Associations Between Dry Eye Disease and Mental Health Conditions in the All of Us Research Program

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• PURPOSE: To determine the association between dry eye disease (DED) and mental health conditions in a sociodemographically diverse nationwide population of Americans.
• DESIGN: Cross-sectional study.
• METHODS: We used the National Institute of Health's All of Us Research Program database to identify 18257 participants with DED who were propensity score matched in a 1:3 ratio to participants without DED. Univariate and multivariable logistic regression models were used to assess associations between DED and mental health conditions (i.e., depressive disorders, anxiety, bipolar disorder, and schizophrenic spectrum disorder).
• RESULTS: Participants with DED had a significantly higher prevalence of depressive disorders (31.6% vs. 10.7%; $P < .001$), anxiety disorders (34.8% vs. 14.7%; $P < .001$), bipolar disorder (5.5% vs. 2.3%; $P < .001$), and schizophrenia spectrum disorders (2.3% vs. 0.9%; $P < .001$) than controls. Adjusted for medical comorbidities (i.e., hypothyroidism, Sjögren's syndrome, systemic lupus erythematosus), participants with DED had higher odds than controls in having a depressive disorder (odds ratio [OR]: 3.47; 95% CI: 3.32-3.62), anxiety (OR: 2.74; 95% CI: 2.63-2.85), bipolar disorder (OR: 2.23; 95% CI: 2.04-2.44), and schizophrenia spectrum disorder (OR: 2.48; 95% CI: 2.17-2.84). The association between DED and mental health conditions was stronger in Black participants than White participants (OR: 3.68 vs. 3.09, $P < .001$).
• CONCLUSIONS: Participants with DED were significantly more likely to have mental health conditions than matched participants without DED; this association was stronger in Black participants than White participants. Greater efforts should be undertaken to screen DED patients for mental health conditions, particularly in historically medically underserved populations. (Am J Ophthalmol 2025;270: 61–66. © 2024 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.)

INTRODUCTION

Dry eye disease (DED) is a common ocular surface disease affecting around 6%-8% of adults in the United States.[1,2] Characterized by inflammatory damage to the ocular surface and reduced tear film production, DED patients often experience chronic irritation, negatively affecting their day-to-day function and inhibiting their quality of life.[3] Previous studies have shown associations between DED and mental health conditions, such as depression and anxiety.[4-6] However, there is limited understanding of the association between DED and mental health conditions in diverse populations. In this study, we used the publicly available data from the National Institutes of Health's All of Us Research Program (AoURP) database to investigate the association between DED and mental health conditions in a large and diverse nationwide population of American adults.[7]

METHODS

The AoURP is a nationwide study sponsored by the National Institutes of Health to advance population health by seeking diverse recruitment of participants underrepresented in biomedical research.[7] This program, comprised

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of clinical data from a large socioeconomically and ethnically diverse cohort of over 300,000 American adults, is adherent to both the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline and the Declaration of Helsinki. Since the analysis of the AoURP data is considered deidentified patient research, the University of Pennsylvania institutional review board waived approval of this study.

Utilizing electronic health record data in the AoURP database, cases of DED were identified by the Systemized Nomenclature of Medicine (SNOMED) code for dry eyes (162290004), meibomian gland dysfunction (MGD) (397549002), and tear film insufficiency (46152009). Only participants ≥18 years of age were included in this study. Using 1:3 case to control propensity score-matching based on age, sex, race, ethnicity, annual income, employment, highest education, and health insurance status—which were self-reported through survey questionnaires—we controlled for socioeconomic factors that could have biased our study. To control for psychiatric medications that may be associated with DED, we collected information on patient's history of mental health medication. The full list of mental health medications that were collected can be found in eTable 1. The outcome measure included clinical diagnosis of depressive disorders, anxiety-related disorders, bipolar disorder, and schizophrenic spectrum disorders. Diagnosis for these depressive disorders was determined by searching the AoURP database for relevant SNOMED codes listed in eTable 2.

Univariate and multivariable logistic regression models were performed to evaluate associations between DED and mental health conditions. The multivariable analysis was adjusted by medical comorbidities previously found to be associated with both DED and mental health conditions including Sjögren's syndrome, systemic lupus erythematosus (SLE), and hypothyroidism (identified by the SNOMED codes 83901003, 55464009, and 40930008, respectively). We performed these analyses for all participants combined, and for Black and White participants separately to evaluate whether the associations between DED and mental health conditions differ between Black and White Americans. All statistical analyses were performed using R version 4.3.1. The AoURP database v7 2022Q4R9 was used for analysis. Two-sided $P < .05$ was considered statistically significant without adjustment for multiple comparisons.

RESULTS

Among the 328362 participants in the AoURP, 955 (0.3%) had a clinical diagnosis of dry eyes, 2624 (0.8%) had MGD, and 17339 (5.3%) had tear film insufficiency. Combined, 18257 (5.6%) participants had some form of DED. Among the combined cohort of patients with DED, the mean age was 64.9 (SD: 13.5; Range: 18-89) years, 12234 (67.0%) were female, 12708 (69.6%) self-identified as White, 3999 (21.9%) self-identified as Black, 420 (2.3%) self-identified as Hispanic or Latino, 15095 (82.7%) were employed, 14750 (80.8%) had a college education or above, and 17613 (96.5%) had health insurance (Table 1). The DED patients and their propensity score-matched controls were similar in age, gender, race, ethnicity, annual income, employment status, health insurance status, and education level (all $P > .35$, Table 1). However, participants with DED were significantly more likely than controls to have hypothyroidism (20.5% vs. 10.1%; $P < .001$), Sjögren's syndrome (7.1% vs. 0.7%; $P < .001$), SLE (3.3% vs. 0.9%; $P < .001$), and use of mental health medications (15.5% vs. 8.6%; $P < .001$, Table 1).

Compared with propensity score-matched participants without DED, participants with DED had a significantly higher prevalence of mental health conditions (47.4% vs. 20.2%, $P < .001$) including depressive disorders (31.6% vs. 10.7%; $P < 0.001$), anxiety disorders (34.8% vs. 14.7%; $P < .001$), bipolar disorder (5.5% vs. 2.3%; $P < .001$), and schizophrenia spectrum disorders (2.3% vs. 0.9%; $P < .001$) (Table 2). In multivariable analysis with adjustment by medical comorbidities (i.e., hypothyroidism, Sjögren's syndrome, SLE), these significant associations remained—participants with DED had higher odds of having a depressive disorder (OR: 3.47; 95% CI: 3.32-3.62), anxiety (OR: 2.74; 95% CI: 2.63-2.85), bipolar disorder (OR: 2.23; 95% CI: 2.04-2.44), and schizophrenia spectrum disorder (OR: 2.48; 95% CI: 2.17-2.84) and any of these mental health conditions (OR: 3.21, 95% CI: 3.01-3.33) than propensity score-matched controls (Table 2). While significant associations between DED and mental health conditions were both seen in White and Black participants, the associations between DED and mental health conditions were significantly stronger among Black participants than White participants in all mental health conditions except for bipolar disorder (eTable 3). In the multivariable analysis among participants without a history of using mental health medications, DED were still significantly associated with 2-3 times higher odds of depressive disorders, anxiety, bipolar disorder, and schizophrenia spectrum disorder (all $P < .001$) (Table 3).

DISCUSSION

Using the large data from a diverse sociodemographic population of adult participants in the nationwide AoURP, we evaluated associations between DED and mental health conditions. We found that participants with DED were more than 3 times as likely to have mental health conditions, such as depression or anxiety, compared to participants without DED. This finding is consistent with the findings in the current literature.[8] Past studies have identified associations between DED and mental health con-

TABLE 1. Characteristics of Patients With DED and Controls in the AoURP

	Controls ($N = 54765$)	DED ($N = 18255$)	*P*-Value
Age			.69
Mean (SD)	64.9 (13.5)	64.9 (13.5)	
Median (Q1, Q3)	67.0 (58.0, 75.0)	67.0 (58.0, 75.0)	
Range	19.0-89.0	20.0-89.0	
Race			.84
White	37982 (69.4%)	12708 (69.6%)	
Black or African American	12169 (22.2%)	3999 (21.9%)	
Asian	2327 (4.2%)	776 (4.3%)	
Other	2287 (4.2%)	772 (4.2%)	
Ethnicity			.94
Hispanic or Latino	1237 (2.3%)	420 (2.3%)	
Not Hispanic or Latino	52695 (96.2%)	17555 (96.2%)	
Other	833 (1.5%)	280 (1.5%)	
Sex at birth			.81
Female	36754 (67.1%)	12234 (67.0%)	
Male	18011 (32.9%)	6021 (33.0%)	
Current employment status			.97
Employed for wages or self-employed	45279 (82.7%)	15095 (82.7%)	
Not currently employed for wages	9486 (17.3%)	3160 (17.3%)	
Annual household income (USD)			.98
Less than 75k	25607 (46.8%)	8546 (46.8%)	
75k to 150k	11885 (21.7%)	3974 (21.8%)	
More than 150k	7787 (14.2%)	2575 (14.1%)	
Unknown	9486 (17.3%)	3160 (17.3%)	
Highest education			.93
College and above	44239 (80.8%)	14750 (80.8%)	
High school or below	9515 (17.4%)	3176 (17.4%)	
Unknown	1011 (1.8%)	329 (1.8%)	
Health insurance or other health plan coverage			.35
No	951 (1.7%)	347 (1.9%)	
Yes	52930 (96.6%)	17613 (96.5%)	
Unknown	884 (1.6%)	295 (1.6%)	
Hypothyroidism			< .001
No	49229 (89.9%)	14515 (79.5%)	
Yes	5536 (10.1%)	3740 (20.5%)	
Sjögren's syndrome			< .001
No	54383 (99.3%)	16957 (92.9%)	
Yes	382 (0.7%)	1298 (7.1%)	
Systemic lupus erythematosus			< .001
No	54294 (99.1%)	17652 (96.7%)	
Yes	471 (0.9%)	603 (3.3%)	
Mental health medication use[a]			
No	50031 (91.4%)	15419 (84.5%)	< .001
Yes	4734 (8.6%)	2836 (15.5%)	

[a]Includes antidepressants, antipsychotics, mood stabilizers, and antianxiety medications. See supplementary material for full medication list.

ditions such as anxiety, depression, bipolar disorder, and schizophrenia in Taiwanese and Turkish populations, as well as in patients in North Carolina.[4,5,9] A 2020 secondary analysis of data from Taiwan's National Health Insurance Research Database comprised of 75650 patients with psychiatric disorders found that patients with DED had significantly greater odds of having schizophrenia (OR = 1.34), bipolar disorder (OR = 1.90), and depression (OR = 1.54) than gender and age-matched controls without DED.[9] A cross-sectional German study of 64 patients with DED found that patients with DED had significantly higher depression severity than 582 controls.[10] A study of 7027 patients with DED from 2008 to 2013 from the University of North Carolina's outpatient clinics found that patients with DED had 2.8 greater odds of having anxiety and 2.9 greater odds of having depression compared to age and gender-matched controls.[4] However, these past studies were limited by their size or by their limited geographic and/or

TABLE 2. Prevalence of Mental Health Disorders in Participants With DED and Propensity-Score Matched Controls

Mental Health Disorders	Controls ($N = 54765$)	DED ($N = 18255$)	Univariate Analysis		Multivariate Analysis[a]	
			Odds Ratio (95% CI)	*P*-Value	Odds Ratio (95% CI)	*P*-Value
Depressive disorders (%)	5872 (10.7%)	5769 (31.6%)	3.85 (3.69, 4.01)	< .001	3.47 (3.32, 3.62)	< .001
Anxiety-related disorders disorder (%)	8065 (14.7%)	6350 (34.8%)	3.09 (2.97, 3.21)	< .001	2.74 (2.63, 2.85)	< .001
Bipolar disorder (%)	1261 (2.3%)	1009 (5.5%)	2.48 (2.28, 2.70)	< .001	2.23 2.04, 2.44)	< .001
Schizophrenia spectrum disorder (%)	497 (0.9%)	411 (2.3%)	2.51 (2.20, 2.87)	< .001	2.48 (2.17, 2.84)	< .001
Any of above	11046 (20.2%)	8659 (47.4%)	3.57 (3.45, 3.70)	< .001	3.21 (3.01, 3.33)	< .001

[a] Adjusted by hypothyroidism, Sjögren's syndrome, and SLE.

TABLE 3. Prevalence of Mental Health Disorders in Participants With DED and Propensity-Score Matched Controls Among Participants Without the Use of Mental Health Medications

Mental Health Disorders	Controls ($N = 50031$)	DED ($N = 15419$)	Univariate Analysis		Multivariate Analysis[a]	
			Odds Ratio (95% CI)	*P*-Value	Odds Ratio (95% CI)	*P*-Value
Depressive disorders (%)	4063 (8.1%)	4194 (27.2%)	4.23 (4.03, 4.43)	< .001	3.82 (3.64, 4.02)	< .001
Anxiety-related disorders disorder (%)	6040 (12.1%)	4720 (30.6%)	3.21 (3.08, 3.36)	< .001	2.84 (2.72, 2.97)	< .001
Bipolar disorder (%)	911 (1.8%)	755 (4.9%)	2.78 (2.52, 3.06)	< .001	2.49 (2.25, 2.75)	< .001
Schizophrenia spectrum disorder (%)	332 (0.7%)	310 (2.0%)	3.07 (2.63, 3.59)	< .001	3.03 (2.58, 3.55)	< .001
Any of above	8154 (16.3%)	6530 (42.4%)	3.77 (3.63, 3.93)	< .001	3.40 (3.27, 3.55)	< .001

[a] Adjusted by hypothyroidism, Sjögren's syndrome, and SLE.

sociodemographic representation. In a diverse sociodemographic nationwide population of the United States, our study found even stronger associations than previously described in the literature. Additionally, we found that Black Americans had a stronger association between DED and mental health disorders than White Americans, suggesting that Black Americans with DED are at higher risk of having a mental health disorder than their White peers. Furthermore, we found that while mental health medication use is associated with DED, the presence of depressive disorders, anxiety, bipolar disorder, and schizophrenia spectrum disorder remains strongly associated with DED even in participants who have never used mental health medications. This suggests that the DED itself may play an independent role in the development or exacerbation of mental health conditions,

This increased risk of mental health disorders associated with DED could be a result of both psychological and biological changes. The constant feeling of discomfort from dry eye symptoms has a profound impact on activities of daily living, inhibiting healthy social functioning and sleep.[11] Moreover, the lifelong, unpredictable, and difficult-to-manage symptoms of DED may cause patients to feel a sense of helplessness, leading to mood changes. Inflammatory cytokines associated with depression have also been found elevated in DED patients, suggesting that systemic inflammation could play a biological role in the coexistence of these disorders.[12]

Since the AoURP had limited data on DED signs and symptoms (e.g., OSDI scores) and measures of depression severity, we were unable to evaluate associations between the severity of DED and the severity or duration of depression. Future studies should investigate whether more severe DED is associated with a higher prevalence and severity of mental health conditions. In a study of 535 patients with moderate-to-severe DED, researchers found that more severe DED signs and symptoms were associated with more severe depression, as assessed by the Mental Component Summary.[6] A study of 206 patients with DED from China found higher Ocular Surface Disease Index (OSDI) scores, a marker of DED severity, were significantly associated with a higher risk of depression and anxiety.[13] Additionally, while the AoURP is an expansive database that includes participants from diverse racial and socioeconomic backgrounds, it may not fully capture the complete demographic profile of the nationwide population, which could impact the generalizability of the findings.

Moreover, since our determination of DED was based on medical diagnostic codes, there likely exists participants who had DED yet did not have a formal diagnosis from a medical provider and were thus considered control participants in this analysis. This would have diluted the association between DED and mental health conditions. Thus, the true association may be larger than what we found in our study. While DED affects about 6%-8% of adults in America, studies have estimated that an additional 2.5% of Americans have DED but remain undiagnosed.[1] A study of 78165 Dutch participants found that patients with undiagnosed DED had a significantly increased risk of having a low mental health-related quality-of-life with worsening

dry eye symptoms than patients with diagnosed DED.[14] However, many patients, particularly those typically underrepresented in biomedical research, face challenges in accessing ophthalmic care. Studies have shown that patients with social disparities and barriers to healthcare access are significantly more likely to have visual and eye impairments than patients with greater social support.[15] In addition to our findings, these studies exemplify the importance of screening for DED in medically underserved communities. Future studies should investigate how DED symptoms and signs are related to mental health conditions in medically underserved populations and how treatment of DED can help alleviate mental health conditions in such communities.

CONCLUSIONS

In a sociodemographically diverse population of American adults, DED was associated with a three-fold greater prevalence of mental health conditions such as depression and anxiety. Greater efforts should be undertaken to screen patients with DED for mental health conditions, particularly in historically medically underserved populations. The cause of this association and the effect of DED severity on mental health conditions need further investigation.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

AARON T. ZHAO: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Conceptualization. **JOCELYN HE:** Validation, Software, Resources, Methodology, Formal analysis, Data curation. **YUQING LEI:** Writing – review & editing, Validation, Formal analysis. **YONG CHEN:** Validation, Supervision. **GUI-SHUANG YING:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition, Formal analysis, Conceptualization.

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