

Meibomian Gland Dysfunction and Sex as Risk Factors of Dry Eye Disease in a Cohort of Norwegian 65-year-Olds: A Cross-Sectional Study

Reza A Badian^{1,3}, Vibeke Sundling¹, Janicke Liaaen Jensen⁴, Håvard Hynne⁴, Behzod Tashbayev⁴, Lene Hystad Hove⁵, Tor Paaske Utheim^{1,2,6-11}, Xiangjun Chen^{1,2,4,8,9,12}

¹National Centre for Optics, Vision and Eye Care, Department of Optometry, Radiography and Lighting Design, Faculty of Health and Social Sciences, University of South-Eastern Norway, Notodden, Norway; ²Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway; ³The Norwegian Dry Eye Clinic, Oslo, Norway; ⁴Department of Oral Surgery and Oral Medicine, Faculty of Dentistry, University of Oslo, Oslo, Norway; ⁵Department of Cariology and Gerodontology, Faculty of Dentistry, University of Oslo, Oslo, Norway; ⁶Department of Oral Biology, Faculty of Dentistry, University of Oslo, Oslo, Norway; ⁷Department of Ophthalmology, Oslo University Hospital, Oslo, Norway; ⁸Department of Ophthalmology, Sørlandet Hospital Arendal, Arendal, Norway; ⁹Department of Ophthalmology, Vestre Viken Hospital Trust, Drammen, Norway; ¹⁰Department of Ophthalmology, Vestfold Hospital Trust, Tønsberg, Norway; ¹¹Department of Ophthalmology, Østfold Hospital Trust, Moss/Kalnes, Norway; ¹²Department of Plastic and Reconstructive Surgery, Oslo University Hospital, Oslo, Norway

Correspondence: Reza A Badian, Email rezabadian@gmail.com

Purpose: Dry eye disease (DED) is a multifactorial condition characterized by the loss of ocular surface homeostasis, causing discomfort and ocular symptoms. Higher age, female sex, and meibomian gland dysfunction (MGD) are some of the reported risk factors for DED. However, age-specific studies of DED are rare. This study aimed to determine the prevalence of DED and MGD in a cohort of Norwegians in their mid-60s. Additionally, to investigate potential sex-related differences in the prevalence of DED and MGD.

Methods: For this cross-sectional study, a random sample of 137 demographically homogeneous Norwegian residents of Oslo in their mid-60s was recruited. Participants completed the Ocular Surface Disease Index (OSDI) dry eye symptom questionnaire and underwent clinical dry eye examinations. DED was defined as OSDI ≥ 13 , accompanied by fluorescein break-up time (FBUT) < 10 s and/or ocular surface staining (OSS) ≥ 1 . The presence of MGD was defined as a score of 1 for both meibum quality (MQ) and meibum expressibility (ME) or a score > 1 for either MQ or ME.

Results: The overall prevalence for DED was 20.4% [95% CI: 14.0 to 28.2], and for MGD was 90.5% [95% CI: 84.3–94.9]. No significant sex differences were observed for either condition. MGD was highly prevalent among both DED and non-DED participants: all individuals with DED ($n = 28$) had MGD, while among those without DED ($n = 109$), prevalence was 88.1% (males: 85.7%; females: 90.0%). No significant correlation was found between MGD and sex (r_s ([137] = [0.075], $p = 0.413$). In the whole cohort, OPI and FBUT correlated positively with ME (r_s ([132] = [0.437] and r_s ([132] = [0.296], both $p < 0.001$) and negatively with OSS (r_s ([132] = [-0.315] and r_s ([132] = [0.423], both $p < 0.001$) and lid margin abnormality (r_s ([130] = [-0.222], $p = 0.011$; r_s ([132] = [0.234], $p = 0.007$). FBUT correlated also positively with tear production (r_s ([128] = [0.308], $p < 0.001$). A more frequent use of topical ocular lubricant was found among females ($p = 0.043$). In the symptomatic group, females had significantly lower OPI and FBUT values ($p = 0.046$ and 0.027 , respectively). Among symptomatic participants, categorized as mild (OSDI 13–22), moderate (OSDI 23–32), and severe (OSDI 33–100), only in the severe group did females show higher OSDI scores ($p = 0.042$) but lower OSS ($p = 0.031$) compared to males.

Conclusion: In this cohort of Norwegians in their mid-60s, DED and MGD were highly and equally prevalent among both sexes. The high prevalence of these conditions underscores the need to raise awareness of DED and MGD within the young elderly population.

Keywords: dry eye disease, meibomian gland dysfunction, sex differences, young elderly, prevalence, age-specific

Introduction

Dry eye disease (DED) is a multifactorial disease of the ocular surface, characterized by loss of homeostasis of the tear film accompanied by ocular symptoms.¹ Symptoms of DED include ocular discomfort, pain, a foreign body sensation,

gritty or stinging eyes, and transient blurred vision, which is also referred to as visual disturbance.¹ DED can considerably reduce quality of life and cause a substantial economic burden, as well as reduce work productivity.^{2,3}

DED is among the most common reasons for patients seeking eye care in the US.⁴ The reported prevalence of DED varies across geographical regions and by the diagnostic criteria applied. The Tear Film and Ocular Surface Society Dry Eye Workshop (TFOS DEWS) II reported the prevalence as between 5 and 50%.⁵

Age 65 is considered the start of the young-old age category (65–69).⁶ The United Nations (UN) has applied the age of 65 as the threshold of old age in its reports.^{7,8} The number of individuals aged 65 and older globally is expected to double to 1.5 billion by 2050.⁹ Increased life expectancy and population ageing contribute to a higher prevalence of age-related diseases. As ageing is a risk factor for DED, the prevalence is higher in the older population.^{5,10} The severity of DED also increases with age.¹¹ Moreover, in recent decades, the incidence and prevalence of DED have increased due to the ageing population.¹² Consequently, DED is viewed as a growing public health concern.¹⁰

Women outnumber men globally at older ages due to their higher average life expectancy. In 2019, women comprised 55% of the global population aged 65 and older. In Norway, the figure was slightly lower, at 53.7%.^{8,13} This gender gap becomes more pronounced with increasing age and has important implications for health care, social services, and long-term planning.¹⁴

Multiple studies have reported female sex as a risk factor for DED.^{15,16} A large US population-based study ($n = 39,876$) indicated a 70% age-adjusted increase in risk of DED among females.¹⁷ It has been suggested that sex hormones influence the condition of the ocular surface, with androgens enhancing and oestrogens antagonizing the function of the lacrimal and meibomian glands.¹⁸ Nevertheless, the reported impact of sex on the development of DED varies across clinical studies. A systematic review and meta-analysis of DED prevalence in China found that the female sex was a positive covariate for DED when defined by symptoms and signs; however, no difference was observed when DED was defined by symptoms alone.¹⁹ Several studies have demonstrated that women were significantly more likely to suffer from and report symptoms of DED.^{20,21} In contrast, an Indonesian study reported that the prevalence of DED and dry eye symptoms was higher among males.²² Meanwhile, a lack of association between DED prevalence, objective signs and symptoms, and sex has also been reported.^{5,23}

The meibomian glands are located within the tarsal plate of each eyelid, close to the conjunctival surface. They are responsible for secreting lipids, called meibum, which are necessary for stabilizing the tear film and reducing tear evaporation.²⁴ Meibomian gland dysfunction (MGD) is a chronic condition characterized by anatomical changes, including obstruction of the terminal ducts of the meibomian glands and changes in the quantity and quality of meibum, accompanied by ocular surface inflammation.²⁵ MGD symptoms include eye irritation, itching, burning, and foreign body sensation.^{25,26}

MGD is a significant risk factor for DED and the most common cause of evaporative DED.⁵ It is highly prevalent among patients suffering from dry eye symptoms and patients diagnosed with DED.²⁷ The International Workshop on Meibomian Gland Dysfunction report on MGD epidemiology suggests that prevalence increases with age, but also highlights the lack of age-specific studies.²⁸ Some studies have also indicated that MGD is not only associated with increasing age but also with male sex.^{29,30}

As both DED and MGD impact quality of life and may reduce productivity,^{16,30,31} early detection and appropriate treatment are crucial for alleviating the symptoms and burdens for these patients.³² This study aimed to determine the prevalence of DED and MGD in a cohort of Norwegians in their mid-60s. Additionally, to investigate potential sex-related differences in the prevalence of DED, MGD, and the associated symptoms and signs of both conditions.

Materials and Methods

Participants

This population-based cross-sectional study was conducted between September 2019 and May 2020, as a joint research project of the Faculty of Dentistry at the University of Oslo and the Norwegian Dry Eye Clinic. The study participants were recruited from a larger project focusing on oral health in the population in their mid-60s in Oslo, Norway (OM65).³³ In the OM65 project, participants were recruited according to their residence in the Oslo municipality and birth year of 1954. A random sample of eligible individuals was drawn from the National Population Register, administered by the

Norwegian Tax Administration authorities. The selection was performed by the Norwegian Tax Administration's system, without human involvement, based on the specified criteria: 65-year-olds with a registered home address in Oslo. Probability-based method to select individuals, ensuring each person in the defined category has an equal chance of being chosen /through simple random sampling using a computer to draw numbers vs stratified random sampling. The eligibility criteria were as follows: participants had to be born in 1954 and reside in Oslo, Norway. The names and addresses of the randomly drawn individuals were obtained, and invitation letters were sent out to 1230 individuals. Within two weeks, those invited were contacted by phone and asked if they wanted to participate in the study. All invited individuals who accepted were included in the OM 65 project.³³ A total of 460 individuals (response rate: 58%) took part in the OM65 study. The participants were subsequently asked to take part in a sub-study investigating ocular surface health. The enrolment was stopped in March 2020 after 150 individuals had accepted the invitation to participate in the ocular surface health study. Data on meibomian gland morphology in participants without DED for this sample have been previously published.³⁴ The ophthalmologist examining the participants was not blinded to the participants, as he was a member of the Ocular Health Study.

Inclusion and Exclusion Criteria

All participants in the OM 65 project who accepted the invitation to join the ocular surface health study were included in the study. No exclusion criteria were applied for the initial recruitment to the ocular surface study. Participants with incomplete data for dry eye disease (DED) and/or meibomian gland dysfunction (MGD) were excluded. Data from those who were not born in Norway were excluded from the analysis to enable investigation of Norwegian ethnicity as a factor and to avoid confounding due to population-ethnic stratification-related bias. Hence, 13 of the original 150 participants were excluded from data analysis, resulting in a final sample of 137 individuals.

The Sample

Data from 137 participants born in Norway, all with complete data on dry eye and MGD diagnosis, were included in the analyses.

Clinical Evaluation

The TFOS DEWS II diagnostic criteria for DED, and the report of the International Workshop on MGD for the diagnosis and grading of MGD were applied.^{26,35} All participants underwent a comprehensive ophthalmic dry eye-specific examination at the Norwegian Dry Eye Clinic. Upon arrival, they were asked to answer a dry eye questionnaire: the Ocular Surface Disease Index (OSDI), a tool for measuring the severity of dry eye symptoms.³⁵ Subsequently, all participants underwent the examination in the following order: 1) blink frequency;³⁵ 2) A non-invasive break-up time (NIBUT) test was performed using Oculus Keratograph 5M. The average time interval between a complete blink and occurrence of breaks in tear reflection of the mire rings was recorded³⁵ 3) tear film break-up time/fluorescein break-up time (FBUT), measured after 5 µL of 2% fluorescein was instilled on the inferior palpebral conjunctiva; 4) ocular surface staining (OSS), graded according to the Oxford scheme after the instillation of fluorescein dye;^{35–37} 5) tear production level by Schirmer-I test without anaesthesia;³⁷ 6) slit-lamp microscope evaluation of anatomical lid margin morphology; and 7) meibomian gland function assessment.²⁶

Lid margin abnormality (LMA) was scored from 0 to 4 based on the following four abnormalities: irregularity of the lid margin, lid margin telangiectasia, lid margin hyperaemia, and thickening of the eyelid margin. Meibum expressibility (ME) was assessed using digital pressure on the central five glands of the lower eyelid and recorded as the number of glands that secreted meibum (score range: 0–5). Meibum quality (MQ) was evaluated based on the quality of the secreted meibum from the central five glands of the lower eyelid and graded according to a four-point score (0: clear; 1: cloudy; 2: granular; and 3: toothpaste). A sum score for the five central glands was calculated and converted to a 0–24 scale.²⁶ The criteria for MGD diagnosis were a score of 1 for MQ and ME or a score > 1 for either MQ or ME. The severity of MGD was graded based on MQ and ME scores (grade 0: no MGD; grade 1: ME score = 1 and/or MQ ≥ 2–4; grade 2: ME score = 1 and/or MQ ≥ 4–8; grade 3: ME score = 2 and/or MQ ≥ 8 but < 13; and grade 4: ME score = 3 and/ or MQ ≥ 13 –24).^{26,38}

Diagnostic Criteria and Pathological Values of Dry Eye Tests for DED and MGD

The pathological cut-off values used in the current study were as follows: OSDI ≥ 13 indicated an abnormal symptom load, with 13–22, 23–32, and 33–100 representing mild, moderate, and severe dry eye symptom loads, respectively.³⁵ The worst eye of each participant in terms of clinical signs of DED and MGD was identified. For DED diagnosis, in addition to the presence of OSDI ≥ 13 , the worst eye was defined as the eye with the worst FBUT value and/or worst OSS value. For MGD diagnosis, the eye with the worst ME and/or MQ values was identified as the worst eye. FBUT < 10 seconds indicated reduced tear film stability, and FBUT ≤ 5 seconds indicated severely reduced tear stability.³⁵ Schirmer-I test ≤ 10 mm in 5 minutes was considered a sign of reduced tear production, and ≤ 5 mm in 5 minutes indicated severely decreased tear production.³⁵ Based on the recommendations of the TFOS DEWS II Diagnostic Methodology Subcommittee,³⁵ the criteria for DED diagnosis should include the presence of symptoms and at least one positive test of disrupted tear homeostasis. Accordingly, the DED diagnostic criteria were defined as OSDI ≥ 13 , accompanied by NIBUT_{average} and/or FBUT < 10 s and/or OSS ≥ 1 . MGD diagnosis and its severity were graded from 0 to 4, as described above.^{26,38}

Statistical Analysis

The data were analyzed using IBM SPSS software, version 26 (IBM, Chicago, IL, USA). Data normality was assessed using the Shapiro–Wilk test. The data for the worst eye of each study participant were used for the analyses. Two post-hoc confidence level calculations were conducted to assess the strength of the study, support critical interpretation of the results, identify potentially important non-significant findings, and inform future research. According to the National Population Register, there were 57,146 Norwegians aged 65 years old in 2019. Among the 137 participants included in this study, the observed prevalence of dry eye disease (DED) and meibomian gland dysfunction (MGD) was 20.4% and 90.5%, respectively. Assuming a $\pm 5\%$ margin of error around the observed prevalence, the estimated confidence level (calculated using <https://www.calculator.net>) was 85% for DED and 95% for MGD. Prevalence values for DED and MGD with 95% confidence intervals (CIs) were calculated. Group differences were analyzed using the Mann–Whitney *U*-test and the chi-squared test. The strength of association or correlation between the dry eye parameters of signs and symptoms in relation to sex was examined using Spearman's rank correlation. A *p*-value of < 0.05 was considered statistically significant.

Results

Characteristics of Study Participants

Overall, data from 137 Norwegian participants were included in the analyses, with 78 (56.9% [95% CI: 48.2 to 65.4]) being female. The participant characteristics are summarized in Table 1. Females used topical ocular lubricants more frequently than males (11.5% [95% CI: 5.4 to 20.1] vs 1.7% [95% CI: 0.0 to 0.1], Fisher's Exact Test: *p* = 0.043).

Prevalence of Dry Eye Disease and Its Symptoms and Signs

In all, 28 (20.4%, [95% CI: 14.0 to 28.2]) of participants had DED (Table 2). The prevalence of DED was not significantly different between males, 16.9% [95% CI: 8.4–29.0], and females, 23.1% [95% CI: 14.3 to 34.2], $X^2(1) \geq 0.776$, *p* = 0.378. No correlation was found between DED prevalence and sex (r_s ([28]) = [0.242], *p* = 0.206); females did not have a significantly higher risk of DED than males (relative risk, RR = 1.36 [95% CI: 0.68 to 2.73], *p* = 0.384). Distribution of participants based on DED presence or absence of DED diagnosis and different OSDI categories in the DED group is shown in Figure 1.

In all, 108 (78.9%, [95% CI: 71.0 to 85.3]) of the participants had a normal symptom load (OSDI < 13) (Table 2). Among those who were asymptomatic, 100 (92.6% [95% CI: 86.9 to 96.8]) had at least one positive homeostatic marker or clinical sign for DED (NIBUT/FBUT < 10 s and/or OSS > 1). More females than males without symptoms had signs of DED (96.7% [95% CI: 63.2–83.6] vs 87.5% [95% CI: 74.6–95.3]), and fewer females than males had neither symptoms nor signs of DED (2.6% [95% CI: 0.3–9.0] vs 10.2% [95% CI: 3.8–20.8]). However, these differences were not statistically significant (Fisher's Exact Test, *p* = 0.135).

Table 1 Characteristics of the Study Participants

	All (n=137)		Male (n=59)		Female (n=78)		$r_{s\text{-sex}}$	$p\text{-value}$
	n	%	n	%	n	%		
Systemic disease								
Diabetes	6	4.4	4	6.8	2	2.6	−0.102	0.233
Hypertension	30	21.9	14	23.7	16	20.5	−0.039	0.652
Rheumatic disease	16	11.7	6	10.2	10	12.8	0.041	0.632
Concomitant oral/ocular medication								
Lipids-lowering	34	24.8	18	30.5	16	20.5	−0.115	0.180
Antihistamines	15	10.9	5	8.5	10	12.8	0.069	0.420
Beta-blockers	13	9.5	6	10.2	7	9.0	−0.020	0.813
Use of topical ocular lubricants	10	7.3	1	1.7	9	11.5	0.187	0.028
Diuretics	7	5.1	2	3.4	5	6.4	0.068	0.427
Antidepressants	4	2.9	2	3.4	2	2.6	−0.024	0.776
Use of contact lenses	9	6.6	3	5.1	6	7.7	0.052	0.542
Smoking habits^a							0.071	0.232
Never	61	45.5	27	47.4	34	44.2		
Previous smoking	62	46.2	28	49.1	34	44.2		
Current smoking	11	8.2	2	3.5	9	11.7		

Notes: Missing data for ^a3 persons. Significant $p\text{-value}$ is in bold.

Abbreviations: n, number; $r_{s\text{-sex}}$, Spearman's rank correlation coefficient.

Table 2 Stratification of the Study Population Based on the Presence of Dry Eye Disease, Dry Eye Symptoms and at Least Having One DED Sign, No Symptoms, and No Sign, n (%) [95% CI]

	All n=137	Male n=59	Female n=78
Symptomatic			
At least one DED sign	28 (20.4) [14.0 to 28.2]	10 (16.9) [8.4 to 29.0]	18 (23.1) [14.3 to 34.0]
No DED sign	1 (0.7) [0.2 to 4.0]	1 (1.7) [0.0 to 9.1]	0 (0.0) [0.0 to 4.62]*
Asymptomatic			
At least one DED sign	100 (72.9) [64.8 to 80.2]	42 (71.2) [57.9 to 82.2]	58 (74.4) [63.2 to 83.6]
No DED sign	8 (5.8) [2.6 to 11.2]	6 (10.2) [3.8 to 20.8]	2 (2.6) [0.31 to 9.0]
Dry eye disease ^{***}	28 (20.4) [14.0 to 28.2]	10 (16.9) [8.4 to 29.0]	18 (23.1) [14.3 to 34.0]

Notes: *One-sided 97.5% CI. **Chi-square test showed no significant difference in DED between males and females: $\chi^2(1) = 0.776$; $p = 0.378$. *** Comparing females to males: Relative risk (RR) = 1.36; 95% confidence interval (CI): 0.68–2.73; $p = 0.384$.

Abbreviations: n, number; percentage in parentheses; CI, confidence interval in brackets; DED, dry eye disease; $r_{s\text{-sex}}$, Spearman's rank correlation coefficient.

Prevalence of Meibomian Gland Dysfunction

In total, 124 of study participants (90.5%, [95% CI: 84.3–94.9]) had MGD (Table 3). The prevalence of MGD was not significantly different between males and females (88.1% [95% CI: 77.1 to 95.1] vs 92.3% [95% CI: 84.0 to 97.1], $\chi^2(1) \geq 0.681$, $p = 0.409$). No significant correlation was found between MGD and sex (r_s ([137] = [0.075], $p = 0.413$), and females were not at a significantly higher risk of having MGD than males (RR = 1.02 [95% CI: 0.79 to 1.33], $p = 0.854$).

Among participants, all those diagnosed with DED were also diagnosed with underlying MGD. The prevalence of MGD among participants with DED was 100% (97.5% one-sided CI: 87.7–100), compared to 88.1% (95% CI: 80.5–93.5) among non-DED participants. This difference was not statistically significant between the sexes (Fisher's Exact Test, $p = 0.070$). Among participants both with and without DED, all MGD severity grades (1–4) were represented in both males and females. Among participants with DED, the distribution of MGD grades was as follows: grade 1 – males 10% [95% CI: 0.3 to 44.4], females 5.6% [95% CI: 0.1 to 27.3]; grade 2 – males 10% [95% CI: 0.3 to 44.4],

Distribution of participants based on the presence or absence of DED diagnosis and DED symptom severity (OSDI) groups

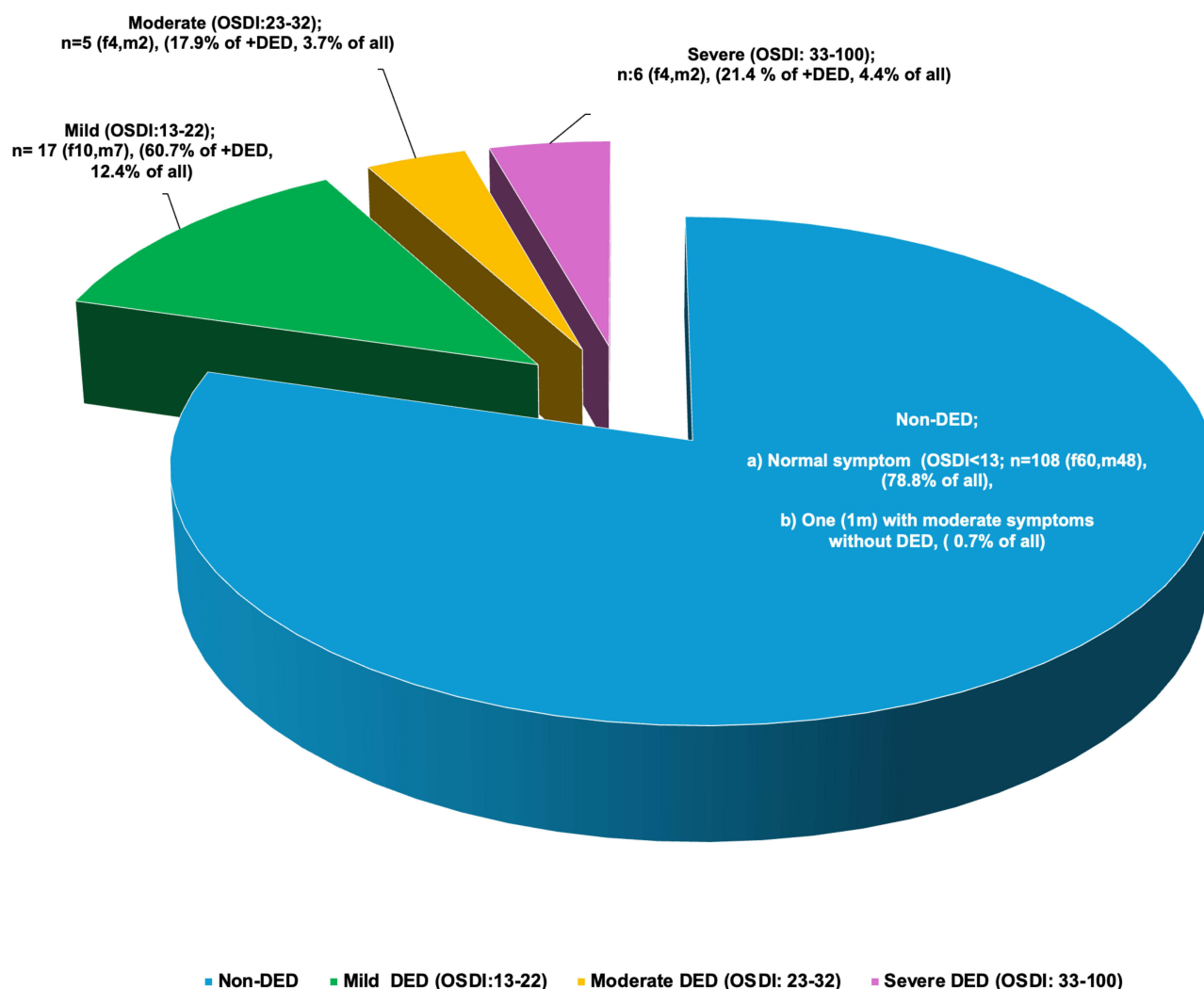


Figure 1 Overview of the distribution of subjects in the total population based on OSDI scores.

females 16.7% [95% CI: 3.5 to 41.4]; grade 3 – males 30% [95% CI: 6.7 to 65.3], females 44.4% [95% CI: 21.5 to 69.2]; and grade 4 – males 50% [95% CI: 18.7 to 81.3], females 33% [95% CI: 13.3 to 59.0]. Among participants without DED, the distribution was: grade 1 – males 12.2% [95% CI: 4.6 to 24.8], females 15.0% [95% CI: 7.1 to 26.6]; grade 2 – males 14.3% [95% CI: 5.9 to 27.2], females 18.3% [95% CI: 9.5 to 30.4]; grade 3 – males 32.7% [95% CI: 20.0 to 47.5], females 40.0% [95% CI: 27.6 to 53.5]; and grade 4 – males 25.6% [95% CI: 15.0 to 41.1], females 16.7% [95% CI: 8.3 to 28.5]. An overview of the distribution of dry eye symptom severity categories, measured by OSDI, among those without and with MGD diagnosis, and across different MGD grades (1–4), is shown in [Figure 2](#).

Among all asymptomatic participants (OSDI <13), 95 (87.5% [95% CI: 80.3 to 93.4]) had some degree of MGD ([Table 3](#)). Among the 13 participants without MGD and with normal OSDI scores, there were slightly more males (14.6% [95% CI: 6.1 to 27.8]) than females (10.0% [95% CI: 3.8–20.5]). Although the proportion of females with MGD and normal symptom load was slightly higher (90.0% [95% CI: 79.5–96.2]) than that of males with MGD (85.4% [95% CI: 72.2 to 94.0]), the difference in symptom load between sexes, both with and without MGD, was not statistically significant ($\chi^2(1) = 0.249$; $p = 0.617$). Distribution of different MGD grades (1–4) in various groups of dry eye symptoms severity (OSDI scores) is shown in [Figure 3](#).

Table 3 Overview of Participants Stratified Based on Presence (+MGD) and Absence of MGD (No MGD), MGD Severity Grades, Dry Eye Symptom Severity (OSDI Categories), and Sex

OSDI categories	N		No MGD	+MGD	MGD grade				$\chi^2(1)$	p-value
			Grade 0		1	2	3	4		
Normal symptom load /Asymptomatic (<13)	48	Male	7 (14.6)	41 (85.4)	6 (12.5)	7 (14.6)	15 (31.2)	13 (27.1)		
	60	Female	6 (10.0)	54 (90.0)	9 (15.0)	11 (18.3)	24 (40.0)	10 (16.7)		
	108	All	13 (12.0)	95 (88.0)	15 (13.9)	18 (16.7)	39 (36.1)	23 (21.3)	0.529	0.047
Mild dry eye symptoms (13–22)	7	Male	0 (0.0)	7 (100.0)	0 (0.0)	1 (14.3)	2 (28.6)	4 (75.1)		
	10	Female	0 (0.0)	10 (100.0)	1 (10.0)	1 (10.0)	4 (40.0)	4 (40.0)		
	17	All	0 (0.0)	17 (100.0)	1 (5.9)	2 (11.8)	6 (35.3)	8 (47.1)		
Moderate dry eye symptoms (23–32)	2	Male	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	1 (50.0)	1 (50.0)		
	4	Female	0 (0.0)	4 (100.0)	0 (0.0)	1 (25.0)	2 (50.0)	1 (25.0)		
	6	All	0 (0.0)	6 (100.0)	0 (0.0)	1 (16.7)	3 (50.0)	2 (33.3)		
Severe dry eye symptoms (33–100)	2	Male	0 (0.0)	2 (100.0)	1 (50.0)	0 (0.0)	1 (50.0)	0 (0.0)		
	4	Female	0 (0.0)	4 (100.0)	0 (0.0)	1 (25.0)	2 (50.0)	1 (25.0)		
	6	All	0 (0.0)	6 (100.0)	1 (16.6)	1 (16.6)	3 (50.0)	1 (16.6)		
Asymptomatic/ Normal symptom load (<13)	48	Male	7 (14.6)	41 (85.4)	6 (12.5)	7 (14.6)	15 (31.2)	13 (27.1)		
	60	Female	6 (10.0)	54 (90.0)	9 (15.0)	11 (18.3)	24 (40.0)	10 (16.7)		
	108	All	13 (12.0)	95 (88.0)	15 (13.9)	18 (16.7)	39 (36.1)	23 (21.3)	0.529	0.047
Symptomatic (13–100)	11	Male	0 (0.0)	11 (100.0)	1 (9.1)	1 (9.1)	4 (36.4)	5 (45.5)		
	18	Female	0 (0.0)	18 (100.0)	1 (5.6)	3 (16.7)	8 (44.4)	6 (33.3)		
	29	All	0 (0.0)	29 (100.0)	2 (6.9)	4 (13.8)	12 (41.4)	11 (37.9)		
All***	59	Male	7 (11.9)	52 (88.1)	7 (11.9)	8 (13.6)	19 (32.2)	18 (30.5)		
	78	Female	6 (7.7)	72 (92.3)	10 (12.8)	14 (17.9)	32 (41.0)	16 (20.5)		
	137	All	13 (9.5)	124 (90.5)	2 (12.4)	22 (16.1)	51 (37.2)	34 (24.9)	0.681	0.409

Notes: Chi-square tests showed no significant differences in MGD between males and females, and no significant difference in symptom load between males and females with or without MGD. The relative risk of MGD in females compared to males was RR = 1.02; 95% CI [0.79–1.33], $p = 0.854$. Significant p -values in bold.

Abbreviations: NA, not applicable; MGD, Meibomian gland dysfunction; OSDI, Ocular Surface Disease Index questionnaire score; n, number; (%), percentage in parentheses.

Findings of Clinical Dry Eye Tests

The findings on dry eye symptoms and clinical signs are presented in Table 4. In the cohort, there were no statistically significant differences in dry eye signs or symptoms between males and females. Among participants with abnormal symptom load (OSDI ≥ 13), the mild symptom group was the largest ($n = 17$), followed by moderate ($n = 6$) and severe ($n = 6$). Within the symptomatic group, further categorized as mild (OSDI 13–22), moderate (OSDI 23–32), and severe (33–100), only in the severe group showed sex differences: females showed significantly higher OSDI scores ($p=0.042$), but lower OSS ($p=0.031$) than males.

Among the participants with a DED diagnosis, 60.7% [95% CI: 40.6–78.5] had mild DED symptoms (OSDI 13–22), while 17.9% [95% CI: 6.1–36.9] and 21.4% [95% CI: 8.3 to 41.0] reported moderate (OSDI 23–32) and severe (OSDI ≥ 33) DED symptoms, respectively. All participants with DED had MGD, and 46.2% [95% CI: 26.6 to 66.6] had reduced tear production (Schirmer-I test ≤ 10 mm in 5 minutes). There were no significant between-sex differences for clinical signs and symptoms, except for NIBUT, which was lower in males than in females (Mann–Whitney U -test, $U = 123.5$, $z = 2.186$, $p = 0.027$).

Overview of the distribution of dry eye symptom severity (measured by OSDI) across different grades of meibomian gland dysfunction (MGD)

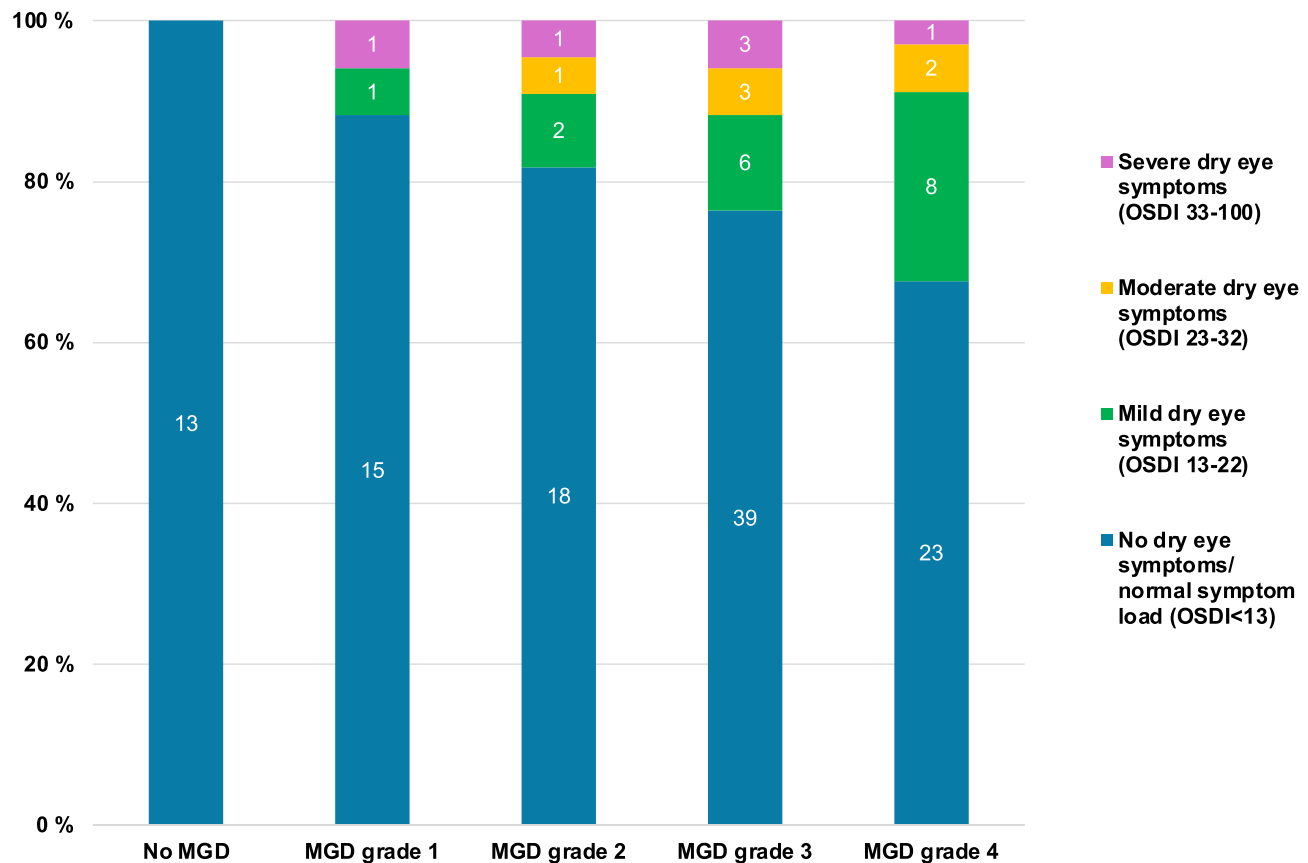


Figure 2 Overview of subjects based on dry eyes symptom severity (OSDI categories) based on the presence or absence of MGD and various MGD grades. The number of subjects in each group is shown in the color-coded sections of the bar chart.

Among the 109 non-DED participants, one (0.9% [95% CI: 0.0 to 5.0]) had moderate dry eye symptoms without positive homeostasis markers for DED. The remaining 108 patients were asymptomatic. Among asymptomatic patients (or normal symptom load/OSDI<13); 78 (72.2% [95% CI: 62.9–66.6]) had an unstable tear film (FBUT < 10 seconds), and 41 (37.9% [95% CI: 28.8 to 47.8]) had a severely reduced FBUT of ≤ 5 seconds. Reduced tear production (Schirmer-I test ≤ 10 mm/5 min), MGD, and a combination of reduced tear production and MGD were present in 59.3% [95% CI: 49.3 to 68.6], 88% [95% CI: 80.3 to 93.4], and 50.0% [95% CI: 40.2 to 59.8] of asymptomatic participants, respectively. There were no significant between-sex differences in clinical signs and symptoms, except for OPI and FBUT, which were significantly lower in females than in males. For OPI, the Mann–Whitney *U*-test yielded $U = 1054.5$, $z = -1.989$, $p = 0.047$; for FBUT, $U = 1004.0$, $z = -2.197$, $p = 0.028$.

In the whole cohort, OPI and FBUT correlated positively with ME (r_s ([132] = [0.437] and r_s [132] = [0.296], for both $p < 0.001$) and negatively with OSS (r_s ([132] = [-0.315] and r_s ([132] = [0.423], for both $p < 0.001$) and LMA (r_s ([130] = [-0.222], $p = 0.011$; r_s ([132] = [0.234], $p = 0.007$). FBUT also correlated positively with tear production (r_s ([128] = [0.308], $p < 0.001$).

Discussion

This is the first study of its kind to investigate the prevalence of DED and MGD in a population of ethnically Norwegian individuals in their mid-60s from the normal population. This approach effectively eliminates the influence of age and

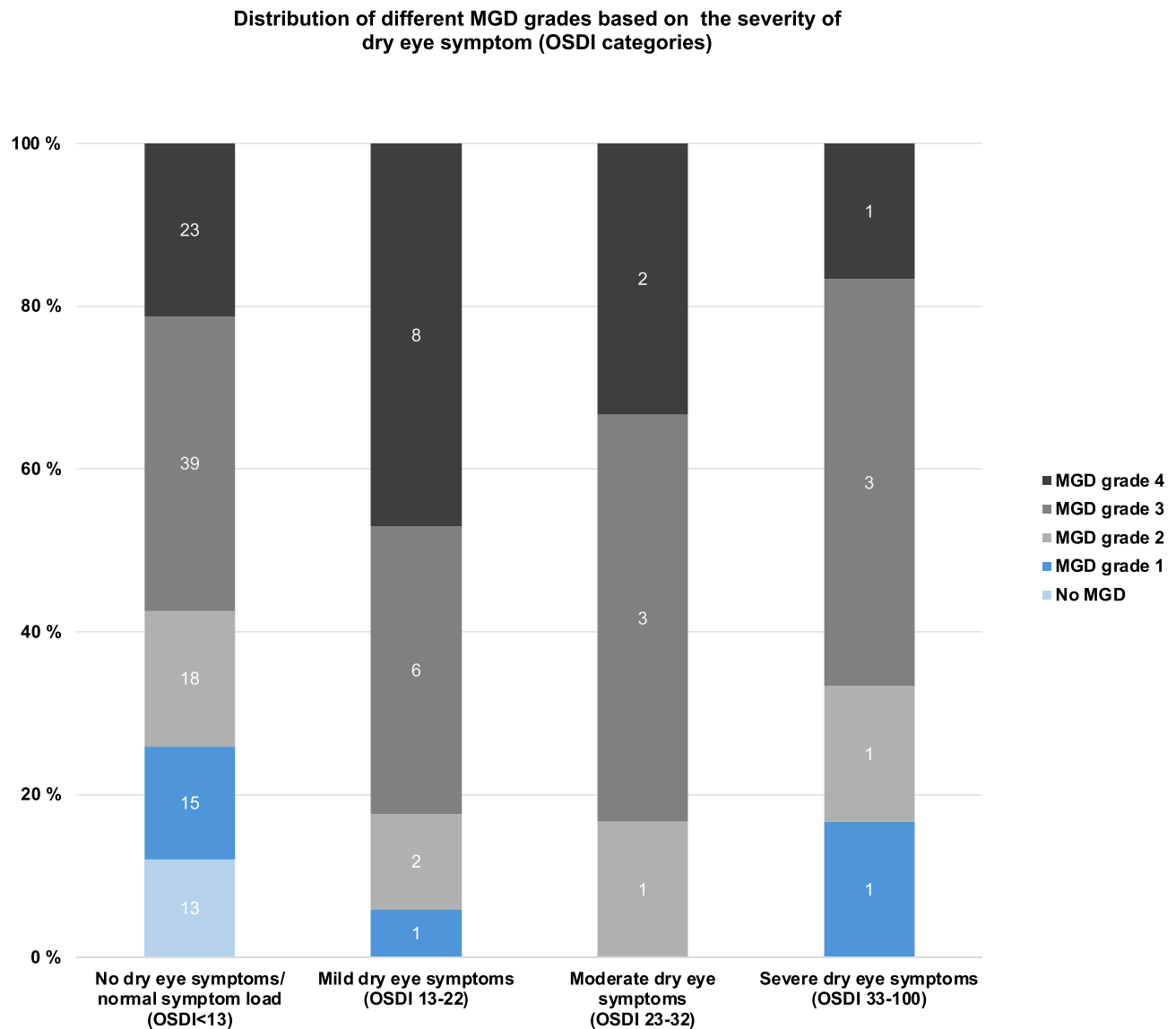


Figure 3 Overview of the distribution of various MGD grades based on different dry eye symptom severity categories. The number of subjects in each group is shown in the color-coded sections of the bar chart.

ethnic variations. The findings of this study enable us to better understand the effect of sex as a risk factor and its possible association with DED and MGD, as well as differences in dry eye symptoms and signs related to sex in this Norwegian population.

The overall prevalence of DED in our study was 20.4%, and females and males were equally affected. When the prevalence results of this study were compared to global DED estimates, the prevalence among Norwegians in their mid-60s was lower in terms of the overall prevalence (20.4% vs 29.5%), as well as the sex-specific prevalence in males (16.9% vs 24.9%) and females (23.1% vs 28.1%).³⁹ It is interesting to consider that many population-based studies of older adults define DED merely based on symptoms. This is not in line with the TFOS DEWS II definition of DED, which includes both symptoms and signs.¹ Globally, the prevalence of DED varies significantly, reported at 3.1% in Australia (60–69 years),⁴⁰ 4.1% in India (≥ 60 years, higher in women),⁴¹ 5% in Malaysia (60–69 years),⁴² 14.2% (65–69 years)⁴³ to 18.9% (65–84 years) in the US,¹⁶ 18.7% (60–69 years)⁴⁴ and 25.7% (≥ 60 years) in Brazil,⁴⁵ 30% in Indonesia (≥ 60 years, no sex difference),²² 30.4% in Korea (65–69 years),⁴⁶ 32.2% in Taiwan (65–69 years, higher in women),⁴⁷ and 61.2% in elderly Tibetans (60–69 years).⁴⁸ Considering the prevalence values reported in meta-analyses

Table 4 Overview of Dry Eye Parameters in the Study Population by Dry Eye Symptom Severity, Median (Q1, Q3)

Dry eye Symptom Severity	Dry eye Parameters	Both Sexes	Male	Female	r _{s-sex}	p-value
All		n=137	n=59	n=78		
	OSDI	4.2 (0.0, 12.3)	2.1 (0.0, 10.4)	4.2 (0.0, 12.5)	0.123	0.152
	OPI ^a	1.0 (0.4, 2.0)	1.2 (0.4, 2.5)	0.9 (0.4, 1.8)	-0.104	0.234
	FBUT ^b	5.0 (3.0, 10.0)	6.0 (4.0, 12.0)	5.0 (3.0, 8.4)	-0.153	0.079
	NIBUT _{average} ^c	4.7 (2.9, 9.2)	4.6 (2.7, 9.7)	6.2 (3.3, 9.2)	0.037	0.694
	OSS	1.0 (0.0, 2.0)	0.0 (0.0, 1.0)	1.0 (0.0, 2.0)	0.164	0.056
	Schirmer ^d	8.0 (5.0, 16.0)	8.0 (5.5, 13.5)	9.0 (5.0, 17.5)	0.036	0.682
	ME	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	1.0 (0.0, 2.0)	0.060	0.490
	MQ	8.0 (5.0, 12.0)	8.0 (3.0, 13.0)	8.0 (5.0, 10.0)	-0.041	0.636
Normal (OSDI<13)	LMA ^d	3.0 (1.0, 4.0)	2.5 (1.0, 4.0)	3.0 (2.0, 4.0)	0.130	0.132
		n=108	n=48	n=60		
	OSDI	2.1 (0.0, 4.5)	0.0 (0.0, 4.2)	2.0 (0.0, 6.7)	0.137	0.158
	OPI	1.0 (0.4, 2.0)	1.2 (0.5, 2.5)	0.8 (0.4, 1.6)	-0.195	0.046
	FBUT	5 (3.3, 9.8)	6.0 (4.0, 12.0)	5.0 (3.0, 8.0)	-0.216	0.027
	NIBUT _{average}	5.2 (3.0, 9.7)	5.7 (2.9, 11.6)	5.0 (3.0, 9.4)	-0.051	0.633
	OSS	1.0 (0.0, 2.0)	0.0 (0.0, 1.0)	1.0 (0.0, 2.0)	0.177	0.066
	Schirmer	8.0 (5.0, 15.0)	8.0 (5.0, 12.0)	8.0 (5.0, 16.0)	0.036	0.711
	ME	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	0.012	0.903
Mild (OSDI 13–22)	MQ	8.0 (3.0, 10.8)	8.0 (2.2, 13.0)	8.0 (3.0, 10.0)	-0.052	0.596
	LMA	3.0 (1.0, 4.0)	3.0 (1.0, 4.0)	3.0 (2.0, 4.0)	0.136	0.166
		n=17	n=7	n=10		
	OSDI	16.7 (14.6, 20.4)	16.7 (14.6, 20.8)	14.8 (14.6, 20.7)	-0.188	0.471
	OPI	1.2 (0.3, 2.5)	1.0 (0.1, 1.6)	1.4 (0.6, 2.8)	0.294	0.268
	FBUT	8.0 (3.5, 11.8)	7.5 (3.6, 10.5)	8.8 (2.9, 14.5)	0.084	0.757
	NIBUT _{average}	4.1 (2.7, 6.1)	2.8 (1.7, 4.7)	4.2 (3.4, 7.1)	0.317	0.215
	OSS	0.0 (0.0, 2.5)	0.0 (0.0, 3.0)	1.2 (0.0, 2.2)	0.187	0.473
	Schirmer	13.0 (7.0, 28.5)	23.0 (7.0, 30.0)	11.8 (6.2, 25.5)	-0.209	0.422
Moderate (OSDI 23–32)	ME	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.5 (0.8, 2.0)	0.132	0.614
	MQ	10.0 (8.0, 13.0)	13.0 (8.0, 14.0)	10.0 (7.5, 13.0)	-0.124	0.634
	LMA	3.0 (1.5, 4.0)	3.0 (2.0, 4.0)	2.5 (1.0, 4.0)	-0.113	0.666
		n=6	n=2	n=4		
	OSDI	26.0 (25.0, 30.0)	28.3 (27.0, -)	26.4 (25.0, 29.7)	-0.440	0.383
	OPI	1.75 (0.7, 2.2)	1.8 (0.9, -)	1.75 (0.4, 2.0)	-0.207	0.694
	FBUT	5.0 (2.5, 10.8)	9.5 (3.0, -)	5.0 (1.9, 8.0)	-0.210	0.690
	NIBUT _{average}	7.5 (3.6, 11.4)	7.6 (1.5, -)	7.5 (4.8, 10.2)	0.000	1.000
	OSS	1.0 (0.0, 4.5)	0.5 (0.0, -)	2.5 (0.3, 5.5)	0.426	0.399
Severe (OSDI 33–100)	Schirmer	10.0 (5.3, 13.2)	8.0 (3.0, -)	10.0 (7.0, 13.0)	0.210	0.690
	ME	1.0 (0.8, 1.3)	1.0 (1.0, 1.0)	1.0 (0.3, 1.8)	0.000	1.000
	MQ	8.0 (7.5, 13.0)	10.5 (8.0, -)	8.0 (6.5, 11.8)	-0.355	0.516
	LMA	3.5 (2.3, 4.0)	1.5 (0.0, -)	4.0 (3.3, 4.0)	0.783	0.066
		n=6	n=2	n=4		
	OSDI	43.2 (34.6, 56.5)	34.1 (33.0, -)	51.1 (39.8, 61.4)	0.828	0.042
	OPI	0.2 (0.1, 5.0)	0.17 (0.17, -)	1.0 (0.1, -)	0.296	0.628
	FBUT	5.0 (2.0, 9.5)	3.5 (2.0, -)	6.0 (2.8, 14.5)	0.426	0.399
	NIBUT _{average} ^c	4.0 (3.3, 11.1)		6.8 (3.1, 11.7)	0.000	1.000
	OSS	1.5 (0.75, 3.0)	3.0 (3.0, 3.0)	1.0 (0.3, 1.8)	-0.853	0.031
	Schirmer	9.5 (5.2, 16.8)		13.0 (5.0, 13.0)	0.258	0.742
	ME	1.0 (0.8, 2.0)	0.5 (0.0, -)	1.5 (1.0, 2.0)	0.671	0.145
	MQ	8.0 (4.3, 12.25)	5.0 (2.0, -)	9.0 (5.8, 16.8)	0.525	0.285
	LMA ^{2,0}	2.0 (1.8, 2.3)	2.0 (2.0, 2.0)	2.0 (1.3, 2.8)	0.000	1.000

Notes: Missing data for the total study population (^a5, ^b20, ^c4, and ^d2 participants). r_{s-sex}: Spearman's rank correlation coefficient. Significant p-values are in bold.

Abbreviations: n, number; OSDI, Ocular Surface Disease Index questionnaire score; OPI, ocular protection index; FBUT, Fluorescein break-up time; NIBUT, Non-Invasive Break-Up Time; OSS, ocular surface staining; ME, meibomian gland expressibility; MQ, meibum quality; LMA, lid margin abnormality; Q, Quartile.

for Brazilian (13%), US (17.4%), and East Asian (20.1%) populations,^{11,49,50} the prevalence in the current study aligns with that in East Asia. More specifically, it was slightly higher than Brazil and the US, and significantly lower than the reported prevalence for Mexico (41%) and Africa (42%).^{49,51} The variety of diagnostic criteria for DED used in population studies highlights the need for the widespread application of standardized diagnostic criteria to allow for more accurate comparisons of prevalence and incidence estimates. Fortunately, with regularly updated global consensus reports by TFOS, this has been improved.

In this study population, we did not find any significant difference in DED prevalence between sexes. This contrasts a US meta-analysis reporting increased prevalence with both age and female sex⁵⁰ and a German study reporting higher DED prevalence among women in all age groups.⁵² Although many studies have reported an association of DED with age and sex,^{17,52,53} other studies have concluded no association between DED with either.^{19,44,51,54} A South Korean population-based study (n = 16,824) demonstrated an increased prevalence of DED symptoms with increasing age in men, with no association between symptoms and ageing in women.⁴⁴ Furthermore, an Iranian study (n = 6,311) did not find any significant association between DED and age,⁵⁴ and a meta-analysis from Africa reported no association between DED and sex.⁵¹ However, a systematic review of DED prevalence in China, applying signs and symptoms in combination as diagnostic criteria, reported a positive association between DED and advanced age, female sex, and higher latitude.¹⁹ They concluded that the overall DED prevalence, diagnosed by symptoms and signs, was 13.6%; the DED prevalence based only on symptoms was 31.4%. Moreover, when applying a symptom-only diagnostic criteria, they reported that only age was associated with increased DED prevalence. These findings underscore the need for standardized diagnostic criteria to facilitate comparisons across studies and populations.

In the current study, we found that all participants with DED had MGD, a substantial percentage (46.2%) had reduced tear production (Schirmer-I test ≤ 10 mm/ 5 min). Further, there were no significant between-sex differences for clinical signs and symptoms, except for NIBUT. A Norwegian study of dry eye patients at the Norwegian Dry Eye Clinic found sex-related differences for FBUT and ME in all age groups, and these two parameters were also influenced by age and sex.⁵⁵ Contrary to that study, we did not find any sex-related differences in FBUT and ME; only NIBUT showed sex-related differences among those with DED in our age group of mid-60s. Furthermore, our results suggest that among this age group with DED, in addition to the presence of MGD, approximately half had reduced tear production, indicating that an element of tear deficiency is one of the underlying etiological factors.

There is a well-known discordance between symptoms and signs of DED.⁵⁶ In the current study, among participants with DED, only NIBUT showed a significant difference between the two sexes. Among participants without DED, both OPI and FBUT were lower among females than males; indicating a higher risk of ocular surface deterioration in females. Poor correlations between the severity of patient-reported symptoms and clinical signs of DED have long been reported.^{56,57} The present study showed that over 72.9% of asymptomatic participants had at least one abnormal clinical dry eye test result. This shows a more substantial percentage compared to a study by Sullivan et al, which reported that 40% of patients who showed objective signs of DED were asymptomatic.⁵⁸

Another finding in the current study was that more females than males used topical ocular lubricants. This could be due to females experiencing dry eye symptoms more severely than males. This reflects findings of the US DREAM study,⁵⁹ reporting that females experience significantly more DED signs, and a German study, reporting that females experience more severe DED symptoms and use ocular therapies more frequently.²¹

The current study also demonstrates that MGD is highly prevalent, even among asymptomatic participants. This agrees with a study by Badian et al of patients at the Norwegian Dry Eye Clinic, finding that MGD was highly prevalent, even among those with normal symptom load (87.8%).²⁷ A high prevalence of asymptomatic MGD has also been demonstrated by Viso et al, showing that asymptomatic MGD was more than twice as common as symptomatic MGD; that asymptomatic MGD was more prevalent among males, while symptomatic MGD was not associated with sex.²⁹

The significant number of asymptomatic participants with signs of DED in this study could partly be attributable to some degree of asymptomatic MGD, rendering adverse effects on the lipid layer and tear evaporation, which may contribute to the vicious circle of dry eye. The absence of symptoms could lead to unnoticed progression of the conditions. This highlights the necessity of targeting MGD and DED and diagnosing the conditions as early as possible,

even MGD in the absence of symptoms, to prevent the development and deterioration of MGD, DED, and subsequent complications.

Strengths and Limitations

In this study, validated diagnostic criteria for DED and MGD as defined by TFOS DEWS II and the International Workshop on Meibomian Gland Dysfunction, respectively, were applied, including both the subjective (OSDI) and objective (MQ, ME, TBUT) measures. Hence, the methodological rigor of the study is strengthened by the use of validated diagnostic criteria, the inclusion of both subjective and objective measures, and the consistency of clinical examinations performed by a trained examiner, which enhances data reliability. Additionally, the focus on a demographically homogeneous cohort contributed to controlling for confounding variables such as age and ethnicity, enhancing the consistency of examinations and data reliability, and providing novel insights into an underrepresented population in dry eye disease research. The equal age and ethnicity of participants facilitated the investigation of the association between sex and DED prevalence in a homogeneous population. The consistent age of participants also contributes to elucidating the role and effect of age (“the young elderly”) in relation to DED, MGD, and signs and symptoms of DED.

Although standardized DED diagnostic criteria were employed in the current study, caution should be exercised when comparing the results with those of other studies, due to the varying diagnostic criteria and study population characteristics in the literature. The relatively smaller sample size compared to larger population studies limits generalisation to the general population. It necessitates caution regarding interpretations interpreting the strata, particularly regarding different levels of MGD and DED symptom severity. Moreover, the small sample size may reduce statistical power and precision, thereby affecting the reliability of observed associations or the lack of such possible associations. The cross-sectional design of the study and its single-center design can also inherently introduce limitations by severely limiting the possibility of causal inference and confining external validity, respectively. In this study, the possible effects of environmental cofounders were not investigated. Furthermore, participants from the original cohort who accepted the invitation to participate in this study may have been motivated to do so, and the lack of response to the invitation by others, as non-response, could have introduced selection bias into the sampling.

Conclusion

This study investigates an underexplored population group by reporting age-specific prevalence of DED and MGD in a demographically homogenous cohort of 65-year-old Norwegians. It contributes to closing a knowledge gap regarding the roles of age, sex, and MGD as risk factors for DED in this population. In this cohort, both DED and MGD were highly prevalent among both sexes. Although DED prevalence was considerable, no statistically significant association was found between DED and sex or MGD. Females reported more frequent use of topical ocular lubricants. Clinical signs and symptoms did not differ significantly between sexes, except that females showed lower OPI and FBUT values in the normal symptom group (OSDI <13) and, in the severe symptom group (OSDI 33–100), higher OSDI scores and lower OSS compared to males. Across the whole cohort, OPI and FBUT correlated positively with ME and negatively with OSS and LMA. FBUT also correlated positively with tear production. The high prevalence of these conditions underscores the need to raise awareness of DED and MGD in the young-old population.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author, RAB, upon reasonable request.

Ethics Approval

This study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (REK 2018/1383) and conducted in compliance with the Declaration of Helsinki’s ethical principles for medical research. The participants were informed about the project upon initial contact prior to recruitment and informed written consent was obtained before the examination.

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