Title: Modifiable lifestyle risk factors for dry eye disease

Authors:

Michael T. M. Wang, MBChB [1]

Alex Muntz, PhD[1]

Brinda Mamidi, BOptom[1,2]

James S. Wolffsohn, PhD FCOptom FAAO FIACLE FBCLA PFHEA FRSB[3]

Jennifer P. Craig, PhD FCOptom FAAO FBCLA FACLS [1]

Author affiliations:

[1] Department of Ophthalmology, New Zealand National Eye Centre, The University of Auckland, New Zealand

[2] Department of Optometry and Vision Science, New Zealand National Eye Centre, The University of Auckland, New Zealand

[3] Ophthalmic Research Group, School of Life and Health Sciences, Aston University, Birmingham, United Kingdom

Corresponding author:

Professor Jennifer P. Craig
Department of Ophthalmology
New Zealand National Eye Centre
The University of Auckland, New Zealand
Private Bag 92019
Auckland 1142
New Zealand

Phone: +64 9 923 8173
Fax: +64 9 367 7173
Email: jp.craig@auckland.ac.nz

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ABSTRACT

Purpose: To examine the association between modifiable lifestyle factors and dry eye disease.

Methods: Three hundred and twenty-two community residents (186 females, 136 males; mean±SD age, 41±22 years) with no major systemic or ophthalmic conditions (other than dry eye disease) were recruited in a cross-sectional study. A lifestyle factor questionnaire was administered, and dry eye symptomology, ocular surface characteristics, and tear film quality were evaluated for each participant within a single clinical session, in accordance with the global consensus recommendations of the TFOS DEWS II reports.

Results: A total of 111 (34%) participants fulfilled the TFOS DEWS II diagnostic criteria for dry eye disease. Multivariate regression analysis demonstrated that advancing age, female sex, East Asian ethnicity, and increased digital screen exposure time were positive risk factors for dry eye disease (all $p<0.05$), while increased caffeine consumption was a protective factor ($p=0.04$).

Conclusions: Increased digital screen exposure time and reduced caffeine consumption were modifiable lifestyle factors associated with higher odds of dry eye disease. These findings might contribute to informing the design of future prospective research investigating the efficacy of preventative intervention and risk factor modification strategies.

KEYWORDS

Epidemiology; lifestyle; risk factor; dry eye; ocular surface; tear film

INTRODUCTION

Dry eye disease is a highly prevalent ophthalmic condition, which is acknowledged to have significant financial and public health burden worldwide.[1, 2] The condition is characterised by homeostatic disturbance of the ocular surface, which leads to a self-perpetuating vicious cycle of tear film instability, hyperosmolarity and inflammation.[3, 4] The resulting symptoms of ocular discomfort and visual blurring can be associated with significant impacts on quality of life and work productivity.[1, 5, 6] In the United States, it is estimated that the total societal expenditure related to dry eye disease, including therapeutic management, physician visits, productivity loss, and other associated costs, amounts to over US$55 billion per year.[2]

On account of the projected increase of the financial and public health burden of dry eye disease with the ageing population,[1, 4, 7] there has been growing interest in the identification of modifiable risk factors for the condition.[1, 8] Indeed, preventative intervention efforts and risk factor modification strategies might potentially be more cost effective than disease treatment at the population level.[1, 2, 8] While the Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) Epidemiology Report identified a number of potential lifestyle factors that might be associated with the development of dry eye disease, it also highlighted the need for further research to clarify the inconsistent findings reported in the contemporaneous scientific literature.[1] Furthermore, the lack of consistency in methodological design and disease definition was acknowledged to introduce significant challenges when interpreting and comparing the findings of earlier epidemiology studies.[1] The purpose of the current cross-sectional study was therefore to evaluate the relationship between lifestyle factors and dry eye disease, incorporating diagnostic criteria and methodology in accordance with the global consensus recommendations of the TFOS DEWS II Diagnostic Methodology report.[9]

METHODS

Subjects

This cross-sectional study adhered to the tenets of the Declaration of Helsinki, and was approved by the University of Auckland Human Participants Ethics Committee. Participants were recruited through open advertisement at a single university centre, between June 2018 and June 2019. To minimise environmental differences, participants were required to be local community residents who had lived in the Auckland region for at least 15 years. Furthermore, eligibility required participants to be at least 16 years of age, with no contact lens wear 48 hours prior to study participation; report no history of major systemic or ophthalmic conditions (other than anterior blepharitis, meibomian gland dysfunction and dry eye disease); no use of systemic or topical medications known to affect the eye in the previous three months; and no previous ophthalmic surgery. Eligible participants were enrolled after providing written consent. The sample size was pragmatically determined by the number of participants enrolled during the recruitment period.

Measurements

Participants were assessed at a single site, with a mean±SD room temperature of 20.2±0.6°C and a mean±SD relative humidity of 63.8±6.4%, and ocular measurements were conducted on the right eye of each participant. Clinical measurements were conducted in accordance with the recommendations of the TFOS DEWS II Diagnostic Methodology subcommittee.[9] To minimise the impact on ocular surface and tear film physiology for subsequent assessments, clinical measurements were performed in ascending order of invasiveness,[9] as listed in Table 1. The diagnostic criteria for dry eye disease was based on the global consensus recommendations of the Tear Film and Ocular Surface Society Dry Eye Workshop II,[9] as summarised in Table 2.

Table 1: Order of clinical assessments conducted during the study visit.

Assessments
1. Lifestyle factor questionnaire
2. OSDI dry eye questionnaire
3. DEQ-5 dry eye questionnaire
4. Tear meniscus height
5. Non-invasive tear film breakup time
6. Tear film lipid layer grade
7. Tear osmolarity
8. Ocular surface staining
9. Infrared meibography

Table 2: Diagnostic criteria for dry eye disease based on the global consensus recommendations of the Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II).[9]

Diagnosis	Criteria
Dry eye disease	• OSDI score ≥13, or DEQ-5 score ≥6 AND • Non-invasive tear film breakup time <10s, tear osmolarity ≥308mOsm/L, inter-ocular difference in osmolarity >8mOsm/L, corneal staining >5 spots, conjunctival staining >9 spots, or lid margin staining ≥2mm length and ≥25% width

A lifestyle factor questionnaire was administered, and included questions on contact lens wear, urban or rural residential area, educational attainment, digital screen exposure, hours spent in air-conditioned or centrally heated environments, exercise, outdoor activity, sleep, diet, water intake, caffeine intake, alcohol consumption, and smoking. The lifestyle risk factors investigated in the current study were based on those identified in the TFOS DEWS II Epidemiology Report and recent dry eye epidemiology studies.[1, 10, 11] The Ocular Surface Disease Index (OSDI) and 5-Item Dry Eye Questionnaire (DEQ-5) questionnaires were then administered to grade the level of dry eye symptomology.[9]

Tear meniscus height, non-invasive tear film breakup time, and tear film lipid layer grade were evaluated using the Keratograph 5M (Oculus Optikgeräte GmbH, Wetzlar, Germany). The lower tear meniscus height was measured using high magnification pre-calibrated digital imaging, and three readings near the centre of the lower meniscus were averaged. Non-invasive tear film breakup time was assessed using automated detection of first break-up, while the subject maintained fixation and was requested to refrain from blinking. Three breakup time readings were averaged in each case.[9] Tear film lipid layer interferometry was graded according to the modified Guillon-Keeler system: grade 1, open meshwork; grade 2, closed meshwork; grade 3, wave or flow; grade 4, amorphous; grade 5, coloured fringes; grade 0, non-continuous layer (non-visible or abnormal coloured fringes).[12, 13]

Tear film osmolarity measurements were performed with a clinical osmometer (TearLab, California, USA), from 50nL tear samples collected from the lower lateral canthal tear meniscus. A measurement was taken for each eye, and the higher reading and the inter-ocular difference recorded.[9]

Sodium fluorescein and lissamine green dyes were applied using the recommended technique described in the TFOS DEWS II Diagnostic Methodology report, in order to

evaluate localised corneal and conjunctival areas of epithelial desiccation, and lid wiper epitheliopathy.[9]

Infrared meibography was imaged with the Oculus Keratograph 5M, with the superior and inferior eyelids everted in turn. From the captured image, the proportion of meibomian glands visible within the tarsal area was graded according to the five-point Meiboscale.[14]

Statistics

Statistical analysis was conducted with Graph Pad Prism version 8.01 (California, USA) and IBM SPSS version 24 (New York, USA). Preliminary univariate logistic regression was used to identify potential predictors of dry eye disease. Multivariate logistic regression for predictors of dry eye disease was then conducted, incorporating variables with a univariate association threshold of $p<0.15$. The number of variables used in the multivariate regression analysis was limited to the number of diagnosed participants divided by 10, to avoid overfitting. All tests were two tailed, and $p<0.05$ was considered significant. Data are presented as mean±SD, median (IQR), or number of participants (% of participants) unless otherwise stated.

RESULTS

The mean ± SD age of the 322 participants (186 females, 136 males) was 41±22 years (range, 16 to 88 years). Demographic, lifestyle, and ophthalmic characteristics of participants are presented in Table 3. Overall, 111 (34%) participants fulfilled the TFOS DEWS II criteria for dry eye disease.

Table 3: Demographic, lifestyle, and ocular surface characteristics of participants. Data are presented as mean ± SD, median (IQR), or number of participants (% of participants). Asterisks denote statistically significant values (p<0.05).

Characteristic	Total (n=322)	TFOS DEWS II diagnostic criteria for dry eye disease		
		Present (n=111)	Absent (n=211)	p
Demographics				
Age (years)	41±22	46±22	38±22	0.005*
Female sex	186 (58%)	75 (68%)	111 (53%)	0.01*
European ethnicity	136 (42%)	37 (33%)	99 (47%)	0.02*
East Asian ethnicity	116 (36%)	49 (44%)	67 (32%)	0.04*
South Asian ethnicity	32 (10%)	11 (10%)	21 (10%)	>0.99
Other ethnicity	38 (12%)	14 (13%)	24 (11%)	0.72
Lifestyle factors				
Contact lens wear	87 (27%)	36 (32%)	51 (24%)	0.12
Urban residential area	310 (96%)	107 (96%)	203 (96%)	>0.99
Work hours per weekday (hours)	8 (6-8)	8 (5-8)	8 (6-8)	0.78
Tertiary educational attainment	208 (65%)	76 (68%)	132 (63%)	0.33
Hours of digital screen exposure per day (hours)	4 (3-7)	5 (4-8)	4 (2-7)	0.02*
Hours spent in air-conditioned or centrally heated environments per day (hours)	4 (0-8)	4 (0-8)	4 (0-8)	0.96
Hours of exercise per day (hours)	1 (0-1)	1 (0-1)	1 (0-1)	0.89
Hours of outdoor activity per day (hours)	2 (1-3)	2 (1-3)	2 (1-3)	0.82
Hours of sleep per day (hours)	7 (6-8)	7 (6-8)	7 (6-8)	0.36
Vegetarian diet	14 (4%)	4 (4%)	10 (5%)	0.78
Water intake per day (cups)	3 (2-6)	3 (2-5)	3 (2-6)	0.65
Caffeine intake per day (servings)	1 (0-3)	1 (0-1)	1 (0-3)	0.03*
Alcohol consumption per week (units)	1 (0-6)	1 (0-5)	1 (0-6)	0.39
Smoking	62 (19%)	21 (19%)	41 (19%)	>0.99
Dry eye symptomatology				
OSDI score (out of 100)	15 (6-33)	8 (2-12)	33 (22-50)	<0.001*
DEQ-5 score (out of 22)	6 (4-10)	5 (4-6)	9 (6-13)	<0.001*
Tear film quality				
Non-invasive tear film breakup time (s)	7.9 (4.7-11.4)	5.5 (3.2-7.3)	9.2 (6.4-15.1)	0.007*
Tear film osmolarity (mOsmol/L)	308±14	312±17	305±12	0.003*
Inter-ocular difference in osmolarity (mOsmol/L)	7 (3-11)	10 (5-16)	6 (2-8)	0.01*
Tear film lipid layer grade (out of 5)	3 (2-4)	2 (1-3)	3 (2-4)	0.02*
Tear meniscus height (mm)	0.28±0.12	0.25±0.11	0.29±0.12	0.006*
Ocular surface characteristics				
Corneal staining >5 spots	61 (19%)	35 (32%)	26 (13%)	<0.001*
Conjunctival staining >9 spots	94 (29%)	53 (48%)	41 (19%)	<0.001*
Lid wiper epitheliopathy ≥2mm length and ≥25% width	114 (35%)	63 (57%)	51 (24%)	<0.001*
Superior meibography grade (out of 4)	1 (0-2)	2 (1-3)	1 (0-2)	0.002*
Inferior meibography grade (out of 4)	1 (0-2)	1 (1-3)	1 (0-2)	0.03*

Unadjusted univariate and multivariate-adjusted odds ratios of dry eye disease by demographic and lifestyle characteristic are presented in Tables 4. Multivariate regression analysis demonstrated that advancing age, female sex, and East Asian ethnicity were positive risk factors of dry eye disease (all $p<0.05$). Increased digital screen exposure time (per 1 hour/day increase) was a significant predictor of higher odds of dry eye disease (OR=1.14, 95% CI 1.04-1.26, p=0.008). Increased caffeine consumption (per 1 serving/day increase) was independently associated with reduced odds of dry eye disease (OR=0.84, 95% CI, 0.72-0.98, p=0.03). Sensitivity analysis demonstrated similar trends following the exclusion of participants with a history of contact lens wear.

Table 4: Logistic regression odds ratio of dry eye disease by demographic and clinical characteristics. Asterisks denote statistically significant values ($p<0.05$).

Characteristic	Unadjusted univariate logistic regression		Multivariate-adjusted logistic regression	
	OR (95% CI)	p	OR (95% CI)	p
Demographics				
Age (per 10 years)	1.16 (1.04-1.28)	0.005*	1.21 (1.06-1.44)	0.006*
Female sex	1.85 (1.14-2.97)	0.01*	1.83 (1.06-3.15)	0.03*
East Asian versus European ethnicity	1.96 (1.16-3.32)	0.01*	2.07 (1.10-3.91)	0.02*
South Asian versus European ethnicity	1.40 (0.62-3.19)	0.42	-	-
Other versus European ethnicity	1.56 (0.73-3.34)	0.25	-	-
Lifestyle factors				
Contact lens wear	1.51 (0.91-2.50)	0.11	1.35 (0.75-2.42)	0.32
Urban residential area	1.05 (0.31-3.58)	0.93	-	-
Work hours per weekday (per hour)	1.03 (0.90-1.17)	0.68	-	-
Tertiary educational attainment	1.30 (0.79-2.12)	0.29	-	-
Hours of digital screen exposure per day (per hour)	1.12 (1.03-1.22)	0.007*	1.14 (1.04-1.26)	0.008*
Hours spent in air-conditioned or centrally heated environments per day (per hour)	1.01 (0.95-1.07)	0.79	-	-
Hours of exercise per day (per hour)	0.96 (0.56-1.66)	0.89	-	-
Hours of outdoor activity per day (per hour)	1.05 (0.94-1.17)	0.39	-	-
Hours of sleep per day (per hour)	1.02 (0.97-1.08)	0.43	-	-
Vegetarian diet	0.75 (0.23-2.45)	0.64	-	-
Water intake per day (per cup)	0.96 (0.88-1.04)	0.33	-	-
Caffeine intake per day (per serving)	0.84 (0.72-0.98)	0.03*	0.82 (0.68-0.99)	0.04*
Alcohol consumption per week (per unit)	1.01 (0.94-1.07)	0.89	-	-
Smoking	0.97 (0.54-1.74)	0.91	-	-

DISCUSSION

The results of this study demonstrated that advancing age, female sex, East Asian ethnicity, and increased digital screen exposure time were positive risk factors of dry eye disease, while increased caffeine consumption was a significant protective factor. The TFOS DEWS II epidemiology report previously identified the lack of methodological homogeneity and disease definition to introduce significant challenges when interpreting the results of dry eye epidemiology studies.[1] To our knowledge, this study is among the first to assess the relationship between lifestyle factors and dry eye disease using the global consensus TFOS DEWS II diagnostic criteria.[9] In addition, recruited participants were required to be residents within the Auckland region over the past 15 years, providing some degree of control to climate and environmental exposure, and none of the participants reported any major systemic or ophthalmic conditions other than dry eye disease.

Consistent with the trends reported in previous studies and the TFOS DEWS II epidemiology report,[1, 15-23] advancing age, female sex, and Asian ethnicity were identified to be non-modifiable positive risk factors of dry eye disease. Indeed, dry eye disease is acknowledged to be an age-related, degenerative condition which progresses with cumulative lifetime exposure to various environmental and physiological factors, that culminate in neurosensory abnormalities, hormonal changes, tear film homeostatic disturbances, and ocular surface inflammation.[1, 4, 7, 24] The association between female sex and dry eye disease has been hypothesised to be partially attributed to the complex inter-relationships between the regulatory action of sex steroids, hypothalamic-pituitary and thyroid hormones on the immune system and ocular surface.[1, 25, 26] The East Asian ethnic propensity to dry eye development has been hypothesised to be related to anatomical differences in orbital structure, that predispose to increased eyelid tension, incomplete blinking, and accelerated rates of meibomian gland dropout.[17, 20, 27]

Increased digital screen exposure time was shown to be positively associated with dry eye disease in the current study. These results are in agreement with the trends reported by earlier observational studies.[28, 29] The association between digital device screen exposure and dry eye disease is thought to be mediated by the suppression of spontaneous and reflex blinking while performing tasks related to significant cognitive loading and visual processing.[30-32] This can lead to decreased blink rate and completeness,[29, 32] thereby reducing the delivery of meibomian gland secretions to the ocular surface and impairing the integrity and quality of the surface tear film lipid layer.[27] A continuous lipid layer has been previously demonstrated to be essential for inhibiting aqueous tear evaporation,[33] and the pathophysiological changes associated with diminished blink quality can result in a vicious cycle of tear film hyper-evaporation, instability, hyper-osmolarity, and ocular surface inflammation.[4, 27] Furthermore, up-gaze associated with the use of certain desktop computer monitors might also increase the exposed ocular surface area between blink cycles,[31, 34] further exacerbating any pre-existing aqueous tear hyper-evaporation.[4]

Increased caffeine consumption was demonstrated to be a protective factor of dry eye disease in the current study, although conflicting findings have been reported in previous studies.[10, 11, 35-38] Although increased tear meniscus height and Schirmer's test values have been observed following caffeine consumption in prospective, placebo-controlled, crossover studies,[35, 36] conflicting results have been reported in earlier observational research.[37, 38] The protective effects of caffeine have been previously hypothesised to be mediated by the stimulation of increased aqueous tear production of the lacrimal glands via the inhibition of 3',5'-cyclic nucleotide phosphodiesterase, although the exact mechanisms remain yet to be fully understood.[11, 35, 36]

The identification of modifiable risk factors, including digital screen exposure time and caffeine consumption, in the current study might inform future research in preventative management strategies.[1, 8] Dry eye disease is recognised to have significant public health

impacts and financial burden;[1, 2] and in the United States, the total societal expenditure related to physician visits, therapeutic management, productivity loss, and other associated costs that amounts to the equivalent of around US$1 billion per week.[2] Preventative intervention and risk factor modification strategies might potentially be more cost effective at the population level.[1, 8] While the observational nature of the current study would preclude the inference of causality, future prospective or randomised studies should be conducted to further investigate the long-term effects of blinking training, digital screen exposure time modification, and caffeine consumption on the ocular surface and tear film.[1, 8, 27, 35, 36]

This study is not without limitations. Lifestyle factors were self-reported by participants, which can introduce recall bias. The inclusion of participants with recent contact lens wear might have contributed to a higher proportion of participants fulfilling the diagnostic criteria for dry eye disease, although sensitivity analysis following the exclusion participants with a history of contact lens wear demonstrated similar trends to the primary analysis. The open recruitment process might also be associated with selection bias. Nevertheless, the same limitations are acknowledged to exist in previous studies with similar designs, and may be partially mitigated to some extent by recruiting from healthy community residents with no other major systemic or ophthalmic conditions through a university research centre, rather than a hospital-based convenience sample of patients. Moreover, a number of additional lifestyle factors, including body mass index and other dietary factors, such as green tea consumption,[39, 40] were not investigated in the current study, and would warrant further investigation in future epidemiological studies.

In conclusion, advancing age, female sex, East Asian ethnicity, and increased digital screen exposure time were positive risk factors of dry eye disease, while increased caffeine consumption was a protective factor. The identification of modifiable risk factors for dry eye disease in the current study might contribute towards informing the design of future

prospective research investigating the efficacy of preventative intervention and risk factor modification strategies.

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