Manuscript title: Demographic and lifestyle risk factors of dry eye disease subtypes: a cross-sectional study

Short title: Demographic and lifestyle risk factors of dry eye subtypes

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ABSTRACT

Purpose: To evaluate demographic and lifestyle factors associated with aqueous deficient and evaporative dry eye disease.

Methods: A total of 1125 general public visitors (707 females, mean±SD age, 33±21, range 5-90 years) at the Royal Society Summer Science Exhibition were recruited in a cross-sectional study. A demographic and lifestyle factor questionnaire was administered, and dry eye symptomology (DEQ-5 score), ocular surface characteristics (conjunctival hyperaemia, and infrared meibography), and tear film parameters (tear meniscus height, non-invasive breakup time, and lipid layer grade) were evaluated for each participant within a single session. The diagnostic criteria for dry eye disease subtypes were adapted from the rapid non-invasive dry eye assessment algorithm.

Results: Overall, 428 (38%) participants fulfilled the diagnostic criteria for dry eye disease, 161 (14%) with aqueous deficient dry eye disease, and 339 (30%) with evaporative dry eye disease. Multivariate logistic regression demonstrated that advancing age, female sex, reduced sleep duration, increased psychological stress, and poorer self-perceived health status were independently associated with aqueous deficient dry eye disease (all $p<0.05$). Significant risk factors for evaporative dry eye disease included advancing age, East and South Asian ethnicity, contact lens wear, increased digital device screen exposure, higher psychological stress, and poorer self-perceived health status (all $p<0.05$).

Conclusions: Both subtypes of dry eye disease were associated with several unique and shared demographic and lifestyle factors. The findings of this study could inform future research design investigating the utility of targeted screening and risk factor modification for the prevention and management of dry eye disease.

KEYWORDS

Risk factor; epidemiology; dry eye; ocular surface; tear film; meibomian gland; lacrimal gland

1. INTRODUCTION

Dry eye disease is a chronic ophthalmic pathology that is recognized to have profound impacts on ocular comfort, visual function and quality of life.[1-3] The disease afflicts between 5% to 50% of the adult population in different parts of the world,[1] and is acknowledged to have significant public health and financial burden globally.[1, 4]

Etiologically, dry eye disease is commonly classified into aqueous deficient and evaporative subtypes, which represent diminished production or excessive evaporative losses from the tear film, respectively.[5, 6] It is recommended that dry eye disease subtype classification should inform targeted management.[7] Evaporative disease occurs at a higher population prevalence than aqueous tear deficiency, and is commonly caused by underlying meibomian gland dysfunction or contact lens wear.[1, 5, 8] Nevertheless, regardless of etiological cause, a self-perpetuating vicious circle of homeostatic disturbance ensues, leading to tear film instability, hyperosmolarity, ocular surface inflammation, and the development and progression of dry eye symptoms.[6, 9]

In recent years, there has been growing interest in the demographic and lifestyle factors associated with the development of dry eye disease,[1, 7] in the context of the projected rise of the public health and financial burden with the ageing population.[1, 6, 10] Indeed, preventative interventions, such as targeted screening, risk factor modification, and health promotion strategies may potentially be more cost effective than disease treatment at the population level.[1, 4, 7] The global consensus Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) Epidemiology Report identified a number of consistent, probable, and inconclusive demographic and lifestyle risk factors for dry eye as a whole, and highlighted the ongoing need for research to further characterise the modifiable and non-modifiable risk factors for dry eye disease.[1] In addition, potential differences in the risk factor profiles between aqueous deficient and evaporative dry eye disease subtypes

requires further investigation, and a number of previous epidemiological studies have been limited by assessment of dry eye symptoms without confirmation by clinical signs.[1, 11] The purpose of this cross-sectional study was therefore to investigate demographic and lifestyle factors associated with the two etiological subtypes of dry eye disease, using an adapted version of the rapid non-invasive dry eye assessment algorithm incorporating the evaluation of both clinical signs and symptoms.[11, 12]

2. MATERIALS AND METHODS

2.1. Subjects

This cross-sectional study adhered to the tenets of the Declaration of Helsinki, and was approved by the institutional ethics committee. Participants were recruited through open advertisement from visitors at the Royal Society Summer Science Exhibition between July 2 to July 8 2018 in London, United Kingdom. Participants provided informed consent electronically after reviewing the study information. No identifying information traceable to an individual participant was collected. Study participants did not receive compensation.

A total of 1125 eligible participants were recruited, exceeding sample size requirement calculations for the multivariable logistic regression with an estimated minimum dry eye subtype prevalence of 15%, which showed that a minimum of 667 participants were required for a model incorporating up to 10 predictor variables, with the number of events per variable (EPV) value being 10.[13] The estimated power was 86.6% for detecting an odds ratio magnitude of 1.25 with the 1125 eligible participants recruited.

2.2. Measurements

Participants were assessed at a single location, and ocular measurements were conducted on the left eye of each participant. Clinical measurements were conducted in accordance with the recommendations of the TFOS DEWS II Diagnostic Methodology subcommittee.[11] To minimise the impact on ocular surface and tear film physiology for subsequent assessments, clinical measurements were performed in ascending order of invasiveness,[11] as listed in Table 1. The diagnostic criteria for dry eye disease, aqueous deficient dry eye disease, and evaporative dry eye disease are summarised in Table 2, and were adapted from the rapid non-invasive dry eye assessment algorithm, which has been previously validated and

demonstrated high diagnostic consistency with the global consensus diagnostic battery and subclassification testing scheme of the TFOS DEWS II and the recommendations of the International Workshop of Meibomian Gland Dysfunction,[11, 12, 14] although the 5-Item Dry Eye Questionnaire (DEQ-5) from the original TFOS DEWS II battery was retained for the symptomology arm of the diagnostic criteria.

A lifestyle factor questionnaire was administered, with questions investigating risk factors identified in previous epidemiology studies,[1] including contact lens wear, as well as the average hours per day of digital screen exposure, exercise, outdoor activity, and sleep. Participants were asked to rate self-reported diet quality on a 4-point scale: 1, poor diet quality; 2, fair diet quality; 3, good diet quality; 4, excellent diet quality; self-reported psychological stress burden on a 4-point scale: 1, minimal stress burden; 2, mild stress burden; 3, moderate stress burden; 4, high stress burden; self-perceived health status on a 4-point scale: 1, poor health status; 2, fair health status; 3, good health status; 4, excellent health status.

The 5-Item Dry Eye Questionnaire (DEQ-5) questionnaire was then administered to grade the level of dry eye symptomology.[15]

Conjunctival hyperaemia, tear meniscus height, non-invasive tear film breakup time, and tear film lipid layer grade were assessed using the Keratograph 5M (Oculus Optikgeräte GmbH, Wetzlar, Germany). Bulbar and limbal conjunctival hyperaemia were graded according to automated objective evaluation of high magnification digital imaging, using the proprietary JENVIS grading scale from 0 to 4, and recorded to 1 decimal place.[16] The lower tear meniscus height was assessed using high magnification pre-calibrated digital imaging, and three measurements near the centre of the lower meniscus were averaged. Non-invasive tear film breakup time was determined by 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.[11] 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).[17, 18]

Infrared meibography was imaged with the Oculus Keratograph 5M, with the superior and inferior eyelids everted in turn.[19] From the captured images, the proportions of meibomian glands visible within the upper and lower tarsal areas were graded according to the five-point Meiboscale.[20]

2.3. 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 subtypes. Multivariate logistic regression for predictors of dry eye subtypes was then conducted, incorporating variables with a univariate association threshold of $p<0.15$. The presence or absence of each dry eye disease subtype were assessed as binary outcomes evaluated in two separate multivariate regression models, and participants with mixed disease concurrently fulfilling the diagnostic criteria for the two subtypes were treated as positive cases in both models. The number of variables used in the multivariate regression analysis was approximately limited to the number of diagnosed participants divided by 10, to avoid overfitting. The Cox and Snell pseudo R^2 was used to assess model fit. 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.

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

Assessments
1. Lifestyle factor questionnaire
2. DEQ-5 dry eye questionnaire
3. Conjunctival hyperaemia
4. Tear meniscus height
5. Non-invasive tear film breakup time
6. Tear film lipid layer grade
7. Infrared meibography

Table 2: Diagnostic criteria for dry eye disease, aqueous deficient dry eye disease, and evaporative dry eye disease. Note some participants were identified as having both aqueous deficient and evaporative dry eye disease.

Diagnosis	Criteria
Dry eye disease	• DEQ-5 score ≥6 AND • Non-invasive tear film breakup time <10s
Aqueous deficient dry eye disease	• Diagnosis of dry eye disease AND • Tear meniscus height <0.2mm
Evaporative dry eye disease	• Diagnosis of dry eye disease AND • Tear film lipid layer grade ≤3, or meibography grade >1

3. RESULTS

The mean ± SD age of the 1125 participants (707 females, 413 males, 5 other sex) was 33±21 years (range, 5 to 90 years). Demographic and lifestyle factors, and ocular surface characteristics of participants are presented in Tables 3 and 4. Overall, 428 (38%) participants fulfilled the diagnostic criteria for dry eye disease, 161 (14%) had aqueous deficient dry eye disease, 339 (30%) had evaporative dry eye disease. In addition, 72 (6%) participants had mixed dry eye disease and exhibited clinical signs of both aqueous deficient and evaporative dry eye disease.

Table 3: Demographic and lifestyle factors of participants. Data is presented as mean ± SD, median (IQR), or number of participants (% of participants).

Characteristic	**Values**
Age	
<20 years	422 (38%)
20 to 29 years	160 (14%)
30 to 39 years	126 (11%)
40 to 49 years	97 (9%)
50 to 59 years	120 (11%)
60 to 69 years	99 (9%)
≥70 years	101 (9%)
Sex	
Male	707 (63%)
Female	413 (37%)
Other	5 (0.4%)
Ethnicity	
White	702 (62%)
Hispanic	19 (2%)
East Asian	86 (8%)
South Asian	135 (12%)
Black	54 (5%)
Other	129 (11%)
Daily activity	
Contact lens wear	197 (18%)
Outdoor activity (hours each day)	3 (2-4)
Exercise (hours each day)	3 (1-5)
Digital screen exposure (hours each day)	4 (2-7)
Sleep (hours each day)	8 (6-8)
Self-reported diet quality score (out of 4)	
1 (poor diet quality)	44 (4%)
2 (fair diet quality)	287 (26%)
3 (good diet quality)	642 (57%)
4 (excellent diet quality)	152 (14%)
Self-reported psychological stress burden score (out of 4)	
1 (minimal stress burden)	103 (9%)

2 (mild stress burden)	348 (31%)
3 (moderate stress burden)	567 (50%)
4 (high stress burden)	107 (10%)
Self-perceived health status score (out of 4)	
1 (poor health status)	36 (3%)
2 (fair health status)	226 (20%)
3 (good health status)	707 (63%)
4 (excellent health status)	156 (14%)

Table 4: Ocular surface characteristics of participants. Data is presented as mean ± SD, median (IQR), or number of participants (% of participants).

Characteristic	**Values**
Dry eye symptomology	
DEQ-5 score (out of 22)	7 (4-11)
Tear film quality	
Non-invasive tear film breakup time (s)	9.4 (6.3-14.4)
Tear film lipid layer grade (out of 5)	3 (2-3)
Tear meniscus height (mm)	0.25±0.11
Ocular surface characteristics	
Superior meibography grade (out of 4)	1 (0-2)
Inferior meibography grade (out of 4)	1 (0-2)
Bulbar conjunctival hyperaemia (out of 4)	0.9±0.5
Limbal conjunctival hyperaemia (out of 4)	0.5±0.3
Dry eye disease diagnostic criteria	
Overall diagnosis of dry eye disease	428 (38%)
Aqueous deficient dry eye disease	161 (14%)
Evaporative dry eye disease	339 (30%)

Unadjusted univariate and multivariate-adjusted odds ratios of dry eye disease, aqueous deficient and evaporative subtypes by demographic and lifestyle factors are presented in Tables 3 to 5. Multivariate logistic regression demonstrated that advancing age, female sex, reduced sleep duration, increased psychological stress, and poorer self-perceived health status were independently associated with aqueous deficient dry eye disease (all $p<0.05$, pseudo $R^2 = 0.367$). Significant risk factors for evaporative dry eye disease included advancing age, East and South Asian ethnicity, contact lens wear, greater screen exposure time, increased psychological stress, and poorer self-perceived health status (all $p<0.05$, pseudo $R^2 = 0.431$).

Table 5: Logistic regression odds ratio of dry eye disease by demographic and lifestyle factors. 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)	1.14 (1.07-1.20)	<0.001*	1.17 (1.09-1.26)	<0.001*
Female versus male sex	1.45 (1.12-1.87)	0.005*	1.40 (1.07-1.84)	0.01*
Hispanic versus White ethnicity	0.83 (0.31-2.20)	0.71	-	-
East Asian versus White ethnicity	1.63 (1.04-2.56)	0.03*	1.68 (1.04-2.70)	0.03*
South Asian versus White ethnicity	1.42 (0.98-2.05)	0.07	1.51 (1.01-2.24)	0.04*
Black versus White ethnicity	1.33 (0.76-2.33)	0.32	-	-
Other versus European ethnicity	1.06 (0.72-1.57)	0.76	-	-
Lifestyle factors				
Contact lens wear	1.57 (1.15-2.14)	0.004*	1.42 (1.02-1.94)	0.04*
Outdoor activity (per hour each day)	1.03 (0.99-1.07)	0.13	1.02 (0.98-1.06)	0.26
Exercise (per hour each day)	1.00 (0.96-1.03)	0.83	-	-
Screen exposure time (per hour each day)	1.08 (1.01-1.14)	0.02*	1.09 (1.02-1.15)	0.006*
Sleep (per hour each day)	0.80 (0.72-0.89)	<0.001*	0.92 (0.82-1.05)	0.21
Self-reported diet quality (per score)	0.97 (0.82-1.15)	0.74	-	-
Self-reported psychological stress burden (per score)	1.29 (1.11-1.51)	0.001*	1.23 (1.03-1.47)	0.02*
Self-perceived health status (per score)	0.74 (0.62-0.89)	0.001*	0.79 (0.64-0.98)	0.03*

4. DISCUSSION

The findings of this study demonstrated that both etiological subtypes of dry eye disease were associated with a number of demographic and lifestyle factors. Female sex and reduced sleep duration were independently associated with higher odds of aqueous deficient dry eye disease, while East and South Asian ethnicity, contact lens wear, and increased screen exposure were identified as risk factors for evaporative dry eye disease. Moreover, advancing age, increased psychological stress, and poorer self-perceived health status were associated with both aqueous deficient and evaporative dry eye subtypes. The identification of demographic and lifestyle risk factors in the current study might help to inform the design of future research investigating targeted screening and risk factor modification strategies for the prevention and management of dry eye disease.

In agreement with previous reports,[1, 21-23] the results of the current study showed that advancing age was associated with increased odds of aqueous deficient and evaporative dry eye disease. Both etiological subtypes are recognised to be age-related degenerative conditions that progress with lifetime cumulative exposure to a diverse range of physiological and environmental factors, which can lead to hormonal changes, ocular surface inflammation, tear film homeostatic disturbances, and neurosensory abnormalities.[1, 6, 10] The current study also demonstrated that female sex was an independent risk factor for the development of aqueous deficient dry eye disease. The association between female sex and aqueous deficient dry eye disease has been previously hypothesised to be mediated by the regulatory action of the hypothalamic-pituitary axis, sex steroids, and thyroid hormones, as well as the complex interactions between the immune system, autonomic pathways, and the lacrimal functional unit.[1, 24]

The positive association between East Asian ethnicity and evaporative dry eye disease in the current study was comparable to the trends reported in earlier studies across various

age groups.[1, 25-28] The East Asian ethnic predisposition to evaporative dry eye disease is thought to be partially attributed to anatomical factors, such as increased axial length, differences in orbital connective tissue distribution, and the more inferior attachment point of the *levator palpebrae superioris* aponeurosis, which lead to increased eyelid tension and a greater propensity towards incomplete blinking and accelerated rates of meibomian gland dropout.[29, 30] Although earlier studies have suggested that the prevalence of dry eye disease might be higher among South Asian populations,[1, 31, 32] the current study is among the first to demonstrate that South Asian ethnicity is an independent risk factor for dry eye disease within a co-located cohort which provides some degree of control to climate and environmental exposure. Moreover, in the current study, the South Asian ethnic predisposition to dry eye disease was limited to the evaporative subtype, and future research is required to further characterise the potential mechanisms underlying this association.

Contact lens wear and increased digital device screen exposure were identified to be risk factors for the development of evaporative dry eye disease in the current study, and these findings were consistent with those reported in earlier studies.[1, 33-35] Contact lens wear can destabilise the surface lipid layer and increase the rate of aqueous tear evaporation, leading to the development of evaporative dry eye disease.[6, 33] The association between digital device screen exposure and dry eye disease has been hypothesised to be related to the suppression of spontaneous and reflex blinking during tasks involving significant levels of cognitive loading and visual processing.[35-38] The resulting decrease in blink rate and completeness can diminish the delivery of meibum to the ocular surface, thereby compromising the integrity and quality of the surface tear film lipid layer and predisposing towards the development of evaporative dry eye disease.[29, 35, 38] In addition, upgaze occurring during the use of desktop display monitors can also increase the exposed area of the ocular surface between blink cycles, thereby exacerbating aqueous tear evaporation and ocular surface desiccation.[37, 39]

Reduced sleep duration was associated with increased odds of aqueous deficient dry eye disease in the current study. These trends were in agreement with previous observational studies that report an association between dry eye disease with sleep disorders, decreased sleep duration and quality, although the underlying mechanisms are not fully understood.[40-44] Reduced sleep duration and quality has been previously reported to result in increased levels of cortisol, adrenaline, and noradrenaline, reduced production of androgens, and decreased parasympathetic tone, which can lead to downregulation of tear secretion from the lacrimal glands.[40-44] Moreover, sleep deprivation can also alter the circadian patterns of the hypothalamic-pituitary-adrenal axis renin-angiotensin-aldosterone system, leading to excessive diuresis, natriuresis and dehydration, which might also impact aqueous tear production.[40, 43, 44]

Poorer self-perceived health status and increased psychological stress were associated with increased odds of both aqueous deficient and evaporative dry eye disease in the current study. Although the observational nature of the current study would preclude the inference of causality, it is possible that these reported associations might be multifactorial.[1, 45, 46] On the one hand, symptoms of dry eye disease, including ocular irritation, visual blurring, and epiphora, are recognised to have profound impacts on ocular comfort, visual function, quality of life, and work productivity, which might negatively influence self-perceived health status and psychological stress burden of patients.[1-3] However, the potential for increased psychological stress to exacerbate pre-existing ocular surface homeostatic disturbances through the modulation of immune, hormonal, and neurosensory systems has also been previously raised by earlier studies which report the association between dry eye disease and mental health disorders, such as depression and anxiety. [1, 2, 6, 24, 47-49]

The identification of demographic and lifestyle factors associated with dry eye disease subtypes in the current study could inform future research investigating targeted screening

and risk factor modification.[1, 7] The significant public health and financial impacts of dry eye disease are well recognised.[1, 4] For example, in the United States, the total societal expenditure associated with dry eye disease is estimated to be over US$55 billion per year, when taking into account costs related to physician visits, therapeutic management, and productivity loss.[4] Targeted screening, risk factor modification, and preventative intervention may potentially be more cost effective strategies than disease treatment at the population level.[1, 7] The observational nature of the current study precludes inferring causality, and future prospective or randomized studies would therefore be required to investigate the potential long-term efficacy of digital screen exposure time modification, blink training, and sleep hygiene as risk factor modification strategies for dry eye disease.[1, 7, 50]

This study is not without limitations. It is acknowledged that the cross-sectional, observational design of the study precludes the inference of causality. The convenience sample based on visitors to a scientific exhibition can introduce selection bias to the demographic and lifestyle characteristics of the participant cohort, including the younger age and potentially higher digital screen exposure than the general population. The open advertisement recruitment process may potentially be associated with volunteer bias, and it cannot be reliably determined whether the method of recruitment might have contributed to a higher than expected proportion of participants with dry eye disease. Lifestyle factors were self-reported by participants, which might lead to recall bias. Confounding effects of systemic comorbidities were not investigated in the current study, which is acknowledged to be a limitation. However, the prevalence of systemic comorbidities was expected to be low in this healthy community cohort of exhibition visitors. The pseudo R^2 values were less than 0.5 for the regression models of both dry eye disease subtypes, which might indicate decreased generalisability of the results. The sample size of the current study is acknowledged to be modest, and future studies with larger sample sizes are required to confirm the trends reported.

5. Conclusions

In conclusion, the results of this study showed that both etiological subtypes of dry eye disease were associated with a wide range of demographic and lifestyle factors. Advancing age, female sex, reduced sleep duration, increased psychological stress, and poorer self-perceived health status were independently associated with aqueous deficient dry eye disease. Risk factors for evaporative dry eye disease included advancing age, East and South Asian ethnicity, contact lens wear, increased screen exposure, greater psychological stress, and poorer self-perceived health status. The identification of demographic and lifestyle risk factors may contribute towards the design of future research investigating the utility of targeted screening and risk factor modification for the prevention and management of dry eye disease.

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