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Systemic, environmental and lifestyle risk factors for dry eye disease in a mediterranean caucasian population

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ABSTRACT

Objectives: To assess systemic, environmental and lifestyle risk factors for dry eye disease (DED) in a Mediterranean Caucasian population.
Methods: A cross-sectional study was performed on 120 Caucasian participants aged between 18 and 89 years (47.0 ± 22.8 years). Medical history, information regarding environmental conditions and lifestyle, Ocular Surface Disease Index, Dry Eye Questionnaire-5, non-Invasive (Oculus Keratograph 5 M) breakup time, tear film osmolarity and ocular surface staining parameters were assessed in a single clinical session to allow DED diagnosis based on the guidelines of the Tear Film and Ocular Surface Society Dry Eye Workshop II Diagnostic Methodology Report. A multivariate logistic regression model was constructed including those variables with a p-value less than 0.15 in the univariate analysis.
Results: A prevalence of 57.7 % for DED was found. No age differences were found between those with and without DED ($U = 1886.5$, $p = 0.243$). Nevertheless, the DED group had more females ($X^2 = 7.033$, $p = 0.008$). The univariate logistic regression identified as potential risk factors for DED the following: female sex, sleep hours per day, menopause, anxiety, systemic rheumatologic disease, use of anxiolytics, daily medication, ocular surgery, poor diet quality, more ultra-processed food in diet, not drinking caffeine and hours of exposure to air conditioning per day. Multivariate logistic regression revealed that hours of sleep per day, menopause and use of anxiolytics were independently associated with DED ($p \leq 0.026$ for all).
Conclusions: DED is associated with systemic, environmental and lifestyle risk factors. These findings are useful to identify potentially modifiable risk factors, in addition to conventional treatments for DED.

1. Introduction

According to the Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II), dry eye disease (DED) is defined as a multifactorial disease characterized by the loss of tear film homeostasis, which is accompanied by symptoms of ocular dryness [1]. The prevalence of DED is increasing substantially worldwide influenced by demographic, systemic and environmental factors. DED prevalence ranges from 5 to 50 % at various ages [2,3], impacting quality of life, visual function, ocular healthiness and work productivity of those who suffer from it [1,2]. Moreover, the multifactorial and heterogeneous aetiology of the disease indicated the tear film and the ocular surface integrity are highly influenced by a wide range of risk factors [2].

The TFOS DEWS II Epidemiology Report listed several risk factors for DED [2]. This *meta*-analysis showed that the prevalence of DED increases with age, female sex and Asian ethnicity. Nevertheless, very few of the studies included in the analysis incorporated young people. Also, the report highlighted that some of the listed risk factors are still inconclusive and there is not yet clear evidence that most of them induce DED [2]. Moreover, studies have significant differences in the methodology and in the procedure followed to diagnose DED, which makes their direct comparison and the building of global conclusions particularly challenging [2,4–6]. In the report, the authors argued that there is still a considerable lack of information about risk factors for DED and that the implementation of studies to assess such factors in different geographic regions is required.

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To the authors' knowledge, there are only two studies [4,6] that have evaluated DED risk factors following the TFOS DEWS II guidelines for the diagnosis and identification of potential risk factors for DED, both performed on a cohort in New Zealand. Authors found that age, ethnicity, migraine, systemic rheumatologic disease, thyroid disease, use of antidepressant medication, oral contraceptive therapy, increased digital screen exposure time and reduced caffeine consumption were independently associated with DED [4,6]. Authors [4,6] also acknowledged the need to analyse non-significant potential risk factors that were not very prevalent in their population. Furthermore, these studies did not consider interactions between demographic, systemic and lifestyle risk factors, since systematic risk factors were assessed separately from lifestyle factors [4,6].

This study is the first to examine DED in a Mediterranean Caucasian population using the standardised TFOS DEWS II criteria and analyzes systemic, environmental and lifestyle DED risk factors [2,5]. In addition, new lifestyle and environmental risk factors have been included in the analysis.

2. Material and methods

One hundred and twenty Caucasian volunteers ranging in age from 18 to 89 years (47.0 ± 22.8 years) participated in this cross-sectional study. In order to evaluate different health and tear film status, no exclusion based on health or tear film parameters was made. Contact lens users were instructed not to wear their contact lenses for the 48 h prior to examination [4,6]. Participants with ocular surgery within the previous three months were excluded. Only volunteers who lived in the region were enroled to minimize environmental differences [4,6]. Only the right eye of each participant was assessed to avoid data bias (except for tear osmolarity which was measured from each eye as recommended). The study was carried out in accordance with the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the University of Valencia. Written consent from each participant was obtained after a verbal explanation of the protocol, nature and possible consequences of the study. Recruitment was carried out by advertisement within University dissemination channels, campus personnel and students, as well as in local public entities in nearby towns.

2.1. Measurements

Ocular surface was assessed using the Oculus Keratograph 5 M (K5 M; Oculus GmbH, Wetzlar, Germany) and the TearLab Osmolarity device (TearLab Corporation, San Diego, CA, USA). Measurements were taken by the same experienced examiner within a single visit. Data was acquired following the guidelines of the TFOS DEWS II Diagnostic Methodology Report, to avoid the destabilization of the tear film, in the following order [5]: Medical history, information regarding environmental conditions and lifestyle, Ocular Surface Disease Index (OSDI), Dry Eye Questionnaire-5 (DEQ-5), Non-Invasive Keratograph Break-Up Time (NIKBUT), tear film osmolarity and ocular surface staining. The temperature and humidity of the room were maintained at 24.1 ± 1.6 °C and 44.9 ± 5.0 %, respectively. Measurements were performed between November 2018 and January 2019, minimizing seasonal variations.

Participants were asked about their lifestyle, medical history, use of oral or topical medications, history of ophthalmic surgery and environmental conditions. The risk factors included in the present study were those reported by the TFOS DEWS II Epidemiology Report [2,4,6]. Participants with rheumatoid arthritis, gout, osteoarthritis, fibromyalgia and osteoporosis were included under the classification of systemic rheumatologic disease, while bradycardia and heart failure were included under the classification of heart disease. Participants graded the quality of their diet as good (excellent or good quality) or poor (poor or fair quality). They were instructed to consider a good diet quality if they believe as having a balanced intake of protein, carbohydrates, fruits and vegetables; whilst a poor diet quality is an unbalanced diet, associated with the intake of ultra-processed food, ready-to-eat products and sugars.

Table 1 shows the risk factors evaluated in the present study. No participant reported a history of Sjögren syndrome, rosacea, acne vulgaris, psoriasis, lupus erythematosus, hepatitis C, steroids deficiency, chronic kidney disease or hematopoietic stem cell transplantation. Moreover, all participants used soft contact lenses daily; therefore, this variable was not included in the analysis since a binary logistic regression was not able to be performed.

The first NIKBUT of the tear film was measured three consecutive times and the median was calculated. Measurements were taken every 3 min to allow tear film stabilization between them [5,7]. Tear film osmometry was performed in both eyes using the TearLab Osmolarity device from 50 nL tear samples collected from the lower lateral canthus tear meniscus. The interocular difference in osmolarity was calculated [4,5].

Ocular surface staining was evaluated with fluorescein strips for the assessment of the cornea, and with lissamine strips for the assessment of the conjunctiva and eyelid margins using the TFOS DEWS II recommended protocol [5]. The number of corneal and conjunctival spots was recorded [4,5,8]. Positive lid wiper epitheliopathy was defined as a lid margin staining ≥ 2 mm in length and/or ≥ 25 % of sagital width (excluding Marx's line) [5,9].

The sample was classified following the indications of the TFOS DEWS II Diagnostic Methodology Report for the diagnosis of DED [5]. Participants were classified into the DED group if they had dry eye symptoms (OSDI ≥ 13 or DEQ-5 ≥ 6) and at least one altered homeostasis marker (NIKBUT less than 10 s; osmolarity ≥ 308 mOsm/L; interocular osmolarity difference greater than 8 mOsm/L; corneal fluorescein staining greater than 5 spots; conjunctival lissamine green staining greater than 9 spots; or lid margin staining ≥ 2 mm length and ≥ 25% width).

2.2. Statistical analysis

Statistical analysis was carried out using SPSS v26.0 for Windows (IBM Corp, Armonk, New York, USA). Results are presented as the mean ± standard deviation (SD), as the median and interquartile range or as the number and percentage of participants, depending on the parameter.

Normality distribution for each group was assessed via the Kolmogorov-Smirnov test or the Shapiro-Wilk test. Significant differences in age between healthy and DED groups were assessed using the Mann-Whitney *U* test, while sex differences between groups were evaluated using the Chi-square analysis.

Univariate logistic regression was performed initially to identify the predictors of DED. Predictors with a p-value less than 0.15 were incorporated into the multivariate logistic regression analysis [4,6]. Collinearity assumption was checked among variables. A p-value of less than 0.05 was considered statistically significant.

The statistical power of the sample was calculated post-hoc using the G*Power 3.1 software [10]. A statistical power of 0.8 was achieved for logistic regression analysis with the sample size of 120 participants and a significance level of 0.05.

3. Results

One hundred and twenty right eyes from 120 participants were measured: 60 females (50 %) and 60 males (50 %). The mean ± SD age of the participants was 47.0 ± 22.8 years, ranging from 18 to 89 years. The comparison between the cohort of the sample and the Spanish population is shown in Fig. 1.

No participant was previously diagnosed with DED. From the total sample, 44 participants (36.7 %) were classified into the healthy group (43.2 ± 21.2 years) and 76 (63.3 %) into the DED group (49.2 ± 23.5 years) according to the criterion described in the TFOS DEWS II Diagnostic Methodology Report. Given that the cohort does not fully

Table 1
Risk factors evaluated in the present study.

Characteristic
Age
Female sex
Lifestyle
Hours of sleep per day
Smoking
Number of cigarettes smoked per day
More than 5 cigarettes smoked per day
Contact lens wear
Hours per week of contact lens wear
More than 56 h per week of contact lens wear
Computer use
Daily hours of computer use
More than 4 h of daily computer use
Exercise
Not walking (sedentary lifestyle)
Hours walking per day
Not practising exercise
Hours practising exercise per week
Medical conditions
Menopause
Allergic rhinitis
Asthma
Hypertension
Ovarian dysfunction
Anxiety
Systemic rheumatologic disease
Diabetes
Hypercholesterolemia
Glaucoma
Migraine headaches
Depression
Heart disease
Thyroid disease
Schizophrenia
Eczema
Stress
Medications
Antihistamines
Antihypertensives
Stomach protector
Oral contraceptive therapy
Anticoagulants
Anxiolytics
Blood glucose regulators
Topical anti-glaucoma medication
Antidepressants
Hypercholesterolemia medication
Anti-inflammatories
Medication for thyroids
Antipsychotics
Daily medication
Ocular surgery
Ocular Surgery
Retinal surgery
Refractive surgery
Pterygium surgery
Glaucoma surgery
Cataract surgery
Diet
Poor diet quality
Non-omnivorous diet
Non-oily fish diet
Percentage of unprocessed food in diet
Percentage of ultra-processed food in diet
Drinking alcohol
Units of alcohol per week
More than 4 units of alcohol per week
Not drinking caffeine
Units of caffeine per day
Litres of water per day
Less than 2 L of water per day
Environment
Working
Hours working per day
Working $\geq$ than 8 h per day
Urban life
Air conditioning
Hours of exposure to air conditioning per day
$\geq$ 8 h of exposure to air conditioning per day
Central heating
Hours of exposure to central heating per day
$\geq$ 8 h of exposure to central heating per day

represent the Spanish population (Fig. 1), a corrected prevalence was calculated by multiplying the DED rate found for each age group by the age proportion in each group. Results show a corrected prevalence of DED using the TFOS DEWS II criteria for the Mediterranean Caucasian population of 57.7 % with a confidence interval of 33.3–80.9 %.

There were no statistically significant age differences between groups (Mann-Whitney $U = 1886.5$, $p = 0.243$). Sixty participants were females (50 %) and sixty males (50 %). Twenty-five per cent of females were classified into the healthy group and 75 % into the DED group, while 48 % of males were classified into the healthy group and 52 % into the DED group. The DED group had statistically higher number of females ($X^2 = 7.033$, $p = 0.008$). Table 2 shows the demographic, clinical characteristics, and environmental and lifestyle factors of participants, while Table 3 shows the ocular surface parameters of the participants.

Table 4 shows the univariate logistic regression and multivariate-adjusted logistic regression analysis, along with the odds ratios of DED for each factor. Given that the cohort does not fully represent the Spanish population, corrected odds ratios were calculated for each risk factor by multiplying the risk factor rate found for each age group by the age proportion in each group. The ratio between the corrected prevalence of that risk factor and the corrected odds ratio was obtained and multiplied for the odds ratio to obtain the corrected odds ratio. This procedure was repeated for each risk factor. In continuous variables, the median value was used to classify participants.

Univariate logistic regression identified the following as potential risk factors for DED (p less than 0.15): Sex, sleep hours per day, menopause, anxiety, systemic rheumatologic disease, use of anxiolytics, daily medication, ocular surgery, poor diet quality, percentage of ultra-processed food in diet, caffeine intake and hours of exposure to air conditioning per day. The interaction between DED and risk factors was statistically significant for sex, sleep hours per day, menopause, anxiety, systemic rheumatologic disease, use of anxiolytics and caffeine intake (p less than 0.05 for all). The multivariate logistic regression revealed that sleep hours per day, menopause and use of anxiolytics were independently associated with DED ($p \leq 0.026$ for all).

4. Discussion

The TFOS DEWS II Epidemiology Report noted that there is an extensive list of risk factors for DED because the tear film and ocular surface form part of a functional unit, which is influenced by lifestyle, environmental conditions, and systemic and ocular disease [2]. The authors acknowledged the need to study the principal and emerging risk factors of DED following the diagnostic guidelines reported in the TFOS DEWS II Diagnostic Methodology Report [2,5].

The TFOS DEWS II Epidemiology Report determined that ageing, feminine sex, Asian ethnicity, computer use, contact lens wear, inadequate environment, and use of antihistamines, antidepressants and anxiolytics were DED risk factors with consistent evidence. Nevertheless, these outcomes cannot be directly compared with the ones reported in the present study, as the TFOS DEWS II Report was constructed on the basis of previous cross-sectional investigations in which the disease diagnosis criterion and methodology differed considerably between studies.

Consequently, the results of the present research can only be directly

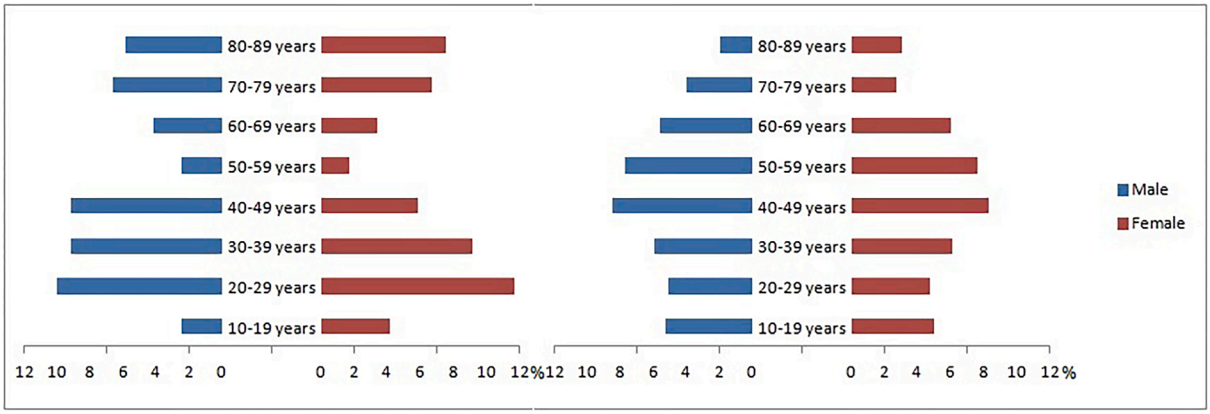

Fig. 1. Tornado plots representing the sample cohort (left) and the Spanish population (right).

compared with the recent studies carried out by Wang et al. [4,6] on a New Zealand population. The present study adds the analysis of the interaction between systemic, environmental and lifestyle DED risk factors. The results of this study showed that DED was independently associated with the use of anxiolytics, menopause and sleep hours per day.

4.1. Age and sex

The association of DED with sex and ageing has been widely reported in previous studies. Several studies found an increase in DED prevalence with age [4,6,11–22], while some did not find a significant association [23–26]. Moreover, some reports indentified that feminine sex was related to DED [11–14,16,18–23,27], while others did not find a relationship [4,23,25,28].

In this study, no independent association was found between DED and age or sex. Even though chi-square analysis showed that the DED group had a statistically higher number of females and that the univariate analysis identified that females were 1.6 times more likely to suffer from DED ($p = 0.009$), feminine sex was not found as statistically associated with DED in the multivariate analysis, which is in agreement with a previous study [24]. Also in consonance with the outcomes of this study, no independent association between sex and DED was found by Wang et al. [4]. Nevertheless, contrary to the Mediterranean Caucasian cohort results reported here, the authors did find an independent association between DED and age in their New Zealand cohort [4,6].

4.2. Medical conditions and medications

Wang et al. [4] also reported an independent association with migraine headaches, systemic rheumatologic disease, thyroid disease and antidepressant medication. In the present work, participants who suffered from systemic rheumatologic disease had 2.8 times more risk to suffer from DED in the univariate regression ($p = 0.047$), but it was not statistically significant in the multivariate analysis. Other studies [13,19,29,30] have also confirmed the relationship between DED and systemic rheumatologic disease since this condition causes an increased concentration of inflammatory cytokines within the tear fluid and conjunctival epithelium, which causes an inflammatory infiltration and structural damage in the lacrimal glands [2,19,31,32].

Additionally, while there is inconclusive evidence as to whether menopause is a risk factor for DED [2], the present study found an independent association with DED. This could be because ovaries produce very low levels of estrogens and progesterone during menopause. It is thought that estrogens are responsible for the regulation of the synthesis of lipids in the meibomian glands, and both estrogens and progesterone modulate the inflammatory response. Researchers have also reported that the decrease in androgens during menopause is also associated with DED [33–36]. Contrary to the outcomes of the present study, Wang et al. [4] found that menopause was only statistically significant in the univariate analysis, but was not statistically significant when its interaction with other variables was analysed.

Several studies have found an association between DED and psychological conditions such as anxiety, depression and stress [11,14–16,29,30,37,38]. However, there is no evidence whether these diseases are a cause or a consequence of DED. The TFOS DEWS II Epidemiology Report acknowledged the need for clarifying the role of anxiolytics and antidepressants in DED [2,11,38]. Different authors [11,13,15,17,38,39] found that anxiolytic medication was a risk factor for the development of dry eye. In support of this, the present study confirmed that anxiolytic medication was independently associated with DED. More precisely, participants who used anxiolytic medication were 5.7 times more likely to suffer from DED. Anxiety was identified as a potential predictor of DED ($p = 0.016$) in the univariate analysis, but was not independently associated with DED in the multivariate analysis. Therefore, the association between DED and anxiety could result as a consequence of the relationship between DED and anxiolytics. Besides, the use of daily medication was identified as a potential risk factor in the univariate analysis, but was not independently associated with DED in the multivariate analysis. Finally, no relationship was found with any other medical conditions.

4.3. Lifestyle, exercise and environmental conditions

Environmental factors such as air pollution, wind, low humidity, use of central heating or air conditioning have been suggested to impact the integrity of the ocular surface [2,24,40–42]. In the present study, air conditioning was identified as a potential risk factor for DED, but it did not show a statistically significant relationship with DED in the multivariate analysis. No other variable related to the environment showed a statistically significant association with DED. In contrast to the outcomes of this study, Roh et al. [19] found that DED was more prevalent in those residing in urban areas and with indoor occupations. Practising regular exercise showed no association with DED either, in agreement with previous studies [6,15,30,37]; although Sano et al. [43] found that physical exercise decreased dry eye symptoms in healthy office workers, which might suggest that exercise has an optimal impact on ocular surface health.

Regarding sleep hours per day, Murube et al. [44] hypothesized that rapid eye movement during sleep serves to increase tear secretion and to humidify and lubricate the ocular surface. The present study confirms that participants sleeping less hours are more likely to suffer from DED. Specifically, each additional sleeping hour reduced the probability of suffering DED by 0.8 times. Conversely, Wang et al. [6] and Na et al. [30] did not find any association between DED and hours of sleep.

It has been also reported that DED is more prevalent in contact lens

Table 2
Demographic, clinical, environmental and lifestyle characteristics of participants.

Characteristic	Results
Age *(mean ± SD)*	47.0 ± 22.8 years
Female sex *(number of participants, percentage of participants)*	60, 50 %
Lifestyle	
Hours of sleep per day *(mean ± SD)*	7.1 ± 1.2
Smoking *(number of participants, percentage of participants)*	31, 26 %
Number of cigarettes smoked per day *(mean ± SD)*	2.6 ± 6.2
More than 5 cigarettes smoked per day *(number of participants, percentage of participants)*	19, 16 %
Contact lens wear *(number of participants, percentage of participants)*	37, 31 %
Hours per week of contact lens wear *(mean ± SD)*	15.6 ± 29.3
More than 56 h per week of contact lens wear *(number of participants, percentage of participants)*	16, 13 %
Computer use *(number of participants, percentage of participants)*	71, 59 %
Daily hours of computer use *(mean ± SD)*	2.9 ± 3.1
More than 4 h of daily computer use *(number of participants, percentage of participants)*	37, 31 %
Exercise	
Not walk (sedentary lifestyle) *(number of participants, percentage of participants)*	29, 24 %
Hours walking per day *(mean ± SD)*	1.1 ± 1.1 h
Not practise exercise *(number of participants, percentage of participants)*	77, 64 %
Hours practising exercise per week *(mean ± SD)*	2.2 ± 4.7 h
Medical conditions	
Menopause *(number of participants, percentage of participants)*	21, 18 %
Allergic rhinitis *(number of participants, percentage of participants)*	19, 16 %
Asthma *(number of participants, percentage of participants)*	7, 6 %
Hypertension *(number of participants, percentage of participants)*	21, 18 %
Ovarian dysfunction *(number of participants, percentage of participants)*	5, 4 %
Anxiety *(number of participants, percentage of participants)*	18, 15 %
Systemic rheumatologic disease *(number of participants, percentage of participants)*	16, 13 %
Diabetes *(number of participants, percentage of participants)*	12, 10 %
Hypercholesterolemia *(number of participants, percentage of participants)*	11, 9 %
Glaucoma *(number of participants, percentage of participants)*	6, 5 %
Migraine headaches *(number of participants, percentage of participants)*	8, 7 %
Depression *(number of participants, percentage of participants)*	8, 7 %
Heart disease *(number of participants, percentage of participants)*	2, 2 %
Thyroid disease *(number of participants, percentage of participants)*	5, 4 %
Schizophrenia *(number of participants, percentage of participants)*	2, 2 %
Eczema *(number of participants, percentage of participants)*	4, 3 %
Stress *(number of participants, percentage of participants)*	10, 8 %
Medications	
Antihistamines *(number of participants, percentage of participants)*	9, 8 %
Antihypertensives *(number of participants, percentage of participants)*	20, 17 %
Stomach protector *(number of participants, percentage of participants)*	4, 3 %
Oral contraceptive therapy *(number of participants, percentage of participants)*	7, 6 %
Anticoagulants *(number of participants, percentage of participants)*	7, 6 %
Anxiolytics *(number of participants, percentage of participants)*	21, 18 %
Blood glucose regulators *(number of participants, percentage of participants)*	9, 8 %
Topical anti-glaucoma medication *(number of participants, percentage of participants)*	6, 5 %
Antidepressants *(number of participants, percentage of participants)*	4, 3 %
Hypercholesterolemia medication *(number of participants, percentage of participants)*	7, 6 %
Anti-inflammatories *(number of participants, percentage of participants)*	3, 3 %
Medication for thyroids *(number of participants, percentage of participants)*	3, 3 %
Antipsychotics *(number of participants, percentage of participants)*	2, 2 %
Daily medication *(number of participants, percentage of participants)*	58, 48 %
Ocular surgery	
Ocular surgery *(number of participants, percentage of participants)*	25, 21 %
Retinal surgery *(number of participants, percentage of participants)*	2, 2 %
Refractive surgery *(number of participants, percentage of participants)*	5, 4 %
Pterygium surgery *(number of participants, percentage of participants)*	1, 1 %
Glaucoma surgery *(number of participants, percentage of participants)*	2, 2 %
Cataract surgery *(number of participants, percentage of participants)*	16, 13 %
Diet	
Poor diet quality *(number of participants, percentage of participants)*	19, 16 %
Non-omnivorous diet *(number of participants, percentage of participants)*	11, 9 %
Non-oily fish diet *(number of participants, percentage of participants)*	79, 66 %
Percentage of unprocessed food in diet *(mean ± SD)*	65 ± 20 %
Percentage of ultra-processed food in diet *(mean ± SD)*	8 ± 11 %
Drinking alcohol *(number of participants, percentage of participants)*	83, 67 %
Units of alcohol per week *(mean ± SD)*	3.2 ± 5.0 units
More than 4 units of alcohol per week *(number of participants, percentage of participants)*	30, 25 %
Not drinking caffeine *(number of participants, percentage of participants)*	28, 23 %
Units of caffeine per day *(mean ± SD)*	1.5 ± 1.5 units
Litres of water per day *(mean ± SD)*	1.7 ± 0.8 L
Less than 2 L of water per day *(number of participants, percentage of participants)*	73, 61 %
Environment	
Working *(number of participants, percentage of participants)*	57, 48 %
Hours working per day *(mean ± SD)*	3.7 ± 4.1 h
Working ≥ than 8 h per day *(number of participants, percentage of participants)*	42, 35 %
Urban life *(number of participants, percentage of participants)*	49, 41 %
Air conditioning *(number of participants, percentage of participants)*	90, 75 %
Hours of exposure to air conditioning per day *(mean ± SD)*	4.2 ± 4.1 h
≥ 8 h of exposure to air conditioning per day *(number of participants, percentage of participants)*	31, 26 %
Central heating *(number of participants, percentage of participants)*	91, 76 %
Hours of exposure to central heating per day *(mean ± SD, years)*	4.7 ± 4.7 h
≥ 8 h of exposure to central heating per day *(number of participants, percentage of participants)*	34, 28 %

Where: SD = Standard Deviation.

Table 3
Ocular surface parameters of participants.

Characteristic	Total	Healthy group	DED group
OSDI score *(median, IQR)*	16.7, 6.3–30.3	4.2, 0–8.3	22.6, 13.9–42.7
DEQ-5 score *(median, IQR)*	7, 4–12	3, 1–5	10, 7–14
NIKBUT *(median, IQR)*	6.69, 4.40–10.66 s	8.54, 4.92–15.29 s	7.76, 4.21–8.36 s
Osmolarity *(median, IQR)*	318.0, 310.5–329.50 mOsmol/L	315.5, 307.75–328.50 mOsmol/L	320.0, 312.0–331.0 mOsmol/L
Difference in osmolarity between eyes *(median, IQR)*	10, 4.5–19 mOsmol/L	9, 4.5–11.5	13, 4–22
Corneal staining greater than 5 spots *(number of participants)*	12	2	10
Corneal staining greater than 9 spots *(number of participants)*	16	3	13
Lid margin staining ≥ 2 mm of length and ≥ 25 % of width *(number of participants)*	31	5	26

Where: IQR = Interquartile range, DED = Dry Eye Disease, DEQ = Dry Eye Questionnaire, mOsmol/L = Milliosmoles per liter, NIKBUT = Non-Invasive Keratograph Break-Up Time and OSDI = Ocular Surface Disease Index.

wearers [2,3,13,23,27,45,46]; nevertheless, the present study did not reveal an association, in agreement with other generally more recent studies [4,12,18]. Wang et al. [4,6], who used the same diagnostic criterion as the present study, did not find an independent association between contact lens wear and DED either, perhaps due to advances in

Table 4
Univariate and multivariate logistic regressions and odds ratios of dry eye disease for demographic and clinical characteristics.

Characteristic	Univariate logistic regression				Multivariate logistic regression			
	Odds ratio/Corrected odds ratio	Lower CI/ Corrected	Upper CI/ Corrected	p-value	Odds ratio/ Corrected odds ratio	Lower CI/ Corrected	Upper CI/ Corrected	p-value
Age	1.012/1.522	0.995/1.516	1.029/1.568	0.164	–	–	–	–
Age (per 10 years)	1.125/1.714	0.945/1.440	1.338/2.039	0.185	–	–	–	–
Female sex	**2.806/1.603**	**1.295/0.740**	**6.081/3.473**	**0.009***	–	–	–	–
Lifestyle								
Hours of sleep per day	**0.654/0.792**	**0.469/0.568**	**0.911/1.103**	**0.012***	0.588/0.712	0.388/0.470	0.891/1.079	0.012*
Smoking	1.298/2.200	0.546/0.926	3.086/5.231	0.555	–	–	–	–
Number of cigarettes smoked per day	1.030/1.746	0.961/1.629	1.104/1.872	0.406	–	–	–	–
More than 5 cigarettes smoked per day	1.307/1.861	0.458/0.652	3.726/5.304	0.617	–	–	–	–
Contact lens wear	0.788/0.770	0.355/0.348	1.747/1.712	0.557	–	–	–	–
Hours per week of contact lens wear	1.001/0.981	0.988/0.968	1.015/0.995	0.825	–	–	–	–
More than 56 h per week of contact lens wear	0.897/0.879	0.301/0.295	2.676/2.622	0.846	–	–	–	–
Computer use	0.745/0.874	0.347/0.418	1.598/1.927	0.449	–	–	–	–
Daily hours of computer use	0.961/1.159	0.852/1.027	1.084/1.307	0.522	–	–	–	–
More than 4 h of daily computer use	0.567/0.766	0.257/0.347	1.254/1.694	0.161	–	–	–	–
Exercise								
Not walk (sedentary lifestyle)	0.636/0.713	0.272/0.305	1.489/1.670	0.297	–	–	–	–
Hours walking per day	1.081/1.146	0.771/0.817	1.514/1.605	0.652	–	–	–	–
Not practise exercise	1.412/1.734	0.655/0.804	3.045/3.740	0.378	–	–	–	–
Hours practising exercise per week	0.827/0.929	0.580/0.651	1.179/1.324	0.293	–	–	–	–
Medical conditions								
Menopause	**7.000/3.458**	**1.546/0.794**	**31.705/ 15.662**	**0.012***	8.759/4.327	1.571/0.776	48.835/2.124	0.013*
Allergic rhinitis	1.307/2.186	0.458/0.766	3.726/6.232	0.617	–	–	–	–
Asthma	1.479/1.039	0.275/0.193	7.964/5.593	0.649	–	–	–	–
Hypertension	2.080/1.502	0.705/0.509	6.138/4.432	0.185	–	–	–	–
Ovarian dysfunction	1001139339/							
624410605.7	0.000	–	0.999	–	–	–	–	
Anxiety	**12.390/14.313**	**1.587/1.833**	**96.698/ 111.706**	**0.016***	–	–	–	–
Systemic rheumatologic disease	**4.742/2.817**	**1.024/0.608**	**21.954/ 13.041**	**0.047***	–	–	–	–
Diabetes	0.791/0.908	0.235/0.270	2.661/3.054	0.705	–	–	–	–
Hypercholesterolemia	1.608/1.765	0.404/0.444	6.406/1.033	0.501	–	–	–	–
Glaucoma	3.028/1.329	0.342/0.150	26.793/ 11.755	0.319	–	–	–	–
Migraine headaches	4.362/3.358	0.519/0.340	36.694/ 28.251	0.175	–	–	–	–
Depression	4.362/1.882	0.519/0.224	36.694/ 15.833	0.175	–	–	–	–
Heart disease	0.573/1.672	0.035/0.102	9.400/27.424	0.697	–	–	–	–
Thyroid disease	0.863/0.346	0.139/0.056	5.375/2.153	0.875	–	–	–	–
Schizophrenia	0.573/0.378	0.035/0.023	9.400/6.204	0.697	–	–	–	–
Eczema	0.566/1.373	0.057/0.138	5.612/13.610	0.627	–	–	–	–
Stress	2.471/4.308	0.501/0.874	12.194/ 21.261	0.267	–	–	–	–
Medications								
Antihistamines	1.171/2.784	0.278/0.661	4.937/11.736	0.829	–	–	–	–
Antihypertensives	1.918/1.404	0.646/0.473	5.699/4.171	0.241	–	–	–	–
Stomach protector	1.767/1.150	0.178/0.116	17.526/ 11.404	0.627	–	–	–	–
Oral contraceptive therapy	3.686/2.027	0.429/0.236	31.666/ 17.410	0.235	–	–	–	–
Anticoagulants	0.759/1.275	0.162/0.272	3.560/5.979	0.727	–	–	–	–
Anxiolytics	**15.357/7.901**	**1.982/1.020**	**118.972/ 61.211**	**0.009***	11.072/5.697	1.338/0.688	91.611/ 47.134	0.026*
Blood glucose regulators	2.130/2.806	0.423/0.557	10.740/ 14.150	0.359	–	–	–	–
Topical anti-glaucoma medication	3.028/1.607	0.342/0.182	26.793/ 14.222	0.319	–	–	–	–
Antidepressants	1.767/1.149	0.178/0.116	17.526/ 11.397	0.627	–	–	–	–
Hypercholesterolemia medication	3.686/4.791	0.429/0.558	31.666/ 41.163	0.235	–	–	–	–
Anti-inflammatories	0.280/0.169	0.025/0.015	3.180/1.921	0.305	–	–	–	–
Medication for thyroids	0.280/0.117	0.025/0.010	3.180/1.328	0.305	–	–	–	–
Antipsychotics	0.573/0.378	0.035/0.023	9.400/6.204	0.697	–	–	–	–

(*continued on next page*)

Table 4 (*continued*)

Characteristic	Univariate logistic regression				Multivariate logistic regression			
	Odds ratio/Corrected odds ratio	Lower CI/ Corrected	Upper CI/ Corrected	p-value	Odds ratio/ Corrected odds ratio	Lower CI/ Corrected	Upper CI/ Corrected	p-value
Daily medication	**1.861/2.037**	**0.873/0.956**	**3.963/4.338**	**0.108**	–	–	–	–
Ocular surgery								
Ocular Surgery	**2.111/1.941**	**0.772/0.710**	**5.770/5.304**	**0.145**	–	–	–	–
Retinal surgery	960552609.3/							
2,802,316,182	0.000	–	0.999	–	–	–	–	
Refractive surgery	2.389/2.070	0.259/0.224	22.075/ 19.128	0.443	–	–	–	–
Pterygium surgery	0.000	0.000	–	1.000	–	–	–	–
Glaucoma surgery	960552609.3/							
421442457.3	0.000	–	0.999	–	–	–	–	
Cataract surgery	1.875/1.524	0.566/0.460	6.216/5.054	0.304	–	–	–	–
Diet								
Poor diet quality	**3.644/3.430**	**0.998/0.939**	**13.312/ 12.532**	**0.050**	3.853/3.627	0.978/0.921	15.168/ 14.279	0.054
Non-omnivorous diet	1.608/1.338	0.404/0.336	6.406/5.329	0.501	–	–	–	–
Non-oily fish diet	1.166/1.558	0.535/0.715	2.539/3.393	0.700	–	–	–	–
Percentage of unprocessed food in diet	0.985/0.615	0.966/0.603	1.006/0.628	0.154	–	–	–	–
Percentage of ultra-processed food in diet	**1.046/1.590**	**0.994/1.511**	**1.102/1.675**	**0.084**	–	–	–	–
Drinking alcohol	1.055/1.328	0.481/0.605	2.315/2.914	0.893	–	–	–	–
Units of alcohol per week	1.026/1.210	0.948/1.118	1.111/1.310	0.529	–	–	–	–
More than 4 units of alcohol per week	1.214/1.432	0.508/0.599	2.900/3.420	0.662	–	–	–	–
Not drinking caffeine	**3.385/1.703**	**1.182/0.595**	**9.690/4.876**	**0.023***	–	–	–	–
Units of caffeine per day	0.892/0.449	0.695/0.350	1.145/0.576	0.369	–	–	–	–
Litres of water per day	0.985/1.116	0.921/1.043	1.053/1.193	0.663	–	–	–	–
Less than 2 L of water per day	1.122/1.271	0.526/0.596	2.396/2.714	0.766	–	–	–	–
Environment								
Working	0.739/0.653	0.351/0.310	1.556/1.375	0.426	–	–	–	–
Hours working per day	0.968/0.855	0.885/0.782	1.059/0.936	0.483	–	–	–	–
Working ≥ than 8 h per day	0.910/0.800	0.419/0.3685	1.977/1.739	0.812	–	–	–	–
Urban life	1.565/1.562	0.725/0.723	3.380/3.373	0.254	–	–	–	–
Air conditioning	1.455/1.682	0.626/0.724	3.381/3.908	0.383	–	–	–	–
Hours of exposure to air conditioning per day	**1.085/1.094**	**0.981/0.989**	**1.201/1.211**	**0.112**	–	–	–	–
≥ 8 h of exposure to air conditioning per day	1.584/1.597	0.654/0.659	3.837/3.867	0.308	–	–	–	–
Central heating	1.074/1.189	0.453/0.502	2.547/2.820	0.871	–	–	–	–
Hours of exposure to central heating per day	0.973/1.077	0.900/0.996	1.051/1.164	0.483	–	–	–	–
≥ 8 h of exposure to central heating per day	1.302/1.667	0.562/0.720	3.015/3.861	0.538	–	–	–	–

Where: CI = 95 % Confidence Interval. * = Statistically significant values. Bold = Variables included in the multivariate analysis ($p < 0.15$).

contact lens materials and greater use of daily disposables [47]. Furthermore, some studies have shown that DED is more prevalent in workers using visual displays as a consequence of a reduced blink frequency and an increase in incomplete blinking during visual display visualization, which have both shown to increase tear evaporation [3,12,27,46]. Wang et al. [6] found that increased hours of digital screen exposure per day was independently associated with DED. Nevertheless, in agreement with other reports [17,24,39], the present study did not reveal an association between DED and digital display use.

It has also been suggested that cigarette smoking is a risk factor for DED [2,30,48–50]. Some studies state that not only is smoking a risk factor by itself, but environmental exposure to smoke can develop dry eye symptoms [48,50]. Nevertheless, other authors did not find a significant association with DED and the TFOS DEWS II Epidemiology Report concluded that it is inconclusive whether smoking is a risk factor for DED [2,12,14,15,17,23,27,39,46]. In this regard, in agreement with the study of Wang et al. [6], the results of this study did not reveal an association between DED and smoking.

4.4. Diet

Diet quality has been also reported as possibly associated with DED. Conditions such as vitamin A or D deficiency, eating disorders or a vegan diet might be related to DED [2,3,51,52]. In the present study, poor diet quality approached the statistical significance cut-off in the multivariate analysis ($p = 0.050$). The percentage of ultra-processed food was included in the multivariate analysis since it was found to be a potential predictor of DED in the univariate analysis ($p = 0.084$). However, it did not reveal an independent association with DED. Essential fatty acids play a relevant role in the tear film and ocular surface healthiness since they enhance the tear film lipid layer and reduce the expression of some inflammatory markers [2,3,53]. This role is still not fully understood, however [2]. The present study did not find an association between DED and non-oily fish or non-omnivorous diet.

Regarding alcohol consumption, the TFOS DEWS II Epidemiology Report considered the evidence as inconclusive as to whether it was a risk factor for DED [2,15]. In agreement with the study of Wang et al. [6], the present study did not find an association between alcohol consumption and DED.

Some studies [2,14,17] have reported that drinking caffeine increases tear production; in the present study this factor did not reveal an independent association with DED, although the univariate analysis showed that participants who did not drink caffeine had 1.7 times more probability to suffer from DED ($p = 0.023$). In the study of Wang et al.

[6] reduced caffeine intake per day was indentified as a risk factor for DED.

4.5. Ocular surgery

Ocular surgery, such as refractive or cataract surgery, have been identified as potential risk factors for DED [2,14,18,20,39,45,54,55]. Ocular surgery was included in the multivariate analysis since it was found to be a potential predictor of DED in the univariate analysis ($p = 0.145$), but it did not reveal an independent association with DED.

The present study has some limitations that must be taken into account. First, dry eye classification subtypes (aqueous deficient and evaporative) were not considered in the analysis. Thus, both types of DED were analysed altogether. Medical history, environmental and lifestyle factors were self-reported by participants, which might have induced recall bias, although this can be considered as an inherent limitation of any cross-sectional study.

The magnitude of the prevalence of DED was higher than in previous studies of similar nature. Thus, the presented prevalence was corrected for the general population and was still notably higher than that reported in New Zealand using the same diagnostic criteria [4,6]. The new DED diagnostic criterion, described in the TFOS DEWS II, is less restrictive and has been reported to increase the prevalence of the disease [4]. Heat and humidity of the region could also have increased the prevalence in a Mediterranean Caucasian population. Previous research [56] found that dry eye was more prevalent in Spain than in another country with different levels of environmental humidity. Moreover, a recent study [57] informed that the number of patients with DED has increased steadily throughout the years in Spain, which might be partially caused by modern-day workplace in Spanish society. In addition, the high prevalence found in the present study might be in agreement with the high incidence of clinical tests, sale of dry eye products and the number of dry eye specialist visits reported in Spain [17,58–61]. Although all these points might explain the high prevalence of DED in the results, the recruitment process through an open advertisement could also have induced a higher prevalence of DED than expected in the general population.Some of these limitations are also acknowledged to exist in previous studies with similar designs [2,4].

Moreover, although participants were assessed in a single visit and in the same laboratory under controlled environmental conditions, seasonal variations may have induced some variability in the results. Nevertheless, such variations can be considered minimal since measurements were performed between November 2018 and January 2019. As in a previous study [4], the wide confidence intervals found, might have decreased the study power, and the high number of variables included might have induced false-positive results. Nonetheless, this issue was partially minimized by the fact that not all these variables were analysed together: although 76 variables were assessed as risk factors in the univariate analysis, only 12 of them were finally analysed together and included in the multivariate logistic regression.

In addition, the cohort of the present study is not completely representative of the Spanish population since there is a gap in the ’50 s and ’60 s. To amend this issue, a corrected prevalence for the Spanish population and a corrected risk factor odds ratio were calculated. Likewise, the chances of finding a significant value are low in the factors that are not common in the cohort. Therefore, factors that have a low percentage of people in the sample cannot be excluded as risk factor for DED. Finally, the main limitation of this work was the number of participants recruited, which could explain the lack of association with factors such as age or sex, although the sample analysis showed that such sample size was able to provide a good level of statistical power. In any case, the results of the present study allow a hypothesis to be built for testing in future studies.

Overall, the present study found that DED following the diagnostic guidelines of the TFOS DEWS II Diagnostic Methodology Report had a prevalence of 57.7 % in a Mediterranean Caucasian population. DED is independently associated with anxiolytic medication, less sleep hours per day and menopause. This work identifies the key risk factors of DED to be used in the screening of the condition. Clinicians should acknowledge the importance of triaging questions, systemic comorbidities and risk factors when managing a patient with dry eye symptoms. Moreover, the present study identifies potentially modifiable risk factors, in addition to conventional treatments for DED. Finally, clinicians should be aware that not only ocular surface assessment, but also systemic and environmental examination are relevant for DED participants.

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