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Systemic risk factors of dry eye disease subtypes: A New Zealand cross-sectional study

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ABSTRACT

Purpose: To evaluate systemic risk factors of dry eye disease, aqueous tear deficiency, and meibomian gland dysfunction.

Methods: Three hundred and seventy-two community residents (222 females, 150 males; mean±SD age, 39±22 years) were recruited in a cross-sectional study. Past medical history, dry eye symptomology, ocular surface characteristics, and tear film quality were evaluated for each participant within a single clinical session. The diagnosis of dry eye disease, aqueous tear deficiency, and meibomian gland dysfunction were based on the global consensus recommendations of the Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) and the International Workshop on Meibomian Gland Dysfunction.

Results: Overall, 109 (29%) participants fulfilled the TFOS DEWS II criteria for dry eye disease, 42 (11%) had aqueous tear deficiency, and 95 (26%) had meibomian gland dysfunction. Multivariate logistic regression analysis demonstrated that systemic rheumatologic disease and antidepressant medication were independently associated with aqueous tear deficiency (both $p<0.05$). Significant risk factors for meibomian gland dysfunction included age, East Asian ethnicity, migraine headaches, thyroid disease, and oral contraceptive therapy (all $p\leq0.01$).

Conclusions: Both etiological subtypes of dry eye disease were associated with a number of systemic risk factors. These findings would support routine systemic inquiry of dry eye disease and associated systemic conditions and medications, in order to facilitate opportunistic screening and timely inter-disciplinary referral where necessary.

KEYWORDS

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

1. INTRODUCTION

Dry eye disease is among the most frequently encountered chronic ophthalmic conditions in clinical practice, and affects between 5% to 50% of the population in different parts of the world.[1] The condition is acknowledged to have profound impacts on ocular comfort, visual function, quality of life, and work productivity, and is associated with significant financial and public health burden worldwide.[1-4]

Dry eye disease is commonly divided into two etiological subtypes, described as aqueous deficient and evaporative disease, which represent inadequate production or excessive evaporative losses from the tear film.[2, 5] Evaporative dry eye disease is recognised to have a higher population prevalence than aqueous tear deficiency, and is commonly triggered by underlying meibomian gland dysfunction.[2, 6] However, regardless of the etiological mechanism, a self-perpetuating vicious cycle of tear film instability, hyper-evaporation, hyperosmolarity, and ocular surface inflammation ensues, resulting in the development and progression of dry eye symptoms.[5]

The recent Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) Epidemiology Report identified a number of probable and inconclusive risk factors for dry eye disease, and also highlighted the need for further research examining the associations of the condition with systemic disease and medications.[1] Considerable heterogeneities in methodologic design and disease definition were also noted to have introduced challenges when interpreting and comparing the findings of earlier epidemiology studies.[1] The purpose of this cross-sectional study was therefore to evaluate the systemic risk factors of two prominent drivers of dry eye disease – aqueous tear deficiency, and meibomian gland dysfunction – using diagnostic criteria and methodology that align with the global consensus recommendations of the TFOS DEWS II Diagnostic Methodology Report.[7]

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 University of Auckland Human Participants Ethics Committee. Participants were recruited through open advertisement at a single university centre between January 2018 and June 2019, as part of a larger multi-arm epidemiology study of which the current cross-sectional study formed part. 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 16 years or older, with no contact lens wear 48 hours prior to study participation, and no ophthalmic surgery in the previous three months. Eligible participants were enrolled after providing written consent. The sample size was pragmatically determined by the number of participants enrolled during the recruitment period.

2.2. Measurements

Participants were assessed at a single site, within a temperature and humidity-controlled environment, with a mean±SD room temperature of 20.1±0.5°C and a mean±SD relative humidity of 63.5±6.2%, 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.[7] To minimise the impact on ocular surface and tear film physiology for subsequent assessments, clinical measurements were performed in ascending order of invasiveness,[7] as listed in Table 1. The diagnostic criteria for dry eye disease, aqueous tear deficiency, and meibomian gland dysfunction were based on the global consensus recommendations of the Tear Film

and Ocular Surface Society Dry Eye Workshop II and the International Workshop on Meibomian Gland Dysfunction,[7-9] as summarised in Table 2.

Past medical history, including diagnosed medical conditions, ophthalmic surgery, oral medications, and topical ophthalmic medications were recorded. The systemic 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, 10-12] and included acne vulgaris, allergic rhinitis, anxiety, asthma, diabetes, depression, dyslipidaemia, eczema, hypertension, malignancy, migraine headaches, menopause, ovarian dysfunction, systemic rheumatologic disease, thyroid disease, cataract surgery, refractive surgery, other ophthalmic surgery, antidepressant medication, antihistamine medication, antihypertensive medication, hormone replacement therapy, oral contraceptive therapy, sedative medication, topical anti-glaucoma medication, topical antihistamine medication. Participants with rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, psoratic arthritis, and ankylosing spondylitis, were included under the classification of systemic rheumatologic disease. None of the participants reported a history of Sjögren syndrome, chronic kidney disease, or hematopoietic stem cell transplantation.

The Ocular Surface Disease Index (OSDI) and 5-Item Dry Eye Questionnaire (DEQ-5) were administered to grade the level of dry eye symptomology, as recommended by the TFOS DEWS II Diagnostic Methodology subcommittee.[7]

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). The lower tear meniscus height was evaluated 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.[7] 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).[13, 14]

Tear film osmolarity measurements were conducted with a clinical osmometer (TearLab, California, USA), from 50nL tear samples collected from the lower lateral canthus tear meniscus. A measurement was taken for each eye, and the higher reading and the inter-ocular difference recorded.[7]

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.[7] Corneal and conjunctival staining was assessed using the Sjögren's Syndrome International Registry classification scheme,[15] and upper and lower lid wiper epitheliopathy was evaluated relative to Korb's grading scheme.[16]

Infrared meibography was imaged with the Oculus Keratograph 5M, with the superior and inferior eyelids everted in turn.[9] From the captured image, the proportion of meibomian glands visible within the tarsal area were graded according to the five-point Meiboscale.[17]

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 disease, aqueous tear deficiency, and meibomian gland dysfunction. Multivariate logistic regression for predictors of dry eye disease, aqueous tear deficiency, and meibomian gland dysfunction 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.

3. RESULTS

The mean ± SD age of the 372 community residents recruited (222 females, 150 males) was 39±22 years (range, 21 to 85 years). Seventy-one (19%) participants were university students, 43 (12%) were university staff members, and 258 (69%) were members of the general public. Demographic, systemic, and ophthalmic characteristics of participants are presented in Tables 3 to 5. Overall, 109 (29%) participants fulfilled the TFOS DEWS II criteria for dry eye disease, 42 (11%) had aqueous tear deficiency, and 95 (26%) had meibomian gland dysfunction. Correlation analysis and the contributions of individual diagnostic tests to disease prevalence are presented in Supplementary Tables 1 and 2.

Unadjusted univariate and multivariate-adjusted odds ratios of dry eye disease, aqueous tear deficiency, and meibomian gland dysfunction by demographic and clinical characteristics are presented in Tables 6 to 8. Multivariate logistic regression demonstrated that systemic rheumatologic disease and antidepressant medication were independently associated with aqueous tear deficiency (both $p<0.05$). Significant risk factors for meibomian gland dysfunction included advancing age, East Asian ethnicity, migraine headaches, thyroid disease, and oral contraceptive therapy (all $p\leq0.01$).

Sensitivity analysis conducted by incorporating depression and all confounding predictors of aqueous tear deficiency with univariate $p<0.15$ in the multivariate logistic regression model, but excluding antidepressant medication, demonstrated no significant association between depression and aqueous tear deficiency ($p=0.31$).

4. DISCUSSION

To our knowledge, this study is among the first to assess systemic risk factors of dry eye disease using the global consensus TFOS DEWS II diagnostic criteria.[7] The results showed that dry eye disease was associated with a number of risk factors including advancing age, East Asian ethnicity, systemic rheumatologic disease, migraine headaches, thyroid disease, antidepressant medication, and oral contraceptive therapy. Although the risk factors identified for aqueous tear deficiency were largely consistent with earlier studies, a number of the systemic associations identified for meibomian gland dysfunction had been previously classified by the TFOS DEWS II Epidemiology report as probable or inconclusive.[1]

In agreement with earlier reports,[1, 18-21] the findings of the current study demonstrated that ageing was positively associated with dry eye disease and meibomian gland dysfunction. Dry eye disease and meibomian gland dysfunction are thought to be degenerative conditions that progress with cumulative lifetime exposure to a myriad of environmental and physiological factors, which contribute to hormonal changes, neurosensory abnormalities, ocular surface inflammation, and tear film homeostatic disturbances.[1, 5, 6]

East Asian ethnicity was identified to be an independent risk factor for dry eye disease and meibomian gland dysfunction in the current study, which was comparable with the trends observed in earlier reports across different age groups.[1, 22-25] It has been previously hypothesised that the East Asian ethnic propensity towards the development of dry eye disease might be related to anatomical differences that lead to increased eyelid tension, including higher axial length, the more inferior aponeurotic attachment point of *levator palpebrae superioris*, and differences in orbital connective tissue distribution.[19] These

factors may contribute to the increased tendency to incomplete blinking, and subsequently accelerated rates of meibomian gland dropout.[24, 26]

Systemic factors associated with meibomian gland dysfunction observed in the current study included migraine headaches, thyroid disease, and oral contraceptive therapy. Although the mechanisms are not yet fully understood, the association between migraine headaches and dry eye disease may be potentially related to underlying inflammatory processes, which play a significant role in the pathophysiology of both conditions, as highlighted by earlier studies which report similar trends.[11, 27-29] Neurovascular inflammatory mediators and cytokines have been implicated in plasma extravasation and trigeminal ganglion hypersensitivity in the development of migraines.[11, 28, 29] It remains yet to be established whether the regulatory action of sex steroids, hypothalamic-pituitary and thyroid hormones on the immune system and ocular surface might also contribute.[30] Moreover, it has been hypothesised that hyper-stimulation of the trigeminal ganglion with ocular irritation and reflex tearing associated with dry eye disease might further exacerbate the progression of migraine headaches.[11, 29] The relationship between thyroid disorders and evaporative dry eye disease has also been identified in previous studies,[31-33] and might be partially mediated by the predisposition to incomplete lid closure incomplete blinking with inflammation and swelling of orbital tissues associated with both hyperthyroidism and hypothyroidism, as well as exophthalmos in Graves' orbitopathy.[1, 26, 33] There have been inconsistent reports of the effects of oral contraceptive therapy on dry eye disease in earlier studies,[1, 34, 35] and it is thought that the association might be related to the role of oestrogen in the downregulation of lipid synthesis in the meibomian glands, as well as the compounding effects of oestrogen and progesterone in modulating inflammatory pathways.[1, 30]

Independent risk factors for aqueous tear deficiency identified in the current study included systemic rheumatologic disease and antidepressant medication. The association between systemic rheumatologic conditions and aqueous deficient dry eye disease has been well

established in earlier studies,[1, 36, 37] and is likely related to inflammatory infiltration and structural damage of the lacrimal glands resulting in compromised secretory function.[1, 5] The suppressant action of antidepressant medication on lacrimal function has been previously reported, and is thought to be mediated by the effects of serotonin on the sensitivity thresholds of corneal nerves and the neuronal regulation of lacrimal secretion.[38-40]

Overall, both etiological subtypes of dry eye disease were associated with a number of systemic risk factors. These findings would support routine systemic inquiry of dry eye symptoms in patients affected by associated conditions and medications, in order to facilitate opportunistic screening and timely referral to eye care practitioners where necessary. The results also highlight the importance of eye care practitioners taking a careful history exploring relevant systemic conditions and medications when evaluating patients with dry eye disease, which might facilitate the identification of potentially modifiable risk factors. [1, 18, 41, 42]

This study is not without limitations. Past medical history was self-reported by participants, which can introduce recall bias. The convenience sample based in a single university centre might introduce selection bias, and the open advertisement recruitment process may potentially be associated with volunteer bias, which might lead to a higher than expected prevalence of dry eye disease among the study cohort. However, it is noted that the current study cohort was comprised of generally healthy community residents, rather than a hospital-based convenience sample of clinic patients. Seasonal variation during the participant recruitment period, from January 2018 to June 2019, is acknowledged to potentially contribute to variability in clinical signs and symptoms of dry eye disease, although participants were assessed in a single site, within a temperature and humidity-controlled environment. It is possible that the measurement of right eye ocular surface parameters might potentially result in underestimation of the prevalence rate of dry eye

disease, although this effect would not be expected to be marked in the context of dry eye disease typically being bilateral and relatively symmetrical.[7] The wide confidence intervals of a number of effect estimates reflect the lower prevalence of the risk factors investigated, and associated limitations of decreased study power. In total, 32 risk factors were tested in three possible outcome variables, which could have led to false positive results, as significance levels were not adjusted for multiple testing. Future studies with larger sample sizes would be required to confirm the hypotheses generated in this exploratory study, but also to further analyse risk factors that did not reach statistical significance in the current study.

5. Conclusions

In conclusion, both etiological subtypes of dry eye disease were associated with a number of systemic risk factors. Migraine headaches, thyroid disease, and oral contraceptive therapy were independently associated with meibomian gland dysfunction, while systemic rheumatologic disease and antidepressant medication were significant risk factors for aqueous tear deficiency. The findings of this study would support routine systemic inquiry in order to facilitate opportunistic screening and timely inter-disciplinary referral for the optimisation of modifiable systemic factors, such as disease activity and medication use, where necessary.

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TABLES

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

Assessments
1. Past medical history
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, aqueous tear deficiency, and meibomian gland dysfunction based on the global consensus recommendations of the Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) and the International Workshop on Meibomian Gland Dysfunction.[7, 8]

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
Aqueous tear deficiency	• Diagnosis of dry eye disease AND • Tear meniscus height <0.2mm
Meibomian gland dysfunction	• Diagnosis of dry eye disease AND • Tear film lipid layer grade ≤3, or meibography grade >1

409 **Table 3:** Demographic and clinical characteristics of participants. Data is presented as mean
410 ± SD, median (IQR), or number of participants (% of participants).
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Characteristic	Values
Demographics	
Age (years)	39±22
Female sex	222 (60%)
Contact lens wear	107 (29%)
European ethnicity	155 (42%)
East Asian ethnicity	142 (38%)
South Asian ethnicity	38 (10%)
Other ethnicity	37 (10%)
Medical history	
Acne vulgaris	16 (4%)
Allergic rhinitis	37 (10%)
Anxiety	25 (7%)
Asthma	16 (4%)
Diabetes	23 (6%)
Depression	27 (7%)
Dyslipidaemia	29 (8%)
Eczema	20 (5%)
Hypertension	49 (13%)
Malignancy	8 (2%)
Migraine headaches	33 (9%)
Menopause	73 (20%)
Ovarian dysfunction	16 (4%)
Systemic rheumatologic disease	11 (3%)
Thyroid disease	18 (5%)
Ophthalmic surgery	
Cataract surgery	13 (3%)
Refractive surgery	15 (4%)
Other ophthalmic surgery	19 (5%)
Oral medications	
Antidepressant medication	23 (6%)
Antihistamine medication	32 (9%)
Antihypertensive medication	38 (10%)
Hormone replacement therapy	9 (2%)
Oral contraceptive therapy	42 (11%)
Sedative medication	31 (8%)
Topical ocular medications	
Topical anti-glaucoma medication	12 (3%)
Topical antihistamine medication	15 (4%)

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414 **Table 4:** Ocular surface characteristics of participants. Data is presented as mean ± SD,
415 median (IQR), or number of participants (% of participants).
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Characteristic	Values
Dry eye symptomology	
OSDI score	12 (6-31)
DEQ-5 score	5 (3-10)
Tear film quality	
Non-invasive tear film breakup time (s)	8.9 (4.8-13.6)
Tear film osmolarity (mOsmol/L)	306±12
Inter-ocular difference in osmolarity (mOsmol/L)	6 (3-12)
Tear film lipid layer grade	3 (2-4)
Tear meniscus height (mm)	0.27±0.12
Ocular surface characteristics	
Corneal staining >5 spots	34 (9%)
Conjunctival staining >9 spots	71 (19%)
Lid margin staining ≥2mm length and ≥25% width	97 (26%)
Superior meibography grade	1 (0-2)
Inferior meibography grade	1 (0-2)
Dry eye disease diagnostic criteria	
Overall diagnosis of dry eye disease	109 (29%)
Aqueous tear deficiency	42 (11%)
Meibomian gland dysfunction	95 (26%)

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Table 5: Frequency of dry eye disease, aqueous tear deficiency, and meibomian gland dysfunction by participant age and sex. Data is presented as number of participants (% of participants).

Age (years)	Sex	Dry eye disease	Aqueous tear deficiency	Meibomian gland dysfunction
16 to 39	Female	23/109 (21%)	8/109 (7%)	19/109 (17%)
	Male	13/86 (15%)	3/86 (3%)	12/86 (14%)
40 to 59	Female	21/58 (36%)	10/58 (17%)	18/58 (31%)
	Male	11/33 (33%)	4/33 (12%)	10/33 (30%)
≥60	Female	27/55 (49%)	11/55 (20%)	24/55 (44%)
	Male	14/31 (45%)	6/31 (19%)	12/31 (39%)

Table 6: 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)	1.15 (1.04-1.27)	0.008*	1.19 (1.05-1.36)	0.007*
Female sex	1.39 (0.87-2.20)	0.17	-	-
Contact lens wear	1.69 (1.05-2.74)	0.03*	1.31 (0.76-2.24)	0.33
East Asian versus European ethnicity	1.82 (1.09-3.04)	0.02*	2.48 (1.35-4.58)	0.004*
South Asian versus European ethnicity	1.05 (0.46-2.41)	0.92	-	-
Other versus European ethnicity	1.18 (0.49-2.79)	0.85	-	-
Medical history				
Acne vulgaris	1.94 (0.70-5.34)	0.21	-	-
Allergic rhinitis	1.35 (0.66-2.76)	0.41	-	-
Anxiety	1.67 (0.61-3.78)	0.23	-	-
Asthma	1.47 (0.52-4.16)	0.45	-	-
Diabetes	0.81 (0.16-4.03)	0.79	-	-
Depression	1.73 (0.78-3.87)	0.18	-	-
Dyslipidaemia	0.75 (0.31-1.82)	0.53	-	-
Eczema	1.32 (0.51-3.40)	0.57	-	-
Hypertension	0.69 (0.23-2.11)	0.51	-	-
Malignancy	0.81 (0.16-4.03)	0.79	-	-
Migraine headaches	2.49 (1.21-5.13)	0.01*	2.96 (1.38-6.37)	0.005*
Menopause	1.81 (1.05-3.08)	0.03*	1.33 (0.59-2.97)	0.49
Ovarian dysfunction	0.80 (0.25-2.52)	0.71	-	-
Systemic rheumatologic disease	4.43 (1.27-15.51)	0.02*	4.39 (1.13-16.23)	0.03*
Thyroid disease	5.29 (1.94-14.51)	0.001*	5.15 (1.69-15.74)	0.004*
Ophthalmic surgery				
Cataract surgery	1.08 (0.32-3.57)	0.91	-	-
Refractive surgery	1.22 (0.41-3.65)	0.73	-	-
Other ophthalmic surgery	1.44 (0.55-3.75)	0.46	-	-
Oral medications				
Antidepressant medication	2.83 (1.21-6.64)	0.02*	3.05 (1.18-7.87)	0.02*
Antihistamine medication	0.95 (0.42-2.10)	0.88	-	-
Antihypertensive medication	0.73 (0.33-1.59)	0.42	-	-
Hormone replacement therapy	1.97 (0.52-7/46)	0.32	-	-
Oral contraceptive therapy	2.20 (1.15-4.24)	0.02*	2.58 (1.23-5.42)	0.01*
Sedative medication	0.94 (0.42-2.10)	0.88	-	-
Topical ophthalmic medications				
Topical anti-glaucoma medication	1.76 (0.55-5.67)	0.33	-	-
Topical antihistamine medication	1.64 (0.57-4.74)	0.36	-	-

Table 7: Logistic regression odds ratio of aqueous tear deficiency 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)	1.13 (0.98-1.31)	0.09	1.08 (0.93-1.26)	0.32
Female sex	1.58 (0.79-3.16)	0.19	-	-
Contact lens wear				
East Asian versus European ethnicity	1.18 (0.59-2.34)	0.51	-	-
South Asian versus European ethnicity	1.53 (0.43-5.49)	0.65	-	-
Other versus European ethnicity	0.44 (0.11-1.96)	0.28	-	-
Medical history				
Acne vulgaris	1.13 (0.25-5.14)	0.88	-	-
Allergic rhinitis	0.95 (0.32-2.82)	0.92	-	-
Anxiety	1.55 (0.51-4.75)	0.44	-	-
Asthma	1.88 (0.51-6.87)	0.34	-	-
Diabetes	1.13 (0.14-9.38)	0.91	-	-
Depression	1.89 (0.68-5.29)	0.23	-	-
Dyslipidaemia	0.90 (0.26-3.11)	0.87	-	-
Eczema	2.07 (0.77-6.49)	0.21	-	-
Hypertension	0.98 (0.22-4.43)	0.98	-	-
Malignancy	2.70 (0.53-13.83)	0.23	-	-
Migraine headaches	1.87 (0.72-4.84)	0.19	-	-
Menopause	2.30 (1.14-4.63)	0.02*	2.63 (0.89-7.81)	0.08
Ovarian dysfunction	1.13 (0.25-5.15)	0.88	-	-
Systemic rheumatologic disease	7.30 (2.12-25.08)	0.002*	6.51 (1.85-22.99)	0.004*
Thyroid disease	0.98 (0.22-4.43)	0.98	-	-
Ophthalmic surgery				
Cataract surgery	0.65 (0.08-5.10)	0.68	-	-
Refractive surgery	1.22 (0.27-5.60)	0.80	-	-
Other ophthalmic surgery	1.51 (0.42-5.42)	0.53	-	-
Oral medications				
Antidepressant medication	3.93 (1.51-10.19)	0.005*	3.23 (1.19-8.79)	0.02*
Antihistamine medication	0.80 (0.23-2.74)	0.72	-	-
Antihypertensive medication	0.65 (0.19-2.21)	0.49	-	-
Hormone replacement therapy	0.98 (0.12-8.05)	0.99	-	-
Oral contraceptive therapy	1.69 (0.70-4.08)	0.25	-	-
Sedative medication	1.58 (0.57-4.35)	0.38	-	-
Topical ophthalmic medications				
Topical anti-glaucoma medication	2.74 (0.71-10.57)	0.14	-	-
Topical antihistamine medication	1.22 (0.27-5.60)	0.80	-	-

437 **Table 8:** Logistic regression odds ratio of meibomian gland dysfunction by demographic and
438 clinical characteristics. Asterisks denote statistically significant values (p<0.05).
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Characteristic	Unadjusted univariate logistic regression		Multivariate-adjusted logistic regression	
	OR (95% CI)	p	OR (95% CI)	p
Demographics				
Age (per 10 years)	1.17 (1.05-1.30)	0.004*	1.24 (1.05-1.48)	0.01*
Female sex	1.29 (0.80-2.10)	0.30	-	-
Contact lens wear	1.66 (1.01-2.73)	0.045*	1.31 (0.74-2.27)	0.36
East Asian versus European ethnicity	2.04 (1.21-3.45)	0.008*	2.79 (1.47-5.30)	0.002*
South Asian versus European ethnicity	1.24 (0.53-2.89)	0.62	-	-
Other versus European ethnicity	1.07 (0.43-2.67)	0.88	-	-
Medical history				
Acne vulgaris				
Allergic rhinitis	1.26 (0.60-2.67)	0.54	-	-
Anxiety	1.41 (0.59-3.37)	0.45	-	-
Asthma	1.80 (0.64-5.09)	0.27	-	-
Diabetes	0.97 (0.19-4.89)	0.97	-	-
Depression	1.51 (0.65-3.48)	0.34	-	-
Dyslipidaemia	0.59 (0.22-1.58)	0.29	-	-
Eczema	0.97 (0.34-2.750	0.96	-	-
Hypertension	0.57 (0.16-2.01)	0.38	-	-
Malignancy	0.97 (0.19-4.89)	0.97	-	-
Migraine headaches	3.56 (1.72-7.36)	0.001*	3.90 (1.76-8.66)	0.001*
Menopause	1.84 (1.07-3.19)	0.03*	1.19 (0.55-2.59)	0.66
Ovarian dysfunction	0.97 (0.31-3.09)	0.96	-	-
Systemic rheumatologic disease	1.69 (0.49-5.93)	0.41	-	-
Thyroid disease	6.53 (2.38-17.94)	<0.001*	5.84 (2.03-16.83)	0.001*
Ophthalmic surgery				
Cataract surgery	1.31 (0.39-4.35)	0.66	-	-
Refractive surgery	1.48 (0.49-4.46)	0.48	-	-
Other ophthalmic surgery	1.76 (0.67-4.60)	0.25	-	-
Oral medications				
Antidepressant medication	1.97 (0.82-4.70)	0.13	-	-
Antihistamine medication	0.97 (0.42-2.24)	0.94	-	-
Antihypertensive medication	0.76 (0.33-1.71)	0.51	-	-
Hormone replacement therapy	2.39 (0.63-9.09)	0.20	-	-
Oral contraceptive therapy	2.20 (1.13-4.28)	0.02*	2.58 (1.21-5.52)	0.01*
Sedative medication	1.43 (0.65-3.15)	0.38	-	-
Topical ophthalmic medications				
Topical anti-glaucoma medication	2.14 (0.66-6.91)	0.20	-	-
Topical antihistamine medication	2.01 (0.71-5.79)	0.18	-	-

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