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A cross-sectional study of non-modifiable and modifiable risk factors of dry eye disease states

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ABSTRACT

Purpose: The present study aimed to determine the relationship of non-modifiable (rheumatoid arthritis, thyroid diseases, and arterial hypertension) and modifiable risk factors (diuretics, antidepressants, or anxiolytics tranquilizers) with the different Dry Eye Disease (DED) diagnostics in a sample adjusted by antihistamines intake.
Methods: A total of 400 participants were included in a cross-sectional study. Before a dry eye examination, participants completed an online self-administered OSDI questionnaire with six additional questions about possible DED risk factors. The Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS-II) diagnostic criteria of DED was used. Based on signs and/or symptoms, participants were divided into 4 groups: No DED, Pre-clinical DED, Predisposition to DED and DED. Since the symptom scores would have been altered by the use of antihistamines, the analysis of each outcome was adjusted for this factor, where those participants were assumed to be symptomatic.
Results: Multivariable logistic regression found thyroid disease as a possible risk factor for DED (OR 4.53, 95 % CI 1.04–19.73; Fisher's exact, $p = 0.044$; Crameŕs V = 0.140, $p = 0.024$). No association was found between the studied parameters and Pre-clinical DED (Fisher's exact, all $p \geq 0.398$; Crameŕs V, all $p \geq 0.242$) or Predisposition to DED (Fisher's exact, all $p \geq 0.065$; Crameŕs V, all $p \geq 0.031$).
Conclusion: Participants with thyroid disease were more likely to develop DED, therefore, thyroid disease could be a risk factor for DED.

The Tear Film and Ocular Surface Society Dry Eye Workshop (TFOS DEWS-II) has defined dry eye disease (DED) as a"*multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles*" [1]. The prevalence range of DED based on symptoms and signs has been estimated to vary between 8.7 and 42.0 %; although if studies that involve symptomatic participants with or without DED signs were considered, the range varies between 5.0 and 50.0 % [2–4].

An extensive list of DED risk factors has been reported by the literature, including age, sex, video displays use, Sjögren syndrome, environmental pollution, low humidity, systemic diseases, and many medications like antihistamines or anxiolytics among others [2]. Researchers like McMonnies and Ho in 1987 designed a dry eye questionnaire that involves items about age, sex, primary and secondary dry eye symptomatology frequency and medication intake [5]. Those authors were concerned that the origin of DED could be influenced by systemic factors and their medical management [5]. The physiopathology and treatment of systemic diseases like rheumatoid arthritis, and thyroid disease can impact the normal function of the ocular surface [2,6], while medication for treating common diseases like allergy or depression has side effects that affect the ocular surface function [2,7]. These disorders and the medication for their treatment are commonly prescribed in daily clinical practice and may be important risk factors for DED due to their high prevalence: 6.7 % for thyroid diseases and between 0.5 and 0.7 % for rheumatoid arthritis, 31.5 % for high blood pressure, and 0.9 to 28.3 % for anxiety [8–11]. Moreover, asthma and atopic dermatitis are the two most prevalent disorders in the field of allergies, with prevalence values of 4.3 % for children, and 8.6 % for

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adults with asthma symptoms, and a prevalence of atopic dermatitis in children between 15.0 and 20.0 %, and in adults between 1.0 and 3.0 % [12,13].

The present study aimed to establish if there is a link between DED and its risk factors, whether non-modifiable (rheumatoid arthritis, thyroid diseases, and arterial hypertension) or modifiable (diuretics, antidepressants, or anxiolytics tranquilizers) in a sample adjusted by antihistamines intake.

1. Methods

1.1. Study and sample design

A total sample of 400 participants was analysed in a cross-sectional study. All attended the Optometry Clinic referred by the Medical Service of the institution to examine their dry eye-related complaints. Before referral, the Medical Service screened for dry eye symptoms using the McMonnies questionnaire, which is an easy-to-use tool to identify patients at risk for DED [5,14].

Prospective participants were contacted by the Optometry Clinic via mail and, after completing an online, self-administered, OSDI questionnaire with six additional questions, an appointment was scheduled. The six additional questions were about possible clinical risk factors for DED, as suggested by McMonnies and others [5,14]: rheumatoid arthritis, thyroid diseases, arterial hypertension, use of antihistamines, use of diuretics, and use of tranquilizers (antidepressants or anxiolytics). All participants signed an informed consent form to be included in the study. The present study adhered to the tenants of the Declaration of Helsinki and was approved by the Bioethics Committee of the institution. Based on the criteria of the TFOS DEWS-II Diagnostic Methodology Subcommittee, a battery of tests was performed to discriminate the possible diagnosis in each participant: OSDI questionnaire, tear osmolarity, tear film break-up time (TFBUT), and corneal staining [1,15,16]. All procedures were performed by the same observer, who was unaware of the results of the questionnaire. The data were masked by an alphanumeric code for subsequent analysis.

1.2. TFOS DEWS-II tests battery and diagnostic

The OSDI questionnaire was self-administered by an online form [17]. A TearLab osmometer (TearLab, San Diego, USA) was used to measure the tear film osmolarity [18]. Slit-lamp Topcon® SL-D4 with a DC-4 video camera (TOPCON Corporation, Tokyo Japan) attached, and non-preserved fluorescein was used for measuring TFBUT and corneal staining [19,20]. A video of each slit-lamp procedure performed was recorded for the post-analysis. Both eyes of every participant were measured in all procedures.

The diagnostic tests cut-off values for the DED diagnosis were OSDI $\geq$ 13, tear osmolarity $\geq$ 308 mOsm/L, TFBUT $<$ 10 s, and corneal staining (Oxford grade) $\geq$ 2 [15].

Following TFOS DEWS-II diagnostic criteria, participants were divided into four possible diagnoses based on the presence of the different combinations of signs and symptoms: No DED, Pre-clinical DED, Predisposition to DED or DED (Table 1).

1.3. Statistical analysis

SPSS statistical software v.25.0 for Windows (SPSS Inc., Chicago, USA) was used for data analyses. Significance was set at a $p \leq 0.05$ for all the analyses. Participants were grouped depending on their diagnosis based on TFOS DEWS-II criteria and included in the corresponding groups (Table 1). Odds ratios (OR) along with 95 % Confidence Intervals (CI) were estimated to represent the magnitude of the identified associations between the risk factors studied and the differential diagnosis groups established. Due to the categorical nature of the data, a Chi-squared design was used to compare by pairs the outcomes of the risk factors presented in the different diagnostics; Fisher's exact test was performed to assess the association between risk factors and the differential diagnosis [21]. Multivariable logistic regression was conducted. Crameŕs V was calculated to evaluate correlations with categorical data. Since the symptom scores could have been altered by antihistamine use (therefore potentially lowering the diagnostic classification of patients), the analysis was adjusted for this factor by assuming these participants to be symptomatic.

Table 1
TFOS DEWS-II criteria. DED = Dry eye Disease.

Differential diagnosis	Symptoms	Signs	
No DED	OSDI score $<$ 13	All conditions must be filled	- Osmolarity in one eye $<$ 308 mOsm/l- Osmolarity difference between eyes $<$ 8 mOsm/l- TFBUT $\geq$ 10 s- Corneal staining (Oxford Scale) $<$ 2 grade
Pre-clinical dry eye state	OSDI score $\geq$ 13		
Predisposition to dry eye	OSDI score $<$ 13	Only one condition must be filled	- Osmolarity in one eye $\geq$ 308 mOsm/l- Osmolarity difference between eyes $\geq$ 8 mOsm/l- TFBUT $<$ 10 s- Corneal staining (Oxford Scale) $\geq$ 2 grade
DED	OSDI score $\geq$ 13		

2. Results

From the 400 recruited participants, the distributions of the differential diagnoses were: 56 participants as No DED (14 % of the total; Mean age $\pm$ SD = 24.3 $\pm$ 10.6 years; 46.4 % men; OSDI score $\pm$ SD = 6.0 $\pm$ 3.6), 30 participants as pre-clinical DED (7.5 % of the total; Mean age $\pm$ SD = 32.6 $\pm$ 16.3 years; 30 % men; OSDI score $\pm$ SD = 26.4 $\pm$ 12.6), 107 participants as predisposed to DED (26.75 % of the total; Mean age $\pm$ SD = 35.1 $\pm$ 17.4 years; 27.1 % men; OSDI score $\pm$ SD = 7.0 $\pm$ 3.5) and, 207 participants as DED (51.75 % of the total; Mean age $\pm$ SD = 46.2 $\pm$ 15,2 years; 18.8 % men; OSDI score $\pm$ SD = 31.7 $\pm$ 14.3).

2.1. Risk factors analyses on No DED vs Pre-clinical DED participants

Table 2 shows the distribution of the No DED and Pre-clinical DED participants, adjusted by antihistamine intake, based on the presence or absence of risk for the studied risk factors. Both univariate and multivariable regression showed that Pre-clinical DED participants were not likely to be under any of the risk factors studied compared to the No DED group (Fisher's exact test, all $p \geq 0.257$, Table 2). In addition, no correlation between any of the studied risk factors with a Pre-clinical DED differential diagnosis was obtained (Crameŕs V analyses, all $p \geq 0.281$, Table 2).

2.2. Risk factor analyses on No DED vs Predisposition to DED participants

Table 3 shows the distribution of the No DED and DED participants, adjusted by antihistamines intake, based on the presence or absence of risk for the studied risk factors. Only on the univariate comparison was it found that participants in the Predisposition to DED group were more likely to have arterial hypertension (OR 7.16, 95 % CI 0.91–56.19; Fisher's exact test $p = 0.023$) than the No DED group. In addition, a correlation was obtained between arterial hypertension and Predisposition to DED differential diagnosis (Crameŕs V = 0.177, $p = 0.031$, Table 3). No correlation was obtained between the other studied risk factors and a Predisposition to DED differential diagnosis (Crameŕs V analyses, all $p \geq 0.500$, Table 5).

Table 2
Distribution of the No DED and Pre-clinical DED participants adjusted by antihistamine intake based on the presence or absence of risk for the studied risk factors. DED = Dry eye Disease. OR = Odds Ratio. CI = Confidence Intervals.

				Univariate logistic regression		Multivariable logistic regression		Crameŕs V	
		No DED	Pre-clinical DED	OR (95 % CI)	p	OR (95 % CI)	p	Value	p
Risk Factor		n = 46	n = 40						
Rheumatoid Arthritis	Yes	1	3	3.65 (0.36, 36.56)	0.257	2.64 (0.29, 30.43)	0.436	0.124	0.242
	No	45	37						
Thyroid Disease	Yes	2	4	2.44 (0.42, 14.12)	0.274	2.30 (0.33, 15.80)	0.398	0.111	0.305
	No	44	36						
Arterial Hypertension	Yes	1	2	2.37 (0.21, 27.15)	0.447	1.53 (0.10, 23.42)	0.751	0.077	0.476
	No	45	38						
Use of diuretics	Yes	1	1	1.15 (0.07, 19.07)	0.465	–	1.000	0.116	0.281
	No	45	39						
Use of tranquilizers (antidepressants or anxiolytics)	Yes	1	2	2.37 (0.21, 27.15)	0.447	1.32 (0.79, 21.93)	0.846	0.077	0.476
	No	45	38						

Table 3
Distribution of the No DED and Predisposition to DED participants adjusted by antihistamines intake based on the presence or absence of risk for the studied risk factors. DED = Dry eye Disease. OR = Odds Ratio. CI = Confidence Intervals.

				Univariate logistic regression		Multivariable logistic regression		Crameŕs V	
		No DED	Predisposition to DED	OR (95 % CI)	p	OR (95 % CI)	p	Value	p
Risk Factor		n = 46	n = 102						
Rheumatoid Arthritis	Yes	1	2	0.90 (0.08, 10.18)	0.676	0.28 (0.14, 5.80)	0.413	0.007	0.932
	No	45	100						
Thyroid Disease	Yes	2	6	1.38 (0.27, 7.09)	0.523	0.97 (0.17, 5.53)	0.974	0.031	0.702
	No	44	96						
Arterial Hypertension	Yes	1	14	7.16 (0.91, 56.19)	0.023	8.70 (0.87, 86.81)	0.065	0.177	0.031
	No	45	88						
Use of diuretics	Yes	1	1	0.01 (0.03, 7.28)	0.689	–	1.000	0.055	0.500
	No	45	101						
Use of tranquilizers (antidepressants or anxiolytics)	Yes	1	6	2.81 (0.33, 24.06)	0.301	2.71 (0.31, 24,06)	0.372	0.081	0.436
	No	45	96						

2.3. Risk factor analyses on No DED vs DED participants

Table 4 shows the distribution of the No DED and DED participants, adjusted by antihistamines intake, based on the presence or absence of risk for the studied risk factors. Compared to the No DED group, DED participants were more likely to have thyroid diseases when both univariate (OR 4.65, 95 % CI 1.08–20.04; Fisher's exact test p = 0.014) and multivariable (OR 4.53, 95 % CI 1.04–19.73; Fisher's exact test p = 0.044) regressions were performed. Also, on univariate analysis, the number of participants with arterial hypertension and using tranquilizers (antidepressants or anxiolytics) seemed to be statistically higher in the DED, than the No DED group (Fisher's exact test, both $p \leq 0.048$, Table 4). A weak correlation was obtained between thyroid disease and a DED differential diagnosis (Crameŕs V = 0.140, p = 0.024, Table 4). No correlation was obtained between the other risk factors studies with a DED differential diagnosis (Crameŕs V analyses, all $p \geq 0.057$, Table 4).

3. Discussion

Antihistamines are usually prescribed in conditions such as allergic rhinitis and conjunctivitis, where previous reports have found that they decrease TFBUT values and increase conjunctival staining by lowering

Table 4
Distribution of the No DED and DED participants adjusted by antihistamines intake based on the presence or absence of risk for the studied risk factors. DED = Dry eye Disease. OR = Odds Ratio. CI = Confidence Intervals.

				Univariate logistic regression		Multivariable logistic regression		Crameŕs V	
		No DED	DED	OR (95 % CI)	p	OR (95 % CI)	p	Value	p
Risk Factor		n = 46	n = 212						
Rheumatoid Arthritis	Yes	1	9	2.00 (0.25, 16.15)	0.441	1.49 (0.17, 12.94)	0.771	0.041	0.696
	No	45	203						
Thyroid Disease	Yes	2	37	4.65 (1.08, 20.04)	0.014	4.53 (1.04, 19.73)	0.044	0.140	0.024
	No	44	175						
Arterial Hypertension	Yes	1	25	6.02 (0.79, 45.58)	0.033	5.06 (0.66, 39.07)	0.120	0.049	0.057
	No	45	187						
Use of diuretics	Yes	1	8	1.76 (0.22, 14.47)	0.203	–	1.000	0.083	0.181
	No	45	204						
Use of tranquilizers (antidepressants or anxiolytics)	Yes	1	23	6.29 (0.83, 47.59)	0.048	4.36 (0.56, 33.87)	0.160	0.114	0.090
	No	45	181						

the aqueous and mucin production of the lacrimal glands and goblet cells [22,23]. Since antihistamines intake can also affect symptomatology, participants in the present study could be miscategorized, if their symptoms are supressed by antihistamine use. To address this, data were analysed after including all these participants in the symptomatic group.

In the present research, only thyroid disease was found to be a risk factor for DED when the univariate and the multivariable logistic regressions were performed, with ORs of 4.65 (95 % CI 1.08–20.04) and 4.53 (95 % CI 1.04–19.73) respectively. Thyroid disorders are highly prevalent, endocrine conditions that affect the function of most organs in the body, and it is one of the most frequent complications of pregnancy and endocrine disorder in infants or children [24,25]. This condition did not seem to be a non-modifiable risk factor in the Pre-clinical or Predisposition DED status groups however.

Researchers like Galor et al. [26] also found thyroid disease to be a DED risk factor and together with the present results, this could imply that thyroid disease has more effect during advanced dry eye conditions, rather than in the early stages of the disease [27,28]. It has already been stated that gender plays an important role as a risk factor for DED and as thyroid hormones are implicated in the development of DED it is noteworthy that female gender is also a risk factor for thyroid disease [9,29,30].

No other potential risk factors for DED were identified in the current research after performing multivariable logistic regression. Other work in this area has been equivocal, with some studies showing that arterial hypertension could be a potential risk factor for DED [26,31,32], while others, such as Yu et al., [27] did not find an association between arterial hypertension and severe dry eye signs.

Tranquilizers include antidepressants and anxiolytics, both of which are antimuscarinic agents that have been shown to affect aqueous and mucous secretions, leading to an alteration of tear film stability [23]. Previous reports found the use of tranquilizers to be a risk factor for DED [26,32,33]. Nevertheless, the multivariable logistic regression of the present study did not show statistically significant results for this risk factor.

A principal limitation of the study could be that factors like rheumatoid arthritis and the use of diuretics were not well represented among the study data. In both cases, the sample size showed few cases for each condition, therefore there was low power to generate significant ORs as possible risk factors of DED. A larger, representative sample in which participants with rheumatoid arthritis and diuretics intake are more strongly represented, should be recruited in future studies.

Another limitation could be the possible misclassification of participants with a neurotrophic condition or neuropathic pain in the Pre-Clinical and Predisposition to DED groups, which could have influenced risk factor identification in those groups. Moreover, Pre-clinical DED participants are “healthy” individuals that have dry eye symptomatology (OSDI $\geq$ 13), but these may be due to other common, external factors such as the overuse of video display terminals, smartphones, etc [1,34] and so not directly DED related.

4. Conclusion

In conclusion, a group of non-modifiable and modifiable, possible risk factors of DED and their association with its three possible states, as proposed by the TFOS DEWS-II Diagnostic Methodology Subcommittee, were studied in the present research: no risk factor was identified in the Pre-clinical DED or Predisposition to DED groups, whereas participants with thyroid disease were at greater risk of being included in the DED group.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, et al. TFOS DEWS II definition and classification report. Ocul Surf 2017;15(3):276–83. https://doi.org/10.1016/j.jtos.2017.05.008.

[2] Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanont K, Malet F, et al. TFOS DEWS II epidemiology report. Ocul Surf 2017;15(3):334–65. https://doi.org/10.1016/j.jtos.2017.05.003.

[3] Akowuah PK, Kobia-Acquah EJO. Prevalence of dry eye disease in Africa: a systematic review and meta-analysis. Optomet Vis Sci 2020;97(12):1089–98. https://doi.org/10.1097/OPX.0000000000001610.

[4] Cai Y, Wei J, Zhou J, Zou W. Prevalence and incidence of dry eye disease in Asia: a systematic review and meta-analysis. Ophthalmic Res 2022. https://doi.org/10.1159/000525696.

[5] McMonnies CW, Ho A. Patient history in screening for dry eye conditions. J Am Optom Assoc 1987;58(4):296–301.

[6] Hackett KL, Newton JL, Frith J, Elliott C, Lendrem D, Foggo H, et al. Impaired functional status in primary Sjögren's syndrome. Arthritis Care Res 2012;64(11):1760–4. https://doi.org/10.1002/acr.21738.

[7] Bron AJ, de Paiva CS, Chauhan SK, Bonini S, Gabison EE, Jain S, et al. TFOS DEWS II pathophysiology report. Ocul Surf 2017;15(3):438–510. https://doi.org/10.1016/j.jtos.2017.05.011.

[8] Almutairi K, Nossent J, Preen D, Keen H, Inderjeeth C. The global prevalence of rheumatoid arthritis: a meta-analysis based on a systematic review. Rheumatol Int 2021;41(5):863–77.

[9] Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F, Galofré JC. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. J Clin Endocrinol Metab 2014;99(3):923–31. https://doi.org/10.1210/jc.2013-2409.

[10] Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nat Rev Nephrol 2020;16(4):223–37. https://doi.org/10.1038/s41581-019-0244-2.

[11] Baxter AJ, Scott KM, Vos T, Whiteford HA. Global prevalence of anxiety disorders: a systematic review and meta-regression. Psychol Med 2013;43(5):897–910. https://doi.org/10.1017/S003329171200147X.

[12] Nutten S. Atopic dermatitis: global epidemiology and risk factors. Ann Nutr Metab 2015;66(Suppl. 1):8–16. https://doi.org/10.1159/000370220.

[13] Asher MI, García-Marcos L, Pearce NE, Strachan DP. Trends in worldwide asthma prevalence. Eur Respir J 2020;56(6). https://doi.org/10.1183/13993003.02094-2020.

[14] Gothwal VK, Pesudovs K, Wright TA, McMonnies CW. McMonnies questionnaire: enhancing screening for dry eye syndromes with Rasch analysis. Invest Ophthalmol Vis Sci 2010;51(3):1401–7. https://doi.org/10.1167/iovs.09-4180.

[15] Wolffsohn JS, Arita R, Chalmers R, Djalilian A, Dogru M, Dumbleton K, et al. TFOS DEWS II diagnostic methodology report. Ocul Surf 2017;15(3):539–74. https://doi.org/10.1016/j.jtos.2017.05.001.

[16] Wolffsohn JS, Wang MTM, Vidal-Rohr M, Menduni F, Dhallu S, Ipek T, et al. Demographic and lifestyle risk factors of dry eye disease subtypes: A cross-sectional study. Ocul Surf 2021;21:58–63. https://doi.org/10.1016/j.jtos.2021.05.001.

[17] Miller KL, Walt JG, Mink DR, Satram-Hoang S, Wilson SE, Perry HD, et al. Minimal clinically important difference for the ocular surface disease index. Arch Ophthalmol 2010;128(1):94–101. https://doi.org/10.1001/archophthalmol.2009.356.

[18] Pena-Verdeal H, García-Resúa C, Vazquez-Sanchez C, Garcia-Queiruga J, Giráldez MJ, Yebra-Pimentel E. Inter-eye osmolarity differences in patients with symptomatic and non-symptomatic dry eyes. Arq Bras Oftalmol 2020;83:103–8. https://doi.org/10.5935/0004-2749.20200024.

[19] Pena-Verdeal H, Garcia-Resua C, Ramos L, Yebra-Pimentel E, Giraldez MJ. Diurnal variations in tear film break-up time determined in healthy subjects by software-assisted interpretation of tear film video recordings. Clin Exp Optom 2016;99(2):142–8. https://doi.org/10.1111/cxo.12324.

[20] Pena-Verdeal H, Ramos L, Garcia-Queiruga J, García-Resúa C, Giráldez MJ, Yebra-Pimentel EJO, et al. Validation of a New Software Application for Tear Break-up Measurement. 2021.

[21] Armstrong RA, Davies LN, Dunne MC, Gilmartin B. Statistical guidelines for clinical studies of human vision. Ophthalmic Physiol Opt 2011;31(2):123–36. https://doi.org/10.1111/j.1475-1313.2010.00815.x.

[22] Jones L, Downie LE, Korb D, Benitez-Del-Castillo JM, Dana R, Deng SX, et al. TFOS DEWS II management and therapy report. Ocul Surf 2017;15(3):575–628. https://doi.org/10.1016/j.jtos.2017.05.006.

[23] Wong J, Lan W, Ong LM, Tong LJTos. Non-hormonal systemic medications and dry eye. Ocul Surf 2011;9(4):212-26. 10.1016/s1542-0124(11)70034-9.

[24] Hashemipour M, Rad AH, Dalili S. Guideline for the treatment of hypothyroidism in prematurity. Int J Prev Med 2021;12:123. https://doi.org/10.4103/ijpvm.IJPVM_424_20.

[25] Martins JRM, Villagelin DGP, Carvalho GA, Vaisman F, Teixeira PFS, Scheffel RS, et al. Management of thyroid disorders during the COVID-19 outbreak: a position statement from the Thyroid Department of the Brazilian Society of Endocrinology and Metabolism (SBEM). Arch. Endocrinol Metab 2021;65(3):368–75. https://doi.org/10.20945/2359-3997000000352.

[26] Galor A, Feuer W, Lee DJ, Florez H, Carter D, Pouyeh B, et al. Prevalence and risk factors of dry eye syndrome in a United States veterans affairs population. Am J Ophthalmol 2011;152(3):377-84. e2. 10.1016/j.ajo.2011.02.026.

[27] Yu K, Bunya V, Maguire M, Asbell P, Ying G-S, Assessment DE, et al. Systemic Conditions Associated with Severity of Dry Eye Signs and Symptoms in the Dry Eye

Assessment and Management Study. Ophthalmology 2021;128(10):1384-92. 10.1016/j.ophtha.2021.03.030.
[28] Kashkouli MB, Alemzadeh SA, Aghaei H, Pakdel F, Abdolalizadeh P, Ghazizadeh M, et al. Subjective versus objective dry eye disease in patients with moderate-severe thyroid eye disease. Ocul Surf 2018;16(4):458–62. https://doi.org/10.1016/j.jtos.2018.07.003.
[29] Sullivan DA, Rocha EM, Aragona P, Clayton JA, Ding J, Golebiowski B, et al. TFOS DEWS II sex, gender, and hormones report. Ocul Surf 2017;15(3):284–333. https://doi.org/10.1016/j.jtos.2017.04.001.
[30] Taylor PN, Albrecht D, Scholz A, Gutierrez-Buey G, Lazarus JH, Dayan CM, et al. Global epidemiology of hyperthyroidism and hypothyroidism. Nat Rev Endocrinol 2018;14(5):301–16.
[31] Uchino M, Nishiwaki Y, Michikawa T, Shirakawa K, Kuwahara E, Yamada M, et al. Prevalence and risk factors of dry eye disease in Japan: Koumi study. Ophthalmology 2011;118(12):2361–7. https://doi.org/10.1016/j.ophtha.2011.05.029.
[32] Ferrero A, Alassane S, Binquet C, Bretillon L, Acar N, Arnould L, et al. Dry eye disease in the elderly in a French population-based study (the Montrachet study: Maculopathy, Optic Nerve, nuTRition, neurovAsCular and HEarT diseases): Prevalence and associated factors. Ocul Surf 2018;16(1):112–9. https://doi.org/10.1016/j.jtos.2017.09.008.
[33] García-Marqués JV, Talens-Estarelles C, García-Lázaro S, Wolffsohn JS, Cerviño A. Systemic, environmental and lifestyle risk factors for dry eye disease in a mediterranean caucasian population. Contact Lens Anterior Eye 2021::101539. https://doi.org/10.1016/j.clae.2021.101539.
[34] Choi JH, Li Y, Kim SH, Jin R, Kim YH, Choi W, et al. The influences of smartphone use on the status of the tear film and ocular surface. PLoS One 2018;13(10):e0206541.