.3 Sleep apnea	12,166	11,752	1.06 (1.03–1.09)
F51.0 Insomnia not due to a substance or known physiological condition	2234	2452	0.93 (0.88–0.99)
F51.8 Other sleep disorders not due to a substance or known physiological condition	136	100	1.39 (1.08–1.80)
F51.9 Sleep disorder not due to a substance or known physiological condition, unspecified	18	26	0.71 (0.39–1.29)
2-yr follow-up duration			
Sleep disorder (G47, F51.0, F51.8, F51.9)	40,141	39,561	1.01 (0.99–1.02)
G47 Sleep disorders	37,600	36,505	1.02 (1.01–1.04)
G47.0 Insomnia	14,429	14,715	0.97 (0.95–1.00)
G47.3 Sleep apnea	20,903	18,973	1.10 (1.07–1.12)
F51.0 Insomnia not due to a substance or known physiological condition	4262	4454	0.95 (0.91–0.99)
F51.8 Other sleep disorders not due to a substance or known physiological condition	233	124	1.87 (1.50–2.32)
F51.9 Sleep disorder not due to a substance or known physiological condition, unspecified	41	26	1.57 (0.96–2.57)
5-yr follow-up duration			
Sleep disorder (G47, F51.0, F51.8, F51.9)	66,167	65,949	1.04 (1.02–1.05)
G47 Sleep disorders	61,943	60,956	1.05 (1.04–1.06)
G47.0 Insomnia	25,926	25,978	1.03 (1.01–1.05)
G47.3 Sleep apnea	33,938	31,799	1.10 (1.09–1.12)
F51.0 Insomnia not due to a substance or known physiological condition	8545	8796	1.01 (0.98–1.04)
F51.8 Other sleep disorders not due to a substance or known physiological condition	448	272	1.70 (1.46–1.98)
F51.9 Sleep disorder not due to a substance or known physiological condition, unspecified	87	53	1.70 (1.21–2.39)

Table 2. Risk of sleep disorder exposed to dry eye compared to non-dry eye.

Stratified analysis between patients with and without dry eye disease

We conducted stratified analyses across various demographic, comorbidity, and medication-related categories (Table 4; Fig. 4). Compared to individuals without dry eye, patients with dry eye exhibited higher risks of developing sleep disorders across most subgroups. In terms of age, elevated risks were observed consistently in the 20–49 (HR = 1.02 [1.002–1.04]), 50–59 (HR = 1.02 [1.003–1.04]), and 60–69 (HR = 1.03 [1.01–1.04]) age groups, while the association was not statistically significant in those aged ≥ 70 (HR = 0.98 [0.96–1.00]).

Stratified by sex, females with dry eye had a significantly increased risk (HR = 1.03 [1.01–1.04]), whereas the association was not significant in males (HR = 0.99 [0.98–1.01]). Regarding ethnicity, a small but significant association was observed in the non-Hispanic or Latino group (HR = 1.01 [1.002–1.02]), while no significant association was found among Hispanic or Latino individuals (HR = 0.97 [0.94–1.01]).

Across racial groups, higher risks were observed in White (HR = 1.02 [1.01–1.04]), Asian (HR = 1.03 [0.99–1.07]), and Native Hawaiian or Other Pacific Islander individuals (HR = 1.23 [1.14–1.33]). No significant associations were observed among Black or African American (HR = 0.99 [0.97–1.01]) and American Indian or Alaska Native individuals (HR = 1.01 [0.88–1.16]).

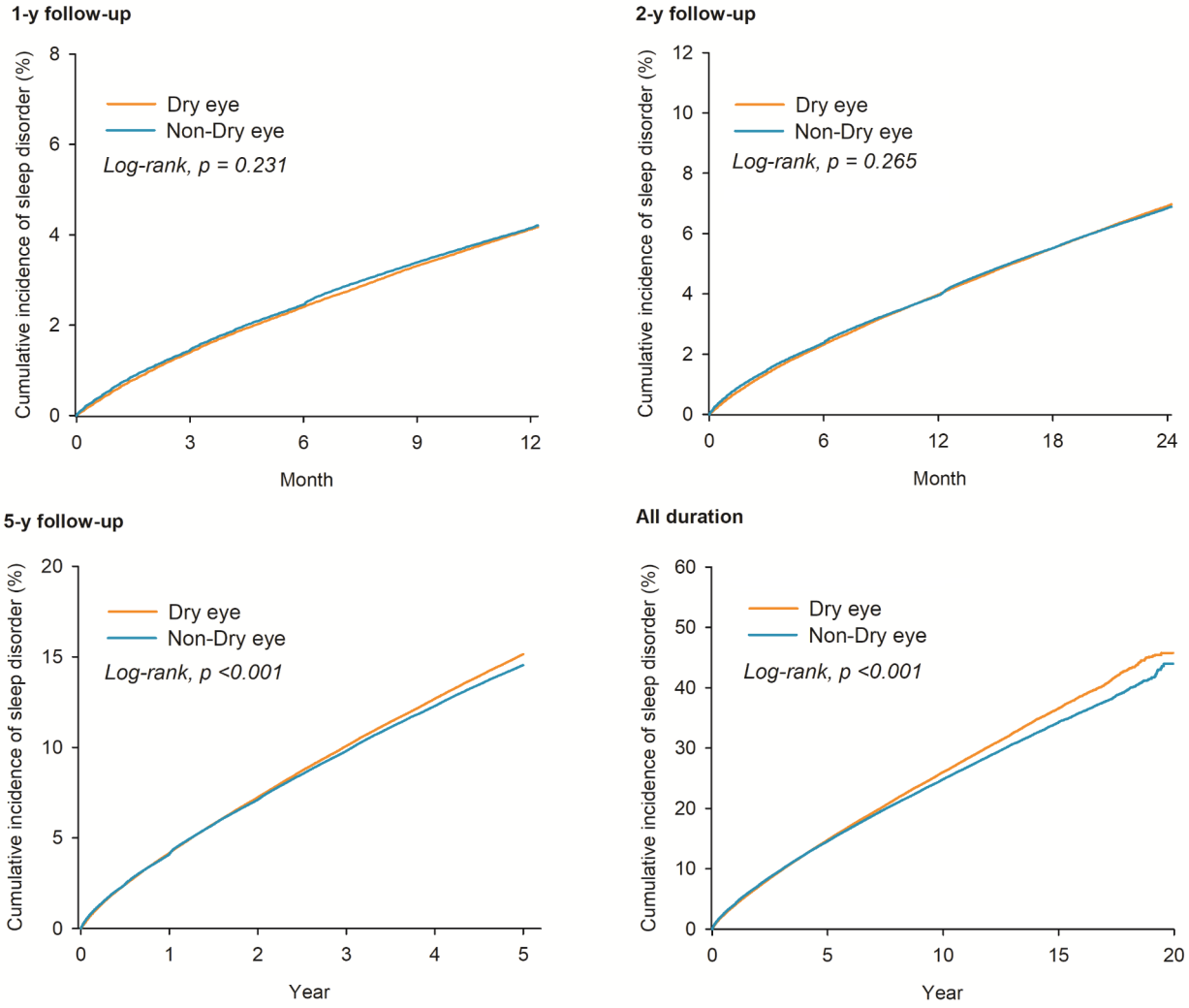

Fig. 2. Kaplan-Meier analyses for risk of sleep disorder.

Within comorbidity subgroups, dry eye was associated with significantly increased risks of sleep disorders in individuals with hypertensive diseases (HR = 1.10 [1.08–1.12]), hyperlipidemia (HR = 1.11 [1.09–1.13]), diabetes mellitus (HR = 1.05 [1.03–1.08]), overweight and obesity (HR = 1.06 [1.02–1.10]), ischemic heart disease (HR = 1.14 [1.09–1.18]), heart failure (HR = 1.12 [1.05–1.20]), tobacco use (HR = 1.17 [1.05–1.29]), and alcohol-related disorders (HR = 1.16 [1.04–1.30]). Elevated risks were also seen in those with chronic obstructive pulmonary disease (HR = 1.09 [1.02–1.15]). In contrast, associations with rheumatoid arthritis (HR = 1.03 [0.97–1.09]), chronic fatigue (HR = 1.10 [0.96–1.26]), and chronic pain not elsewhere classified (HR = 1.03 [0.99–1.08]) did not reach statistical significance.

Additionally, we explored sleep disorder risk in relation to medication use. Dry eye patients exhibited a marginally increased risk among users of hypnotics and sedatives (HR = 0.99 [0.96–1.01]) and benzodiazepine derivatives (HR = 1.02 [0.98–1.06]), though neither association was statistically significant. However, a significant association was observed in patients using anticholinergic medications (HR = 1.06 [1.003–1.12]).

Discussion

The relationship between sleep disorders and DED is increasingly acknowledged, highlighting the complex interactions between physiological and psychosocial factors. To the best of our knowledge, this is currently the only large-scale, multicenter cohort study that extensively explores the relationship between these two conditions.

Novel findings and clinical implications

Our study indicates that when defined as general sleep disorders, DED does significantly increase the risk of sleep disorders. However, this association is not particularly strong, as it showed significant differences at the 5-year and overall durations, but a non-significant relationship was observed at 1-year and the 2-year follow-up.

	Dry eye		Non-Dry eye		
	N	No. of event	N	No. of event	HR (95% C.I.)
Sjögren syndrome (M35.0)					
Sleep disorder (G47, F51.0, F51.8, F51.9)	95,804	14,307	95,804	13,186	1.22 (1.20–1.25)
G47 Sleep disorders	95,804	13,472	95,804	12,098	1.26 (1.23–1.29)
G47.0 Insomnia	95,804	6021	95,804	5789	1.16 (1.12–1.21)
G47.3 Sleep apnea	95,804	7531	95,804	6000	1.41 (1.37–1.46)
F51.0 Insomnia not due to a substance or known physiological condition	95,804	2128	95,804	2201	1.10 (1.04–1.17)
F51.8 Other sleep disorders not due to a substance or known physiological condition	95,804	127	95,804	74	1.89 (1.42–2.52)
F51.9 Sleep disorder not due to a substance or known physiological condition, unspecified	95,804	25	95,804	18	1.59 (0.87–2.92)
Meibomian gland dysfunction of eyelid (H02.88)					
Sleep disorder (G47, F51.0, F51.8, F51.9)	82,119	8884	82,119	12,452	0.98 (0.95–1.01)
G47 Sleep disorders	82,119	8339	82,119	11,601	0.99 (0.96–1.02)
G47.0 Insomnia	82,119	3253	82,119	5102	0.91 (0.87–0.95)
G47.3 Sleep apnea	82,119	4899	82,119	6241	1.10 (1.06–1.14)
F51.0 Insomnia not due to a substance or known physiological condition	82,119	1217	82,119	1849	1.04 (0.97–1.12)
F51.8 Other sleep disorders not due to a substance or known physiological condition	82,119	58	82,119	52	1.68 (1.14–2.47)
F51.9 Sleep disorder not due to a substance or known physiological condition, unspecified	82,119	10	82,119	15	0.64 (0.27–1.51)

Table 3. Risk of sleep disorder among different subtypes of dry eye.

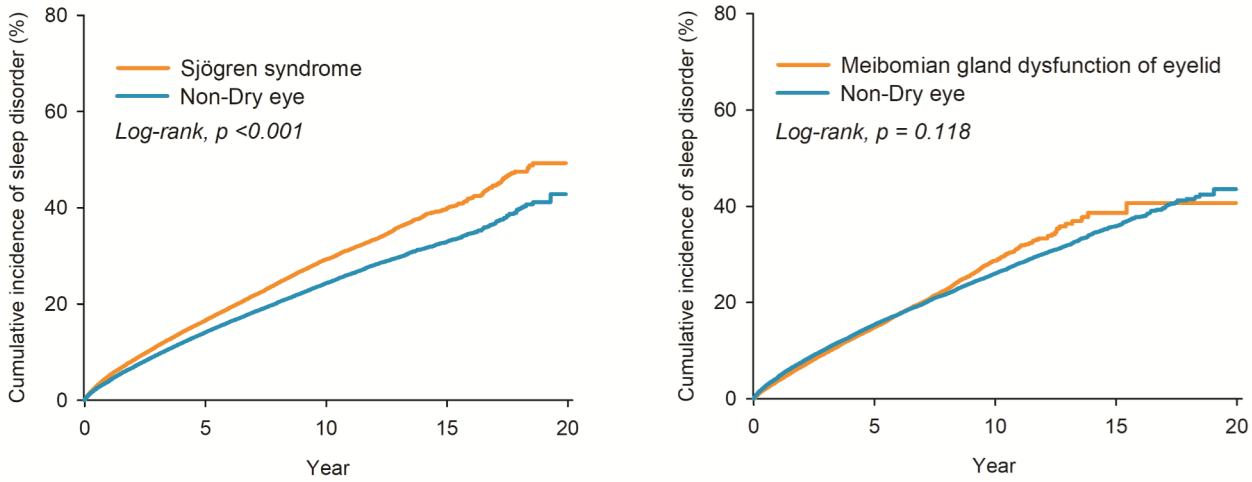

Fig. 3. Kaplan-Meier analyses for risk of sleep disorder among different subtypes of dry eye.

The traditional perspective posits that insomnia and DED are closely interconnected. Insomnia is believed to exacerbate symptoms of eye dryness, while dry eye conditions may, in turn, aggravate insomnia, thereby establishing a detrimental cycle. However, our findings indicate no significant association between DED and insomnia, nor between insomnia not due to a substance or known physiological condition. We speculated on the underlying interactions of insomnia that affect our research analysis. Insomnia is a multifactorial condition, comprising psychological issues, behavioral problems, fatigue, and personal factors such as substance abuse, among others[12]. The various causes of insomnia could not be further delineated within our study population because our research relied on database analysis, and the selection of study participants was based on predefined diagnostic codes.

Recent evidence suggests that the use of sedative medications is associated with an increased risk of DED. Furthermore, depression, which is closely linked to DED, is a common contributor to insomnia. This association was not observed in our study cohort. We believe our study underscores that the role of DED in primary or non-physiologically induced insomnia may have been overemphasized[13,14]. In reality, its impact appears minimal. Previous research has often relied on sleep quality assessments, such as Pittsburgh Sleep Quality Index (PSQI), to evaluate the relationship between DED and insomnia[13–17]. However, PSQI scores primarily assess overall sleep

	Dry eye		Non-Dry eye		
	N	No. of event	N	No. of event	HR (95% C.I.)
Age					
20–49	204,626	22,275	204,626	25,068	1.02 (1.002–1.04)
50–59	139,149	20,437	139,149	22,370	1.02 (1.003–1.04)
60–69	183,123	27,343	183,123	28,260	1.03 (1.01–1.04)
≥ 70	166,216	21,005	166,216	21,487	0.98 (0.96–1.00)
Sex					
Female	354,024	44,433	354,024	47,214	1.03 (1.01–1.04)
Male	224,134	30,406	224,134	33,724	0.99 (0.98–1.01)
Ethnicity					
Not Hispanic or Latino	465,854	66,311	465,854	71,279	1.01 (1.002–1.02)
Hispanic or Latino	57,015	7030	57,015	7098	0.97 (0.94–1.01)
Race					
White	405,646	56,769	405,646	61,684	1.02 (1.01–1.04)
Black or African American	105,759	15,410	105,759	15,911	0.99 (0.97–1.01)
Asian	44,490	4272	44,490	4611	1.03 (0.99–1.07)
American Indian or Alaska Native	2697	379	2697	379	1.01 (0.88–1.16)
Native Hawaiian or Other Pacific Islander	6577	1525	6577	1210	1.23 (1.14–1.33)
Hypertensive diseases	130,935	25,953	130,935	23,993	1.10 (1.08–1.12)
Hyperlipidemia	112,579	21,496	112,579	20,324	1.11 (1.09–1.13)
Diabetes mellitus	62,916	12,115	62,916	11,729	1.05 (1.03–1.08)
Overweight and obesity	30,832	7100	30,832	6549	1.06 (1.02–1.10)
Ischemic heart diseases	24,890	5315	24,890	4622	1.14 (1.09–1.18)
Heart failure	8664	1974	8664	1652	1.12 (1.05–1.20)
Tobacco use	4099	820	4099	720	1.17 (1.05–1.29)
Alcohol related disorders	3480	681	3480	587	1.16 (1.04–1.30)
Rheumatoid arthritis	11,609	2227	11,609	2130	1.03 (0.97–1.09)
Chronic obstructive pulmonary disease	9195	2235	9195	2017	1.09 (1.02–1.15)
Chronic fatigue, unspecified	1904	430	1904	413	1.10 (0.96–1.26)
Chronic pain, not elsewhere classified	24,483	4898	24,483	4727	1.03 (0.99–1.08)
Hypnotics and sedatives	48,799	9213	48,799	8993	0.99 (0.96–1.01)
Benzodiazepine derivatives	22,860	4632	22,860	4665	1.02 (0.98–1.06)
Anticholinergics	11,000	2490	11,000	2262	1.06 (1.003–1.12)

Table 4. Stratification analysis of risk of sleep disorder among different groups.

disturbances rather than specifically addressing primary insomnia. If the observed relationship between DED and sleep disorders is largely influenced by stronger associations, such as those with obstructive sleep apnea (OSA), and prior studies did not account for these distinctions, it could explain the discrepancies in our findings.

The risk of developing sleep apnea among patients with DED differed significantly across all time points, aligning with findings from current studies[18,19]. However, establishing the causality of this association remains challenging. Current evidence suggests that OSA may elevate the risk of DED, likely through a complex interplay of multiple factors. Aqueous-deficient DED is characterized by reduced tear production, whereas evaporative DED is associated with abnormalities in the lipid layer[5,11]. In OSA patients, the condition can lead to alterations in the meibomian glands. Studies have shown that OSA patients frequently exhibit structural and functional alterations in the meibomian glands, which contribute to dysfunction of the lipid layer[20,21]. Additionally, the improper use of continuous positive airway pressure (CPAP) can worsen DED by increasing air circulation around the eyes, leading to accelerated tear evaporation and promoting evaporative DED[22,23]. Lastly, floppy eyelid syndrome, a common complication of OSA, disrupts tear film dynamics and further contributes to an increased rate of tear evaporation[24].

Another perspective suggests that the incidence of OSA is elevated in patients with primary Sjögren's syndrome, possibly due to the associated lymphocytic infiltration[25]. This infiltration affects the structure of the airway glands, leading to drying of the entire airway mucosa and promoting upper airway collapse. A study by Karabul et al. found that 84% of Sjögren's syndrome patients had OSA, a notably high figure[26]. Two other studies reported rates of 28.5% and 64%, respectively[27,28]. Therefore, the relationship between DED and OSA may also be explained by the shared risk factor of xerostomia.

The two main types of DED are aqueous-deficient dry eye and evaporative dry eye. Distinguishing between these two underlying causes is crucial, as they often coexist. In our study, we aimed to differentiate these two types using ICD codes for Sjögren's syndrome and meibomian gland dysfunction (MGD), leading to a novel conclusion: Sjögren's syndrome, or aqueous-deficient dry eye, appears to have a significantly greater impact

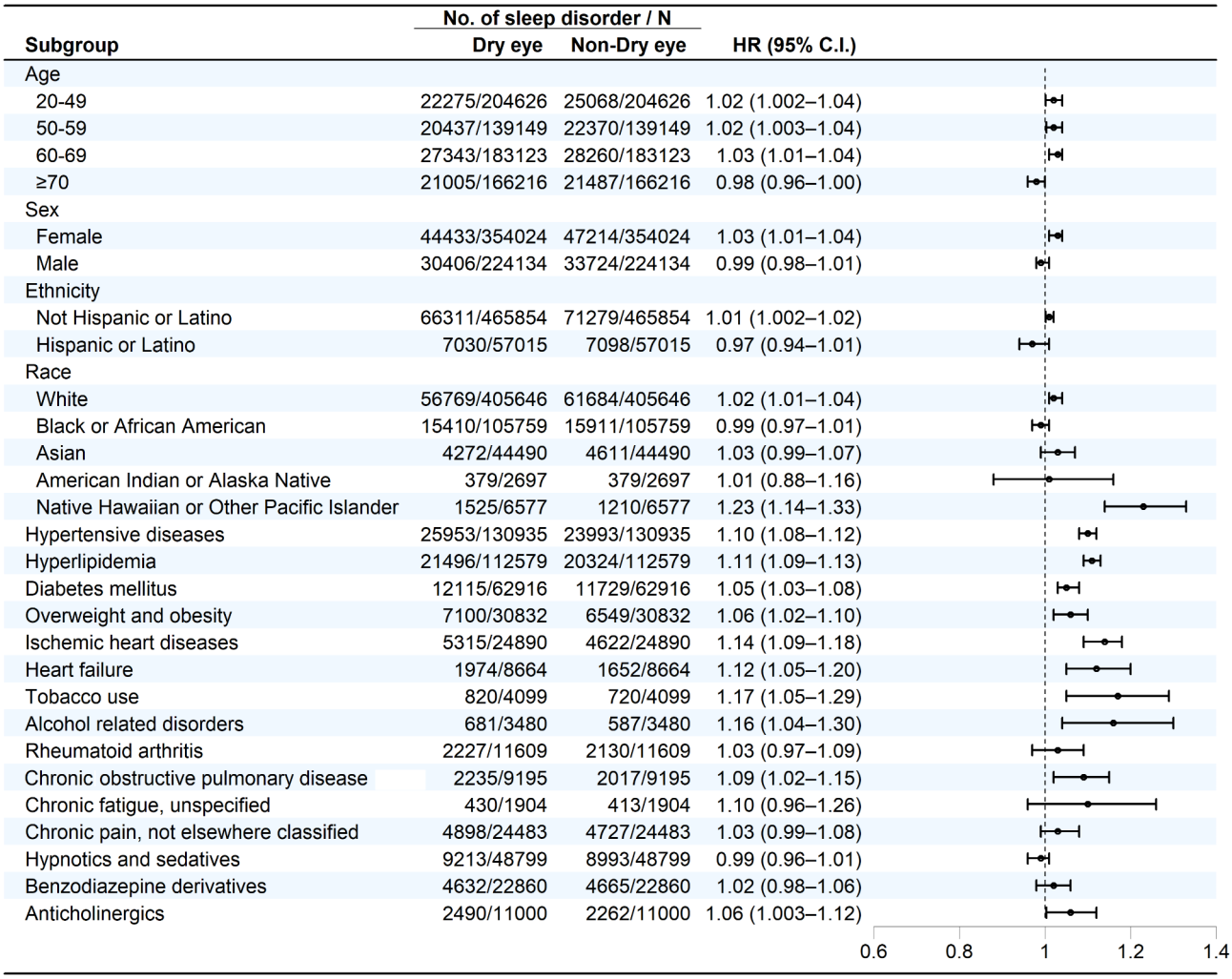

Fig. 4. Forest plot for stratification analysis of risk of sleep disorder.

on sleep disturbances than evaporative dry eye or MGD. Although associations between Sjögren's syndrome and other diseases or environmental factors have been reported[29–31], the specific relationship identified in our study has not been emphasized in previous research. Currently, sleep disturbances are commonly reported in primary Sjögren's syndrome patients and sleep quality is lower in these patients than in healthy controls[32]. We propose that the discrepancy may be attributed to several factors. First, as previously mentioned, a strong correlation existed between sleep disorders, depression, and the severity of DED and Sjögren's syndrome, which may significantly influence the development of sleep disturbances. In contrast, the comorbidities associated with MGD seem to be more straightforward and less impactful on sleep. Secondly, the timing of symptoms may play a role. In Sjögren's syndrome, tear protection diminishes throughout the day due to evaporation, often resulting in the most severe symptoms at night[33]. Conversely, in MGD, the lack of blinking during prolonged sleep prevents the meibomian glands from secreting lipids, leading to discomfort that peaks in the morning. This discomfort is typically alleviated through continuous blinking during the day. These differences in symptom patterns may explain why aqueous-deficient dry eye is more likely to contribute to sleep disturbances.

In the stratification analysis of the risk of sleep disorders among different groups, there were significant differences in almost all groups, regardless of age, gender, race, or comorbidities. The only group that did not show a significant difference was American Indian or Alaska Native, which is likely due to the small sample size. This suggests that the association between DED and sleep disorders is overall and not specific to any population. This is consistent with previous research findings. If we examine the differences between the groups, we observe that the relationship between DED and sleep disorders is stronger in younger individuals compared to older adults. Similarly, the association is also stronger in females compared to males. Additionally, among those with tobacco use, the correlation between DED and sleep disorders is the most pronounced, with a hazard ratio of 1.31. In the study by Ayaki et al., both PSQI and Hospital Anxiety and Depression Scale (HADS) scores were poorer in male and female dry eye patients[10,13]. While the PSQI scores were similar between genders, the HADS scores were lower in women. This aligns with our findings: although both genders are affected, women seem to be more significantly impacted. Even more interestingly, Ayaki et al. noted that the decrease in HADS scores was

more severe in younger women with DED compared to older women[10]. This is consistent with the conclusions drawn from our age-group analysis.

Disruptions in circadian rhythm have emerged as a significant factor contributing to the pathogenesis of DED, with growing evidence indicating that altered sleep-wake cycles can influence ocular surface homeostasis through both physiological and behavioral mechanisms[34–36]. Individuals with evening-type circadian preferences (E-types), who typically experience poor sleep quality, increased insomnia symptoms, and heightened psychological distress, are disproportionately affected by DED, potentially due to overlapping neurochemical and metabolic pathways[37]. Notably, serotonin (5-hydroxytryptamine, 5-HT), a key neurotransmitter involved in circadian regulation[38], has been implicated in the sensitization of nociceptors and is found at elevated levels in the tear fluid of patients with symptomatic aqueous-deficient DED, suggesting a neuroinflammatory link[39]. Furthermore, circadian misalignment is associated with systemic metabolic disorders—such as obesity and diabetes—that are independently correlated with DED. Behavioral traits commonly observed in E-type individuals, such as excessive nighttime screen exposure and increased tobacco use, further exacerbate tear film instability and oxidative stress on the ocular surface, aggravating DED symptoms[40,41]. Collectively, these findings underscore a complex interplay between circadian rhythm disturbances and DED, mediated through neurochemical, metabolic, and behavioral pathways, warranting integrated therapeutic approaches that address both ocular and systemic circadian health[42].

Strengths and limitations

Our study has several strengths. First, it is the first large-scale database study to encompass a cross-racial and cross-national population. Additionally, in analyzing sleep disorders, we rigorously controlled for the potential influence of psychiatric conditions and substance use disorders by using ICD codes, rather than relying solely on sleep quality scores, thereby minimizing potential confounding factors. We also conducted extensive subgroup analyses, distinguishing between insomnia and OSA, and found that the impact of insomnia on sleep quality may have been overestimated in previous studies. Moreover, we categorized DED based on its underlying mechanisms and highlighted the significant association between Sjögren's syndrome and sleep disorders, addressing an important gap in prior research.

Our study has several limitations, primarily related to the constraints of using ICD codes. We established a positive association between OSA and DED; however, determining causality remains challenging. It is unclear whether OSA directly causes DED, whether both conditions share a common underlying cause, such as Sjögren's syndrome, or if other mechanisms are involved. Additionally, we could not assess the role of CPAP therapy—a well-recognized contributor to DED—in our study. Other limitations that arise from TriNetX database itself should be mentioned. This database can only provide information on ethnicity or race and does not disclose the proportion of non-U.S. patients. Our study utilized de-identified patient records primarily from HCOs in the United States; therefore, any extrapolation of our results should be approached with caution. Regarding the stratification analyses, hazard ratios across different strata should not be directly compared, as multiple comparison corrections—such as the Bonferroni adjustment—are not available on the TriNetX platform. Consequently, it is not possible to ascertain whether the differences in risk across demographic subgroups are statistically significant. The potential for Type I error persists. In practice, the results from our stratification analyses should be interpreted as exploratory findings.

Furthermore, while insomnia, dry eye, and depression are known to be interrelated, our analysis did not consider depression, which could serve as an important confounding factor. This omission limits our ability to fully understand the indirect pathways linking these conditions. Regarding the mechanisms underlying excessive evaporation in DED, multiple potential causes exist. Although MGD of the eyelid is a common mechanism, relying solely on it to explain the impact of excessive evaporation on insomnia may be overly simplistic and may not encompass the broader spectrum of contributing factors. In our study, Sjögren's syndrome was used as a surrogate marker for aqueous-deficient dry eye (ADDE). However, recent research has shown that patients with Sjögren's syndrome exhibit more severe meibomian gland destruction in the upper eyelid compared to non-Sjögren's syndrome patients[43]. Since MGD is also a significant contributor to Sjögren's syndrome–associated dry eye, some patients may have been misclassified as having ADDE when their symptoms were primarily related to MGD[44]. This misclassification introduces bias into our study.

Lastly, we did not investigate potential dose-dependent relationships. For instance, analyzing the severity of DED in relation to sleep disorders, including the use of sleep medications, could yield more nuanced insights. Addressing these limitations and examining these factors in future research could enhance our understanding of the complex interplay between DED and sleep disorders.

Conclusions

The relationship between sleep disorders and DED is increasingly acknowledged. This study underscores the importance of sleep apnea development in patients diagnosed with DED. Furthermore, the influence of DED on primary or non-physiologically induced insomnia has been overstated. Notably, aqueous-deficient dry eye appears to exert a significantly greater impact on sleep disturbances compared to evaporative dry eye.

Data availability

The TriNetX platform is a fully de-identified, multinational, cloud-based database that complies with all relevant standards outlined in Section §164.514(b)(1) of the Health Insurance Portability and Accountability Act (HIPAA) as well as ISO 27001:2013. Due to privacy restrictions, data from the TriNetX database is not publicly available. However, the population-level aggregate and de-identified data supporting the findings of this study can be accessed upon reasonable requests to the TriNetX administrators through their website (https://trinetx.c

om/) or by contacting them directly at Privacy@TriNetX.com. Alternatively, the corresponding author can also be reached at doctoraga@gmail.com.

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Author contributions

BQW, HTK, AYH, YCS, NYH, CTL, HT, CCC, CJL, HSC, YHW, YYT, MYH, JCCW wrote and edited the main text of the paper.BQW, HTK, AYH, YCS, NYH, CTL, HT, CCC, CJL, HSC, YHW, YYT, MYH, JCCW participated in the design of the study and drafting of the paper.BQW, HTK, AYH, YCS, NYH, CTL, HT, CCC, CJL, HSC, YHW, YYT, MYH, JCCW designed, discussed, edited and guided the overall process of the paper.BQW, HTK, AYH, YCS, NYH, CTL, HT, CCC, CJL, HSC, YHW, YYT, MYH, JCCW contributed to the drafting of the paper. BQW, HTK, AYH, YCS, NYH, CTL, HT, CCC, CJL, HSC, YHW, YYT, MYH, JCCW contributed to the design of the study.BQW, HTK, AYH, YCS, NYH, CTL, HT, CCC, CJL, HSC, YHW, YYT, MYH, JCCW provided valuable insight and contributed to the drafting of the paper.All authors (BQW, HTK, AYH, YCS, NYH, CTL, HT, CCC, CJL, HSC, YHW, YYT, MYH, JCCW) contributed equally to the manuscript revisionsAll authors (ABQW, HTK, AYH, YCS, NYH, CTL, HT, CCC, CJL, HSC, YHW, YYT, MYH, JCCW) approved the final version of the manuscript and agree to be held accountable for the content therein.

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Declarations

Conflict of interest

All the authors have no conflict of interest.

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None.

Ethics statement

The study adhered to the principles outlined in the Declaration of Helsinki. Since the TriNetX database consists of de-identified data, obtaining written consent from study participants was considered unnecessary. The Western Institutional Review Board granted TriNetX a waiver for informed consent, as this platform only aggregates counts and statistical summaries of de-identified information. Additionally, approval from the China Medical University Hospital Institutional Review Board was not required because only de-identified data were utilized for this retrospective analysis. This study received approval from the Institutional Review Board of the Chung Shan Medical University Hospital Research Ethics Committee (CS2 - 21176).

Additional information

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