The subcommittee reviewed the prevalence, incidence, risk factors, natural history, morbidity and questionnaires reported in epidemiological studies of dry eye disease (DED). A meta-analysis of published prevalence data estimated the impact of age and sex. Global mapping of prevalence was undertaken. The prevalence of DED ranged from 5 to 50%. The prevalence of signs was higher and more variable than symptoms. There were limited prevalence studies in youth and in populations south of the equator. The meta-analysis confirmed that prevalence increases with age, however signs showed a greater increase per decade than symptoms. Women have a higher prevalence of DED than men, although differences become significant with age. Risk factors were categorized as modifiable/non-modifiable, and as consistent, probable or inconclusive. Asian ethnicity was a mostly consistent risk factor. The economic burden and impact of DED on vision, quality of life, work productivity, psychological and physical impact of pain, are considerable, particularly costs due to reduced work productivity. Questionnaires used to evaluate DED vary in their utility. Future research should establish the prevalence of disease of varying severity, the incidence in different populations and potential risk factors such as youth and digital device usage. Geospatial mapping might elucidate the impact of climate, environment and socioeconomic factors. Given the limited study of the natural history of treated and untreated DED, this remains an important area for future research.

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3. Goal 1: assess and summarize knowledge on the prevalence and incidence of dry eye

3.1. DED definition and ascertainment

3.2. Prevalence of DED

3.2.1. Prevalence of DED based on the Women’s Health Study (WHS) criteria

3.2.2. Prevalence of symptomatic disease

3.2.3. Prevalence of dry eye signs

3.2.4. Prevalence of DED based on symptoms and signs

3.2.5. Prevalence of MGD

3.2.6. Global mapping of dry eye prevalence

3.2.7. Incidence of dry eye

3.2.8. Meta-analysis of existing prevalence data

3.2.9. Summary and recommendations

4. Goal 2: to assess and summarize knowledge on the risk factors for DED

4.1. Age

4.2. Sex

4.3. Meibomian gland dysfunction (MGD)

4.4. Asian race

4.5. Contact lens wear

4.6. Hematopoietic stem cell transplantation

4.7. Sjogren syndrome

4.8. Environmental exposures

4.9. Visual display use

4.10. Vitamin A deficiency/nutritional issues

4.11. Dietary supplementation

4.12. Refractive surgery

4.13. Diabetes

4.14. Affective and somatoform disorders

4.15. Heritability and genetic risk factors

4.16. Summary and recommendations

5. Goal 3: to evaluate available data on the natural history of DED and disease morbidity

5.1. Natural history of DED

5.2. Morbidity of dry eye

5.2.1. Economic burden of dry eye

5.2.2. Quality of life questionnaires

5.2.3. Effects of dry eye on quality of life

5.2.4. Impact of dry eye on quality of vision

5.2.5. Impact of dry eye on mental health

5.2.6. New methods for measurement of dry eye related QoL

5.2.7. Future research directions

6. Goal 4: review of instruments and their use/applicability in epidemiological research

6.1. McMonnies Dry Eye History Questionnaire

6.2. Women’s Health Study (WHS) questionnaire

6.3. Dry eye questionnaire (DEQ)

6.4. North Carolina Dry Eye Management Scale (UNC DEMS)

6.5. Subjective Evaluation of Symptom of Dryness (SESoD)


6.7. Dry Eye Epidemiology Project (DEEP)

6.8. Summary/recommendations - utility for patients/patient acceptance

7. Conclusions and recommendations

Financial disclosures

Acknowledgments

Questionnaires not yet validated

Canada Dry Eye Epidemiology Study (CANDEES)

Salisbury eye evaluation

Melbourne visual impairment project

Bjerrum questionnaire

Japanese dry eye awareness study

Supplementary data

References

1. Introduction

Epidemiological studies describe the distribution of disease, identify factors that influence that distribution, and measure the impact and morbidity of disease in defined populations. The 2007 report of the Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop (DEWS) Epidemiology subcommittee summarized the available evidence on dry eye prevalence, incidence, risk factors, and impact; and reviewed instruments for the diagnosis and assessment of dry eye disease (DED) in clinical trials [1]. Key recommendations from this report for future research included; adoption of a consensus in dry eye diagnostic criteria to improve...
future epidemiological studies; implementation of well-designed studies to estimate the incidence of disease and establish natural history of treated and untreated disease; expansion of studies to assess disease prevalence in additional geographic regions and to establish the impact of race and ethnicity; initiation of prospective studies to elucidate additional risk factors and to provide evidence for equivocal factors in the 2007 report and, importantly, to develop strategies to inform public and practitioner education to improve eye and general health.

Since the publication of the 2007 report, there has been considerable progress in many of these areas. The purpose of this report is to review and summarize the available evidence on the epidemiology of DED and to update the recommendations for future needs and research opportunities.

2. Goals of the epidemiology subcommittee

The goals of the TFOS DEWS II Epidemiology subcommittee were:

1. To assess and summarize knowledge on the prevalence and incidence of DED from well-designed population studies carried out in the past 10 years and to perform a meta-analyses of existing study data to determine prevalence of DED stratified by age and sex.
2. To assess and summarize available knowledge on risk factors of DED from well-designed studies.
3. To evaluate data available on natural history of DED and disease morbidity.
4. To review available instruments and determine their use/applicability in epidemiological research.

3. Goal 1: assess and summarize knowledge on the prevalence and incidence of dry eye

3.1. DED definition and ascertainment

One of the major challenges historically for epidemiological studies has been the lack of clear standardization of a disease definition and classification system for DED. This definition and classification system would need to include well-defined objective and subjective diagnostic criteria, with good sensitivity and specificity in differentiating dry eye from normal that could be broadly applied across studies in different regions and populations and be sensitive to change due to treatment or disease progression. The lack of a single validated diagnostic test or combination of tests to confirm a diagnosis further complicates interpretation of epidemiological study results. The initial TFOS DEWS Epidemiology subcommittee report reviewed the major international epidemiological studies and concluded that the prevalence of DED ranged from 5 to 30% in individuals over the age of 50 [1]. Their consensus was that the prevalence of severe disease was likely to be at the low end of this range and that the prevalence of mild or episodic disease was closer to the upper limit. Higher rates were generally observed with studies using clinical criteria only, followed by questionnaire-based studies, with lower rates amongst intention-to-treat or treatment studies.

Since the publication of the original TFOS DEWS report, either meibomian gland dysfunction (MGD) or evaporative dry eye has been accepted as the most common subtype of DED in both clinic and population based studies [2–5], but other subtypes have been proposed, including dry eye manifesting as either signs only or non-obvious disease. It is worth noting that epidemiological studies of MGD are similarly confounded by a lack of standardized definition and grading [6,7].

As a consequence, the subcommittee examined data from a range of large cohort studies and considered different methods of disease ascertainment and definition, including studies involving the type, frequency and severity of symptoms, patient self-report of a diagnosis of dry eye by an eyecare practitioner (ECP) and studies that involved a clinical examination.

3.2. Prevalence of DED

Prevalence of a disease is a measure of the proportion of disease within a population at a given point in time. Prevalence estimates for DED vary with the operational definition of dry eye used and the characteristics of the population studied. For the purpose of this report, a search of published, peer-reviewed literature was conducted using PubMed in September 2015 for articles that reported the prevalence of dry eye. The following terms: (dry eye syndrome, OR dry eye, OR keratoconjunctivitis sicca, OR MGD/abnormalities OR blepharitis, NOT Sjögren syndrome) AND (epidemiology OR prevalence OR incidence) were used to identify potential articles. Only human studies published over the last 10 years (2005–2015) were considered. Eligible studies included those reporting either or both prevalence of dry eye symptoms and signs. Observational studies (cross-sectional or cohort) were included if they were population-based, with a minimum of 500 subjects, and presented the study outcome as dry eye versus non-dry eye. Studies were excluded if no variance in the measure of prevalence was available in the manuscript, or if it was not possible to calculate it from the data presented or if the publication was an editorial or a review article. The flowchart below describes the studies identified and reasons for exclusion (Fig. 1).

Four hundred and thirty seven studies were identified (updated 17 Sep 2015). Estimates of the prevalence of DED from 24 large international cohort studies, stratified by diagnostic criteria, are summarized in Table 1 [2,7–29].

A searchable excel format of this table is available at XXX. Prevalence of disease for studies involving symptoms with or without signs ranged from approximately 5% to 50%. Studies where the diagnosis was based primarily on signs generally reported higher and more variable rates of disease, up to 75% in certain populations. The signs included vary between studies and some studies have focussed on secondary outcomes, including measures
Table 1

Summary of population based cross sectional epidemiological studies of dry eye, stratified by diagnostic criteria and racial group.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>N</th>
<th>Age (mean ± SD)</th>
<th>M:F (%, (n))</th>
<th>Race</th>
<th>Sampling technique</th>
<th>Prevalence (% [95%CI])</th>
<th>Prevalence (% [95%CI])</th>
<th>Prevalence (% [95%CI])</th>
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</thead>
<tbody>
<tr>
<td>Uchino 2008 [8]</td>
<td>Japan</td>
<td>3433</td>
<td>15–18</td>
<td>74.4:25.6 (2848:585)</td>
<td>1</td>
<td>Japanese high school students, 100% consent of those invited</td>
<td>n/a</td>
<td>Boys 21 [20.1–21.8]; Girls 24.4 [23.9–25.0]</td>
<td>Boys 4.3 [3.9–4.6]; Girls 8.0 [7.4–8.4]</td>
</tr>
<tr>
<td>Schaumberg 2009 [9]</td>
<td>USA</td>
<td>25444</td>
<td>50-99 (Median 64.4)</td>
<td>100% Male</td>
<td>3</td>
<td>Participants from longitudinal Physicians Health Studies I (N = 18596) and II (N = 6848). All physicians in AMA invited to participate</td>
<td>Age adjusted 4.34 [4.1–4.6]; 50–54 3.90 [3.1–4.7]; 80 &lt; 7.67 [6.5–8.9]</td>
<td>12.5 [10.7–14.5]; Women 21.6 [19.5–23.9]</td>
<td>Men 11.5 [9.7–13.4]; Women 18.7 [16.7–20.8]</td>
</tr>
<tr>
<td>Uchino 2011 [10]</td>
<td>Japan</td>
<td>3294</td>
<td>&gt;40</td>
<td>46.2:53.8 (1221:1423)</td>
<td>1</td>
<td>Rural mountain town population sampled from residential registry. Self-administered questionnaire distributed and later collected from individual households</td>
<td>Boys 23.7 [21.8–25.7]; Girls 23.1 [21.3–25.1]</td>
<td>1.3 [0.9–2.0]</td>
<td></td>
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<tr>
<td>Zhang 2012 [11]</td>
<td>China</td>
<td>1885</td>
<td>n/a</td>
<td>50.8:49.2</td>
<td>1</td>
<td>Multistage stratified random cluster sampling of Chinese high school students</td>
<td>16 [14.6–17.3]; Men &gt; 40 10.7 [9.1–12.2]; Women &gt; 40 20.6 [18.5–22.2]</td>
<td>8.0 [7.3–8.7]</td>
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<tr>
<td>Ahn 2014 [12]</td>
<td>South Korea</td>
<td>11666</td>
<td>19-95 (49.9 ± 16.7)</td>
<td>42.8:57.2</td>
<td>1</td>
<td>Stratified, multistage, clustered sampling method based on 2009 National Resident demographics. Weighted prevalence calculated per 5th annual Korea National Health and Nutrition Examination Survey [KNHANES V]</td>
<td>All 20.2 [18.5–21.9]; Men 19.9 [18.4–21.4]; Women 20.6 [19.1–22.1]</td>
<td>8.0 [7.3–8.7]</td>
<td></td>
</tr>
</tbody>
</table>

Authors: Country: N: Age (mean ± SD): M:F (%, (n)): Race: Sampling technique: Prevalence (% [95%CI]): Prevalence (% [95%CI]): Prevalence (% [95%CI])

Symptomatic disease

Lu 2008 [14]: China 2632 >40 (56.3 ± 12.3) | 56.44 1 | Stratified, clustered, random sampling | One or more symptoms or dry eye often or all the time. Positive response to the question, “for the past 3 months or longer, have you had dry eyes?” “foreign body sensation with itching and burning, sandy feeling, not related to allergy” | 52.4 [50.2–54.7]; Men 52.1; Women 52.9 | All 21.6 [19.9–23.3]; Men 17.2; Women 25.0 |

Moss 2008 [15]: USA 2414 48-91 (63 ± 10) | 44.56 3 | 5 and 10 year follow up examinations in Beaver Dam Eye Study population | One or more symptoms of dry eye often or all the time. | 21.8 [21.2–22.8] |

Jie 2009 [16]: China 1957 40-84 (56.5 ± 9.3) | 43.2:56.8 (835:1112) 1 | From the 4439 participants in the Beijing Eye Study 2001, a random sample of 1957 were selected | One or more symptoms of dry eye often or all the time. | 21 [19.2–22.8] |

Tian 2009 [17]: China 1085 20-95 (51 ± 18) | 38.6:61.4 (419:666) 1 | 6% of the target population from Jiangning District, Shanghai, was randomly selected (1266 subjects) using randomized block methods | One or more of 6 dry eye symptoms often/constantly (dryness, irritation, burning sensation, redness, deposits, heavy eyelid sensation) | 32.81 [30.08–35.66] |

Tong 2009 [18]: Singapore 3280 40–80 | 1576:1704 2 | Random sample of the Malay population residing in 15 residential districts in Southwestern Singapore drawn from a random list of 16,069 Malay names provided by the Ministry of Home Affairs | One or more of the 6 symptoms of dry eye often or all the time. | 6.5 [5.7–7.4]; Men 8.2 [6.9–9.7]; Women 4.9 [3.9–6.0] |

Guo 2010 [19]: China 1816 >40 (54.9 ± 11.7) 1 | Stratified, clustered, random sampling method in Henan County China. Native Mongolian population living at high altitude. | One or more of the 6 symptoms of dry eye often or all the time. | 50.1 [47.8–52.4]; Men 49.3 [46.8–53.3]; Women 50.2 [46.8–53.6] |

Han 2011 [20]: South Korea 657 65-95 (72 ± 5.9) | 48.2:51.8 1 | 10% of the population chosen through systematic random sampling based on residential rosters; 1060 invited to participate, 657 consented | One or more symptoms of dry eye often or all the time (dry, gritty/sandy, burning, sticky, watery/tearing, redness). | 30.3 [26.9–33.9]; Men 25.6; Women 34.7 |

(continued on next page)
<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>N</th>
<th>Age (mean ± SD)</th>
<th>M:F (%, (n))</th>
<th>Race</th>
<th>Sampling technique</th>
<th>Diagnostic criteria</th>
<th>Prevalence (% [95%CI])</th>
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<tbody>
<tr>
<td>Viso 2009/Viso 2011 [2,21]</td>
<td>Spain</td>
<td>654</td>
<td>40-96 (63.6 ± 14.4)</td>
<td>37.2:62.8 (243:411)</td>
<td>3</td>
<td>Age-stratified random sample of the population 40 years and older was drawn from the National Health Service Registry. Part of Salines Eye Study. Subsample of 5190, identified from 6311 subjects in Sharoud, Iran from 300 clusters derived through random cluster sampling</td>
<td>Symptoms often or all of the time</td>
<td>18.4 [15.4–21.3]; Men 12.5; Women 21.8</td>
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</tbody>
</table>
| Hashemi 2014 [22]  | Iran     | 1008 | 40–64           | 41.0:59.0 (413:595) | 6                   | Subsample of 2011 [2,21] 
Viso 2009/Viso 2011 | Spain    | 654 | 40-96 (63.6 ± 14.4) | 37.2:62.8 (243:411) | 3                   | Age-stratified random sample of the population 40 years and older was drawn from the National Health Service Registry. Part of Salines Eye Study. Subsample of 5190, identified from 6311 subjects in Sharoud, Iran from 300 clusters derived through random cluster sampling | Symptoms (OSDI score) ≥23 | 18.3 [15.9–20.6] |
| Malet 2014 [23]   | France   | 915  | 73-94 (80.1 ± 4.4) | 38.7:61.3 (354:561) | 3                   | Subsample of 2104 Bordeaux participants of the Three City Study of vascular risk factors for dementia 2003,1450 surviving participants were offered an eye examination between 2006 and 2008 | OSDI ≥22 | All 39.2 [36.1–42.4]; Men 30.5 [25.9–35.5]; Women 44.7 [40.7–48.9] |
| Paulsen 2014 [24] | USA      | 3275 | 21-84 (49)       | 45.4:54.6 (1486:1789) | 3                   | Participants in the Beaver Dam Offspring Study; the adult children of the population-based Epidemiology of Hearing Loss Study (EHLS) | Symptoms sometimes or more often and moderately bothersome or greater (dry, gritty or burning feeling) or those using rescue med at least once per day for dry eye | 14.5 [13.29–15.71]; 21–49 years: 14.1 [12.48–15.72]; 50 < years: 15.2 [13.39–17.01]; Men 30.5 [8.94–12.06]; Women 17.9 [16.12–19.68] |
| Vehof 2014 [25]   | England  | 3824 | 20–87           | 100% Female | 3                   | Adult twins registry held at St Thomas' Hospital, London | Have you had dry eyes in the past 3 months or longer, FB sensation with itching and burning, sandy feeling not related to allergy | 20 [19.01–20.99] |
| Na 2015 [26]      | Korea    | 6655 | ≥19             | 100% Female | 1                   | Stratified multistage probability sampling method of participants from the KNHANES V who had undergone an ophthalmological examination | Eyes tend to dryness, foreign body sensation with itching and burning or sandy feeling lately. | 12.3 [10.3–14.4]; Men 9.0 [6.5–12.1]; women 14.8 [12.0–18.0] |
| Tan 2015 [27]     | Singapore| 1004 | 15-83 (38.2 ± 15.5) | 44.1:55.9 (443:561) | 6                   | 46 of 62 train stations in Singapore were randomly selected to be study sites. Members of the public interviewed at stations and in nearby locations. | McMonnies Questionnaire; at least one of five self-reported symptoms that were reported as often or constantly (soreness, scratchiness, dryness, grittiness, burning sensation) | 12.3 [10.3–14.4]; Men 9.0 [6.5–12.1]; women 14.8 [12.0–18.0] |

**Signs**

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<tr>
<th>Authors</th>
<th>Country</th>
<th>N</th>
<th>Age (mean ± SD)</th>
<th>M:F (%, (n))</th>
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<th>Sampling technique</th>
<th>Diagnostic criteria</th>
<th>Prevalence (% [95%CI])</th>
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<tbody>
<tr>
<td>Uchino 2006 [28]</td>
<td>Japan</td>
<td>113</td>
<td>&gt;60 (67.5 ± 5.7)</td>
<td>44.2:55.8% (50:63)</td>
<td>1</td>
<td>Twelve thousand letters were sent out to pensioners of Chiba city, Honshu Island older than 60 years of age</td>
<td>Ocular surface staining with fluorescein or Rose Bengal and Schirmer &lt;5 mm or TBUT&lt;5s.</td>
<td>12.3 [10.3–14.4]; Men 9.0 [6.5–12.1]; women 14.8 [12.0–18.0]</td>
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<td>Lu 2008 [14]</td>
<td>China</td>
<td>2632</td>
<td>&gt;40 (56.3 ± 12.3)</td>
<td>56:44</td>
<td>1</td>
<td>Stratified, clustered, random sampling</td>
<td>TBUT &lt;10s; Schirmer &lt;5 mm (with anesthesia); fluorescein score ≥1</td>
<td>12.3 [10.3–14.4]; Men 9.0 [6.5–12.1]; women 14.8 [12.0–18.0]</td>
</tr>
<tr>
<td>Jie 2009 [16]</td>
<td>China</td>
<td>1957</td>
<td>40-84 (56.5 ± 9.3)</td>
<td>43.2:56.8 (835:1112)</td>
<td>1</td>
<td>From the 4439 participants in the Beijing Eye Study 2001, a random sample of 1957 were selected</td>
<td>Def 1: TBUT &lt;10s or Schirmer &lt;5 mm or fluorescein score ≥1 or telangiectasia; or plugging of the gland orifices. Def 2: TBUT &lt;10s and Schirmer &lt;5 mm and fluorescein score ≥1 and telangiectasia and plugging of the gland orifices. Def 3: TBUT &lt;4s or Schirmer &lt;4 mm or fluorescein score ≥2. Def 4: TBUT &lt;4sand Schirmer &lt;4 mm and fluorescein score ≥2 Def 5: TBUT &lt;4s or Schirmer &lt;4 mm irrespective of other signs. Def 6: TBUT &lt;4s and Schirmer &lt;4 mm irrespective of other signs. (with anesthesia)</td>
<td>12.3 [10.3–14.4]; Men 9.0 [6.5–12.1]; women 14.8 [12.0–18.0]</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>N</td>
<td>Age Range</td>
<td>Signs</td>
<td>Symptoms</td>
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<td>Guo 2010 [19]</td>
<td>China</td>
<td>1816</td>
<td>≥40 (54.9 ± 11.7)</td>
<td>TBUT ≤ 10s; Schirmer ≤ 5mm (with anesthesia); fluorescein score ≥ 1</td>
<td>One or more of 6 dry eye symptoms (dryness, irritation, burning sensation, redness, deposits, heavy eyelid sensation) and at least 2 of the following clinical assessments (+): BUT ≤ 5s (+) or ≤ 10s (+); Schirmer ≤ 5mm (+) or ≤ 10mm (+); Corneal staining ≥ grade 1 (+)</td>
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<tr>
<td>Han 2011 [20]</td>
<td>South Korea</td>
<td>657</td>
<td>65-95 (72 ± 5.9)</td>
<td>10% of the population chosen through systematic random sampling based on residential rosters; 1060 invited to participate, 657 consented</td>
<td>Stratified, clustered, random sampling method in Henan County China. Native Mongolian population living at high altitude.</td>
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<td>Viso 2009/Viso 2011 [21]</td>
<td>Spain</td>
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<td>40-96 (63.6 ± 14.4)</td>
<td>Age-stratified random sample of the population 40 years and older was drawn from the National Health Service Registry. Part of Salines Eye Study. Subsample of 2104 Bordeaux participants of the Three City Study of vascular risk factors for dementia 2003.1450 surviving participants were offered an eye examination between 2006 and 2008</td>
<td>Stratified, clustered, random sampling method in Henan County China. Native Mongolian population living at high altitude.</td>
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<td>Malet 2014 [23]</td>
<td>France</td>
<td>915</td>
<td>73-94 (80.1 ± 4.4)</td>
<td>6% of the target population from Jiangning District, Shanghai, was randomly selected (1266 subjects) using randomized block methods</td>
<td>One or more of 6 dry eye symptoms (dryness, irritation, burning sensation, redness, deposits, heavy eyelid sensation) and at least 2 of the following clinical assessments (+): BUT ≤ 5s (+) or ≤ 10s (+); Schirmer ≤ 5mm (+) or ≤ 10mm (+); Corneal staining ≥ grade 1 (+)</td>
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<tr>
<td>Tian 2009 [17]</td>
<td>China</td>
<td>1085</td>
<td>20-95 (51 ± 18)</td>
<td>6% of the target population from Jiangning District, Shanghai, was randomly selected (1266 subjects) using randomized block methods</td>
<td>One or more of 6 dry eye symptoms (dryness, irritation, burning sensation, redness, deposits, heavy eyelid sensation) and at least 2 of the following clinical assessments (+): BUT ≤ 5s (+) or ≤ 10s (+); Schirmer ≤ 5mm (+) or ≤ 10mm (+); Corneal staining ≥ grade 1 (+)</td>
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<tr>
<td>Vehof 2014 [25]</td>
<td>England</td>
<td>3824</td>
<td>20-87</td>
<td>Adult twins registry held at St Thomas’ Hospital, London</td>
<td>One or more of 6 dry eye symptoms (dryness, irritation, burning sensation, redness, deposits, heavy eyelid sensation) and at least 2 of the following clinical assessments (+): BUT ≤ 5s (+) or ≤ 10s (+); Schirmer ≤ 5mm (+) or ≤ 10mm (+); Corneal staining ≥ grade 1 (+)</td>
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<tr>
<td>MGD</td>
<td>Uchino 2006 [28]</td>
<td>Japan</td>
<td>113</td>
<td>&gt;60 (67.5 ± 5.7)</td>
<td>Twelve thousand letters were sent out to pensioners of Chiba city, Honshu Island older than 60 years of age.</td>
<td>MGD grade 1 or above per Bron classification.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jie 2009 [16]</td>
<td>China</td>
<td>1957</td>
<td>40-84 (56.3 ± 9.3)</td>
<td>From the 4439 participants in the Beijing Eye Study 2001, a random sample of 1957 were selected</td>
<td>Twelve thousand letters were sent out to pensioners of Chiba city, Honshu Island older than 60 years of age.</td>
<td>Telangiectasia or plugging of the gland orifices</td>
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<td>China</td>
<td>1085</td>
<td>20-95 (51 ± 18)</td>
<td>38.6:61.4 (419:666)</td>
<td>1</td>
<td>6% of the target population from Jiangning District, Shanghai, was randomly selected (1266 subjects) using randomized block methods</td>
<td>Grade ≥ 1; Grade 0-no block; Grade 1-clear-mild milky secretion with pressure; Grade 2: thick, milky to pasty secretion with pressure, Grade 3: no secretion and with significant blockage. The highest grading each eye was used for analysis</td>
<td>53.2 [50.2–56.1]; Men 53.5 [48.7–58.2]; Women 53.0 [49.2–56.8]</td>
</tr>
<tr>
<td>Han 2011 [20]</td>
<td>South Korea</td>
<td>657</td>
<td>65-95 (72 ± 5.9)</td>
<td>48.2:51.8 (243:411)</td>
<td>1</td>
<td>10% of the population chosen through systematic random sampling based on residential rosters; 1060 invited to participate, 657 consented</td>
<td>MGD definition: presence of gland orifice plugging (grade &gt;−1)</td>
<td>51.8 [43.6–60.0]</td>
</tr>
<tr>
<td>Viso 2009/Viso 2011 [2,21]</td>
<td>Spain</td>
<td>654</td>
<td>40-96 (63.6 ± 14.4)</td>
<td>37.2:62.8 (243:411)</td>
<td>3</td>
<td>Age-stratified random sample of the population 40 years and older was drawn from the National Health Service Registry. Part of Salnes Eye Study.</td>
<td>Viscous or waxy discharge expressed</td>
<td>30.5 [26.9–34.1]</td>
</tr>
<tr>
<td>Siak 2012 [29]</td>
<td>Singapore</td>
<td>3271</td>
<td>40-80 (58.7 ± 11.0)</td>
<td>48.1:51.9 (1574:1697)</td>
<td>1</td>
<td>Age stratified (by 10 year age groups) random sample drawn from list of 16069 Malay names in 15 residential districts provided by Ministry of Home affairs.</td>
<td>Either lid margin telangiectasia, or orifice plugging in at least one eye of each participant.</td>
<td>Age standardized prevalence 56.3 [53.3–59.4]; Men 62.9 [58.3–67.8]; Women 50.5 [46.8–54.6]</td>
</tr>
<tr>
<td>Viso 2012 [7]</td>
<td>Spain</td>
<td>619</td>
<td>40-96 (63.4 ± 14.5)</td>
<td>37.0:63.0 (229:390)</td>
<td>3</td>
<td>Age stratified random sample of the population 40 years and older from Salnes region drawn from National Health Service Registry. Sample 1155.</td>
<td>One or more of: 1. absent, viscous or waxy white secretion upon digital expression, 2. presence of two or more lid margin telangiectases and 3. plugging of 2 or more gland orifices. Symptoms (dryness, grittiness, burning, redness, lash crusting, and eyelids getting stuck) reported “often” (at least once a week), and “all the time” (at least daily)</td>
<td>Men 35.3 [29.4–41.7]; Men asympt 26.5 [21.2–32.7]; Men sympt 9.0 [5.9–13.3]; Women 27.5 [23.3–32.1]; Women asympt 19.1 [15.5–23.4]; Women sympt 8.4 [6.1–11.3]</td>
</tr>
</tbody>
</table>

Race allocated as follows for more than 90% of sample.

1 = South East Asian.
2 = North Asian (India, Pakistan, Bangladesh).
3 = Caucasian.
4 = Black.
5 = Arabic.
6 = Mixed.
Sympt = symptomatic.
Asympt = asymptomatic.
TBUT = Tear Break Up Time.
FB = Foreign Body.
of tear quality or tear stability, and others on specific lid signs. The section below summarizes the prevalence studies broadly grouped by diagnostic criteria, although it should be noted that different studies do differ in their operational definitions and it is important to consider these differences when comparing between studies.

3.2.1. Prevalence of DED based on the Women’s Health Study (WHS) criteria

Six studies have reported rates of disease based on severe symptoms of dryness and irritation and/or a physician’s diagnosis of dry eye, as reported by the participant (Table 1). Five of the six studies were carried out in Asia [10–13,30], and the sixth was a study conducted in American males, which reported the lowest age adjusted prevalence of 4.3% [9]. In the Asian studies, the overall prevalence of disease based on symptom report ranged between 14.4 and 24.4% [10–13,30]. Two studies evaluated high school students in China and Japan, where symptoms of DED were reported by 21–24% of participants [11,30], which was considerably higher than rates in adults, of 9.8–11.5% in men and 18.7–19.4% in women [10,12,13]. Women consistently had a higher prevalence than men in all studies stratified by sex.

3.2.2. Prevalence of symptomatic disease

Population-based studies reporting the prevalence of symptomatic DED are heterogeneous, not only in their population characteristics such as age and sex but also in their definitions of dry eye. In general, studies have defined symptomatic disease using three different methods (below), however, even within these categories several different criteria and descriptions are used (see Table 1).

1. Frequency of symptoms, having at least one of several symptoms of dry eye often or all of the time, such as foreign body sensation, dryness, irritation, itching, or burning [31].
2. Self-reported diagnosis by agreeing with a sentence that describes dry eye that includes several symptoms,
3. Using a cut-off value of the total score of the 12 item Ocular Surface Disease Index (OSDI) symptom questionnaire [32].

Studies performed in South East Asia used definition (1), and these reports showed the highest prevalence rates of symptomatic DED, ranging from 20.0 to 52.4% [14,16,17,19,20]. An exception to this region is Singapore, where two studies showed a prevalence of only 6.5% [18] and 12.3% [27]. Studies in Spain and USA using similar definitions showed a prevalence of 18.4% [21] and 14.5% [24], respectively. Two studies in the United Kingdom and Korea, using a form of definition 1 [31], identified a similar prevalence of symptomatic DED of around 20% [25,26]. Using definition 3 [32], a study in France [23] showed a relatively high prevalence of symptomatic dry eye of 39.2% using an OSDI above 22, while in Iran a prevalence of 18.3% was found using the same cut-off value [22].

The majority of studies reported a significantly higher prevalence in women compared to men, ranging from 1.33 to 1.74 times higher [16,20–24,27], except for two studies in China and Mongolia that showed no significant sex difference [14,19] and one study in Singapore that found a significantly lower (0.6 times) prevalence in women [18]. Most studies were performed in people aged 40 years and older, with only two studies reporting separate results in younger age categories. Both showed a slightly but not significantly lower prevalence of 10–20% symptomatic DED in those aged 20–40 years [24,25]. Despite the difficulty of comparing studies directly because of their heterogeneity, symptomatic DED is generally more common in women than men and more common in Asian than Caucasian populations.

3.2.3. Prevalence of dry eye signs

There is considerable variation in the prevalence of DED diagnosed using clinical signs only. Some studies report a single clinical sign and others a combination of tear stability, tear production and ocular surface damage signs. For example, the prevalence of a tear breakup time (TIBUT) of ≤ 10 s in one or both eyes varied between studies from 15.6 to 85.6%, of a Schirmer test score of ≤ 5 mm from 19.9 to 37%, and of a fluorescein score of ≥ 1 (based on corneal damage graded as 0 (no staining), 1 (mild staining limited to less than one-third of the cornea), 2 (moderate staining of less than half of the cornea), or 3 (severe staining of half or more of the cornea)) from 5.8 to 77% [14,19–21,23,28]. Such differences in prevalence estimates may be due not only to the variation in techniques for measuring and interpreting conventional dry eye tests, coupled with the lack of established cut-off values and the poor repeatability of these tests, but also to the characteristics of the study population including age, sex, ethnicity, pre-existing conditions, medication use and lifestyle or environmental factors [33–35].

Several studies found an association between older age and an increase in positive dry eye signs [14,19,28]. Tear instability, as defined by a TIBUT of ≤ 10 s or low tear production, such as a Schirmer test score of ≤ 5 mm have been reported in ‘normal’ populations [36,37], thus the associations between normal and dry eye subjects. Certain signs, such as corneal staining, may not be an intrinsic feature of dry eye but may also reflect other conditions, however, ocular surface staining appears to have a strong association with disease severity [38,39]. Ocular surface homeostasis may adapt to the normal age-related reduction in tear film and tear production. It is not well established how the pathological thresholds for tear instability, tear production and staining of the cornea should be adjusted with regard to age, although the DEWS II Diagnostic subcommittee report [40] considers a cut-off at ± 2 standard deviations from the mean value.

Race is likely to be a confounding factor in the prevalence estimates of abnormal tear function. Using the same diagnostic criteria and similar age range, Asians have a higher prevalence of tear instability and ocular surface staining than Caucasians (Table 1). This may reflect geographical difference and/or differences in the susceptibility to the disease between Asian and other populations. A relationship between sex and objective signs of dry eye remains controversial. Two studies reported no significant sex differences in clinical signs [14,21]. Many topical or systemic medications and ocular surface disorders such as MGD are associated with positive dry eye signs both in clinic and population-based studies. Others such as pterygia, pinguecula and punctal stenosis are associated with positive dry eye signs in clinical studies [34,41,42], but not in population based studies [2]. Inclusion of participants with ocular surface disease, such as MGD or using certain medications, may increase the prevalence of symptoms and particularly dry eye signs. It is important to note that the ocular surface environment is very sensitive to any external stimuli and most diagnostic tests are fairly invasive, so that the results of sequential tests might be affected [43].

As was previously described [1], the prevalence of DED based on clinical testing, broadly tear stability, tear production and ocular surface staining, does not correspond to subjectively diagnosed dry eye based on symptoms alone. The inconsistencies between signs and symptoms could be explained by the heterogeneity of the DED itself and the poor standardization with a lack of well-defined diagnostic criteria of clinical tests in common use [44]. Moreover, each dry eye test assesses only certain properties of dry eye and certain dry eye parameters may not be evaluated by the tests currently employed [16]. Other factors include variability in pain thresholds, the psychosomatic component that may be present to a variable extent in symptomatic diseases, cognitive responses to
questions about ocular sensation, and reduction in ocular surface sensitivity as a result of the normal aging process or disease progression [1,45].

3.2.4. Prevalence of DED based on symptoms and signs

Five population-based studies reported on a combination of symptoms and signs, with an overall prevalence ranging from 8.7 to 30.1%, however very different criteria were applied in each of the studies [17,21–23,25]. As would be expected based on the discussion above, it is difficult to draw conclusions given the heterogeneity of the disease definitions. Two studies estimated disease prevalence based on symptoms reported often or constantly, and compared with 11, 8.6.

rose bengal staining score of Schirmer test score of study conducted in China [17] demonstrated a prevalence of almost wide age range of randomly sampled participants; however the disease in MGD, stratification of diagnostic criteria in the different population groups are required.

The limited number of studies, disparate clinical signs of MGD applied and association was not corroborated in the Asian study. The limited data available is inconclusive but it may be conceivable that telangectasia is not an intrinsic feature of MGD but may also be present in other conditions.

The information available on the impact of sex and age on MGD is limited because most prevalence studies fail to provide sex and age specific data. One study showed similar rates overall for men and women in an Asian population [17], although this appears to be dependent on disease severity. The Singapore Malay Study [29] and the Spanish Salnes Eye Study [7] showed a higher rate of MGD in men. In the Spanish study, this effect of sex was limited to asymptomatic disease and the rates for symptomatic disease were similar between men and women [7], which is consistent with the similar rates between men and women found in clinic-based studies, where participants are mostly symptomatic [46]. An association with age was found in the Salnes Eye Study, but this association was not corroborated in the Asian study. The limited number of studies, disparate clinical signs of MGD applied and population differences limit the broad generalizability of these findings and would indicate that further studies with similar diagnostic criteria in the different population groups are required to fully explore the prevalence of asymptomatic and symptomatic disease in MGD, stratified by age, sex and race.

3.2.6. Global mapping of dry eye prevalence

Other than racial variations, differences in prevalence rates between studies may be attributed to other geographic, climatic or environmental variations. Information on the location (e.g. city, region or state, country) of studies was collected for mapping and descriptive analyses. The diagnostic criteria per Table 1 were considered in the analysis. The locations of the population sampled were geo-referenced using the latitude and longitude coordinates by cross-checking the names with Wikipedia:GeoHack (https://www.mediawiki.org/wiki/GeoHack). The coordinates of the midpoint of the capital of the region or country were used as a proxy for the locations that could not be allocated exact latitude and longitude coordinates. All the relevant information was entered into an Excel worksheet and data were mapped using the geographical information systems (GIS) software ArcGIS 10.3 (ESRI, Redlands, CA) to produce maps of DED prevalence distribution according to five diagnostic criteria (WHSS definition, diagnosed dry eye, symptomatic disease, MGD and TBUT). The prevalence maps are shown in Figs. 2–4. A searchable Excel file of the abstracted data and electronic geospatial ArcGIS files are available at XXX.

Overall, study locations ranged in latitudes from 1.28° north (Singapore) to 51.5° north (England) of the equator. No studies reported on the prevalence of dry eye symptoms south of the equator during the last 10-year period. Studies covered a broad range of longitudes from –100° west (USA) to 139.7° east (Japan) of the prime meridian. All studies included both sexes, except for the Physicians’ Health Study results in the USA [9] (which included males only) and the Twins UK study in England and the KNHANES-V study in South Korea (which included females only) [25,26]. Studies were mostly conducted in adult populations, ranging in age from 20 to 96 years. A number of Asian studies also included a younger population aged 15–19 years [8,11,12], as does the Twins UK study [25].

Fig. 2 displays the prevalence of dry eye according to the WHSS definition (top panel) or equivalent. This included eight studies where dry eye was defined as the presence of either a previous clinical diagnosis of DED or severe symptoms (both dryness and irritation either constantly or often) [9–13,30], or self-reported dry eye confirmed by the use of artificial tears [25] and/or OSDI greater than 22 [23], or diagnosed DED and use of artificial tears or symptoms sometimes or more often that are at least moderately bothersome, or those who reported currently using eye drops at least once a day for dry eyes [24]. These studies were conducted in North America (USA), Asia (China, Japan, South Korea), and Europe (England, France). The prevalence ranged from 4.1% to 23.7%. The Physicians’ Health Study results in the USA reported a prevalence of 4.3% [9] and the Twins UK study in England reported a prevalence of 9.6% [25] in males and females, respectively. Seven of these eight studies also reported the prevalence of diagnosed DED separately, as mapped in the bottom panel of Fig. 2. The prevalence of diagnosed DED was generally lower, with six of seven studies reporting prevalence at or below 11.4%. The prevalence of diagnosed DED ranged from 1.3% in the Shouguang Chinese study [11] to 29.6% in the Alienor study conducted in France [23].

Seventeen population studies, including many of those listed in Fig. 2, provide data on the prevalence of symptomatic dry eye (Fig. 3). These were conducted in North America (USA), Asia (China, Iran, Japan, Singapore, South Korea) and Europe (England, France, Spain). Fig. 2 includes studies where dry eye was defined as severe symptoms (both dryness and irritation, either constantly or often) [9–13,30], or studies where dry eye was at least one symptom of dry eye often or all the time [2,14–16,18–21,25–27], or an OSDI score of >22 [22,23]. The average prevalence of dry eye symptoms across these studies was 22.8 ± 13.3%, ranging from 6.5% in the Singapore Malay Eye study [18] to 52.4% in Chinese Tibetans [14]. All studies included both sexes, except for the Physicians’ Health Study results in the USA, the Twins UK study in England, and the KNHANES-V study in South Korea where 6.8% of males, 20.8%, and 20.0% of females reported dry eye symptoms, respectively. In studies where both values were reported, the prevalence of dry eye symptoms was consistently higher than that of diagnosed dry eye.

The lower panel of Fig. 3 presents a magnified view of the reported prevalence of symptoms of dry eye in nine of these studies conducted in South Eastern Asian countries (China, Japan, South Korea). A cartographical representation of the World Urban Areas data was downloaded from the Natural Earth website (http://www.naturalearthdata.com, accessed on 5 June 2016) and layered on to
Fig. 2. Prevalence map according to the WHS diagnostic criteria (upper panel) and self-report of clinically diagnosed dry eye (lower panel).
Symptomatic Disease

Inset presents a magnified view of the South East Asian prevalence data

Fig. 3. Prevalence map of symptomatic disease (upper panel) and expanded view of studies carried out in South East Asia (lower panel).
the bottom panel of Fig. 3. This dataset was derived from Moderate Resolution Imaging Spectroradiometry (MODIS), Defense Meteorological Satellite Program (DMSP) nighttime lights, and gridded population data [47].

Fig. 4 maps available data on the prevalence of MGD (top panel) and TBUT (bottom panel) in population studies of dry eye patients. The prevalence of MGD was evaluated in five studies and ranged from 30.5% [21] to 68.3% [16]. The prevalence of TBUT < 5–10 s, ranged from 15.6% [21] to 85.6% [20]. This wide range in MGD prevalence and abnormal TBUT in the same populations may not only reflect different diagnostic criteria. MGD is not invariably associated with abnormal TBUT and, conversely, abnormal TBUT may be associated with tear film deficiencies other than lipid.

Overall, the mapping of the prevalence of dry eye data shows no clear pattern of DED prevalence with latitude. Notwithstanding the diagnostic criteria used, the prevalence of dry eye appears slightly higher in Asia than other continents. The mapping exercise clearly highlights the dearth of prevalence data from the African continent and, to a certain extent, America, where no studies to date have looked at Central and South America.

3.2.7. Incidence of dry eye

Incidence of disease describes the rate of new or incident cases of a disease over a period of time. A limited number of studies have reported the incidence of DED. The Beaver Dam Eye Study established in a Caucasian population aged 48–91 that 13.3% (95% CI 12.0–14.7%) of individuals developed symptomatic DED over 5 years and 21.6% (95% CI 19.9–23.3%) over 10 years [15]. Incidence was higher in women (25%) than men (17.3%) over the 10-year period after adjusting for age. Age was a risk factor for increased incidence, with an odds ratio of 1.2x (1.1–1.3) for each 10-year increment.

More recently, participants of the Twins UK study completed a dry eye questionnaire in 2011 and 2013 [25], which has allowed estimation of the incident cases of symptomatic dry eye both as defined by the WHS criteria and as defined by the Beaver Dam Eye Study above [15], in females aged 20–87. The incidence of dry eye as defined by the WHS criteria was 4.4% (95% CI 3.5–5.3%) in this 2-year period. The incidence of symptomatic dry eye as defined by the Beaver Dam Eye Study [15], where dry eye is defined as a foreign body sensation with itching and burning, not related to allergy and experienced for at least 3 months, was 10.4% (95% CI 9.1–11.7%) over the same period.

3.2.8. Meta-analysis of existing prevalence data

A meta-analysis was conducted to determine the prevalence of dry eye for different diagnostic criteria stratified by age and sex. Using the search strategy described above, population based prevalence studies published since 1980 were included. Hospital based studies were excluded. After data were abstracted, confidence intervals on the measures of prevalence were estimated using [square root of p times q over n], where p was the proportion with dry eye, was applied. For studies where prevalence was 0%, the exact Poisson confidence limits were computed [48] for the proportion and the width of that interval, divided by 3.92 to approximate the standard error.

For descriptive analyses, box plots were produced using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA). The number of studies for most age categories within diagnosis category was small. When there was only a single study in the category, the prevalence was reported as originally reported by the study. If there were two or more studies in the category, a pooled rate was calculated by using a suite of SAS macros marandom developed by Weir and Senn [49]. These macros include summary statistics for the DerSimonian and Laird [50] approach.

A regression analysis of the pooled prevalence estimates from the meta-analyses on age was carried out for studies that reported both sexes in aggregate. The prevalence estimates were weighted by the inverse of their standard error.

1. Prevalence by age.

Fig. 5 shows the prevalence of symptomatic disease (upper panel), WHS criteria (central panel) and clinically diagnosed dry eye (lower panel) by age. Both report of symptoms and a clinical diagnosis of dry eye show a modest change below the age of 49, with a gradual increase from aged 50 and a more marked increase beyond the age of 80. Symptom report prevalence shows the greatest variability.

Fig. 6 shows the prevalence by age for 40 years and above based on disease signs, including tear stability (TBUT), tear production (Schirmer test) and corneal damage (fluorescein staining) and MGD. Both tear signs and corneal staining show a similar pattern of prevalence change with age, with a similar degree of variability. The absolute values of prevalence of MGD with age do increase, however there is wide variability in the estimates, which may be consistent with the range of different clinical parameters used in the diagnosis.

Regression analyses by age for each diagnostic subgroup are summarized in Table 2. Overall for all subgroups, except for the WHS criteria, the
Meibomian Gland Dysfunction (MGD)

![Prevalence map of MGD (upper panel) and tear film instability (TBUT <8-10 sec) disease (lower panel).](image)

Tear Break Up Time (TBUT)

![Prevalence map of MGD (upper panel) and tear film instability (TBUT <8-10 sec) disease (lower panel).](image)

- **0 - 33%**
- **34 - 66%**
- **67 - 100%**

*Fig. 4.* Prevalence map of MGD (upper panel) and tear film instability (TBUT <8-10 sec) disease (lower panel).
prevalence of dry eye increased significantly and showed a linear association with age. For each diagnostic group the increase in prevalence of dry eye with each decade of increasing age is shown as the slope estimate (Table 2). The prevalence increased between 2.0% (self-report of a clinical diagnosis of dry eye) and 10.5% (based on a positive Schirmer test) by decade depending on the diagnostic group. Generally, the increase in prevalence for signs of dry eye showed a greater increase than for a diagnosis based on symptoms. The prevalence of MGD increased by 5.3% per decade.

2. Prevalence by sex

Figs. 7 and 8 illustrate the prevalence of DED by sex for the diagnostic criteria described above. There appeared to be minimal and inconsistent sex differences in the prevalence of DED. In symptomatic disease and clinically diagnosed DED, the differences between sexes become clearer at ages above 50.

Fig. 8 shows the prevalence by age and sex for 40 years and above based on disease signs, including tear stability (TBUT), tear production (Schirmer test) and corneal damage (fluorescein staining) and MGD. In general, females show a higher prevalence with increased age than males, although there is considerable variability. A different trend was observed for MGD than for other dry eye diagnostic criteria; males had a slightly higher prevalence for most age categories, although the differences were not statistically significant, except in the age 80+ group. However it is worth noting that only two studies reported data for MGD prevalence that were stratified by age and sex, therefore any conclusions may be premature and stratification would be an important consideration in future studies.

3.2.9. Summary and recommendations

This report has summarized the results of published population based studies of prevalence and, to a lesser degree, incidence. A meta-analysis has enabled rational combination of studies to evaluate the effects of age and sex on disease prevalence. Spatial mapping has summarized the prevalence estimate by region and electronic resources have been made available to allow further exploration of environmental and population factors including climate, population density, air quality index, weather, altitude and to incorporate new data as these become available. The prevalence mapping described here could also be used to examine overlap with the human development index (a composite statistic of life expectancy, education, and income per capita) and the distributions of different dry eye interventions.

Key findings are as follows:

- The prevalence of dry eye increases linearly with age. The increase in prevalence by decade is greater with clinical signs of dry eye compared with symptoms report and with self-report of a clinical diagnosis. Similarly, the rate of MGD increases linearly with age. There remains a great need for more clinical signs of dry eye data in populations younger than 40 years.
- Perhaps surprising is the relatively high prevalence rates reported in younger subjects and in school children, which would certainly support further studies in this age group and evaluation of potential risk factors such as digital device use.
- Differences in prevalence rate by sex become significant generally only with age, although there is considerable variability, with women having a higher prevalence of dry eye than men. As only two studies report data for MGD prevalence that stratify by age and sex, any conclusions may be premature and

![Fig. 5. Prevalence of symptomatic disease (upper), WHS criteria (central) and clinically diagnosed dry eye (lower panel) by age. The number of studies reporting prevalence is shown above the x-axis.]
stratification would be an important consideration in future studies.

- There have been no population-based studies from the Southern Hemisphere published in the last 10 years. Geographical mapping approaches will allow future exploration of the impact of climate, socioeconomic and environmental factors on dry eye.

- There are limited studies evaluating disease incidence and access to large population data sets from longitudinal studies would be of value.

4. Goal 2. to assess and summarize knowledge on the risk factors for DED

In evaluating risk factors for DED, the Epidemiology subcommittee found a large number of published studies compared with the previous report [1]. The limited number of population-based studies included in the TFOS DEWS report of 2007 [51–57] was supplanted by more recent robust data [9,10,12,16–21,23,25,26]. New studies performed in different populations around the world.
provided valuable information about DED by geographic region. However, there is still a considerable lack of information needed in order to provide a comprehensive understanding of risk factors for DED, due partly to methodological differences between studies, differences in population groups and diagnostic criteria. Overall, a review of the existing data generates an extensive list of risk factors, which is to be expected since the tear film and ocular surface form part of a highly integrated functional unit, influenced by life style, environmental exposures, conditions such as connective tissue and metabolic diseases and their treatment and ocular diseases, such as MGD. However, these risk factors have been neither equally substantiated nor equally evaluated by the different studies (Table 3).

Studies on risk factors for DED can provide important information that enables advances in diagnostic methodology, elucidation of pathophysiological mechanisms and relationships, therapeutic perspectives, public education and strategies to improve both general and ocular health. For the purpose of this report, the search strategy for risk factor publications studies used PubMed and Scopus databases with the following terms: (Dry eye syndrome OR dry eye OR tear dysfunction OR tear deficiency or insufficiency, OR keratoconjunctivitis sicca OR sicca syndrome OR MGD OR blepharitis) AND (epidemiology OR risk factor OR correlation OR association OR relation). Duplicate articles were excluded and eligible studies included those reporting either or both symptoms and
The majority of studies have reported an increase in dry eye prevalence with age [9,12–16,21,22,25,53–55,64–68], while a smaller number of others did not find a significant association [18,20,27,51,56].

4.2. Sex

Similarly, female sex is consistently associated with DED [10,12,13,15,16,20–24,64–66,69–72], although some studies have found otherwise [18,19,27,67,73]. In a population-based, cross-sectional study comprising a cohort of 3824 British female twins aged 20–87 years [25], the prevalence of dry eye increased significantly per age decade, with a peak increase in the 40–50 year old group, and identified immune-mediated disease, ocular surgery and chronic pain syndromes as important risk factors in women.

4.3. Meibomian gland dysfunction (MGD)

DED has been divided into evaporative and aqueous deficiency subtypes [74], the former being frequently associated with MGD [16,75]. Consistent with the findings of the previous TFOS DEWS epidemiology report [1], the TFOS MGD epidemiology report published in 2011 [6] found a lack of agreement for the definition and classification of MGD, which limited the epidemiologic investigation of this disorder. In addition, they noted that there was a lack of clarity regarding objective and subjective methods used to diagnose and evaluate this common ocular condition. In this regard, new analytical and descriptive techniques have shown promise [76–81], but these procedures are not applicable to epidemiological research so far because of their complexity and because they are not yet standardized. This report also noted that many risk factors implicated in DED also play a role in MGD, and the interplay of the tear film, ocular surface and meibomian glands influence the development and progression of both conditions [6]. In line with this observation, MGD is associated with DED signs and symptoms not only in clinical studies, but also in population-based studies [2,3,29,82], where signs are present in more than two thirds of subjects with dry eye in clinic-based studies and in approximately half in population-based studies. This overlap in clinical signs, with the exception of Schirmer testing for tear production, might suggest that MGD causes a local histopathologic effect on the ocular surface, in contrast to the hyposecretory effect on tears associated with certain drugs and systemic disorders [83,84]. However, more research is needed to understand the relationship between MGD and the ocular surface and to elucidate the basis for symptoms.

Rosacea-associated MGD is a variant of MGD, with distinct epidemiological and clinical characteristics [85,86]. This form of MGD deserves particular attention, especially in children, because it is usually associated with a more severe disease, inflammatory complications of the ocular surface, and its diagnosis may be elusive since cutaneous signs may be minimal or absent [7,77,85–87].

**Table 2**

Regression analysis of prevalence data by age for each diagnostic subgroup.

<table>
<thead>
<tr>
<th>Diagnostic subgroup</th>
<th>No of studies</th>
<th>Slope estimate (per decade of age)</th>
<th>Std error of slope estimate</th>
<th>p-value (H0: slope = 0)</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Symptoms or OSDI&gt;22</td>
<td>8</td>
<td>3.43</td>
<td>0.57</td>
<td>0.001</td>
<td>0.858</td>
</tr>
<tr>
<td>2. Self-report of a clinician diagnosis of dry eye</td>
<td>8</td>
<td>2.01</td>
<td>0.73</td>
<td>0.034</td>
<td>0.556</td>
</tr>
<tr>
<td>3. WHS Criteria</td>
<td>8</td>
<td>–0.44</td>
<td>0.57</td>
<td>0.475</td>
<td>0.088</td>
</tr>
<tr>
<td>a. Schirmer</td>
<td>5</td>
<td>10.55</td>
<td>1.78</td>
<td>0.010</td>
<td>0.921</td>
</tr>
<tr>
<td>b. TRUT</td>
<td>5</td>
<td>9.71</td>
<td>1.20</td>
<td>0.004</td>
<td>0.956</td>
</tr>
<tr>
<td>c. G. Corneal staining</td>
<td>5</td>
<td>7.63</td>
<td>1.67</td>
<td>0.020</td>
<td>0.875</td>
</tr>
<tr>
<td>d. MGD</td>
<td>5</td>
<td>5.23</td>
<td>1.44</td>
<td>0.036</td>
<td>0.815</td>
</tr>
</tbody>
</table>

a Indicates that there is no change in prevalence by age for the WHS criteria.
b Regression analyses are based on estimates of prevalence from age 40–49 and up (i.e., missing values for prevalence for ages 15–18, 19–29, and 30–39).
Other chronic ocular surface disorders such as pinguecula or punctal stenosis are associated with DED in clinical studies \[41,42\], but not in population-based studies \[2,57\], which might reflect the homeostatic ability of the lacrimal functional unit to respond and adapt to changes in the ocular surface environment \[88\]. Conversely, MGD often causes tear film instability and signs of damage to the ocular surface, although it is asymptomatic in most patients. The presence of symptoms apparently depends on comorbidities and other factors, and is not consistently associated with more severe disease \[7\]. Although allergic conjunctivitis and other ocular surface disorders are associated with symptoms indistinguishable in many cases from dry eye, they are not considered risk factors in a number of epidemiological studies \[52,54\], but rather distinct clinical entities. There is evidence to suggest that allergic diseases such as vernal and atopic keratoconjunctivitis and allergic conjunctivitis are associated with a

![Graph showing prevalence of symptomatic disease, clinically diagnosed dry eye, and WHS criteria by age and sex.](image-url)
higher risk of dry eye in clinical populations [89–91], although this has not been confirmed in population-based studies. Nevertheless, such inflammatory diseases should be differentiated from primary dry eye because their associated factors and management differ.

4.4. Asian race

As discussed in Goal 1, the body of evidence suggests that Asian race is a significant risk factor for DED once gender and age are controlled for, with an odds ratio of 1.5–2.2x that of Caucasians, depending on the diagnostic group. However, studies carried out in Singapore show a similar rate to Caucasians for symptomatic disease [18,27].

4.5. Contact lens wear

Contact lens (CL) wearers frequently report increased ocular dryness compared to non-lens wearers, a decrease in daily wearing time and ultimately discontinuation of use [92]. DED appears to be up to 4 times more prevalent in CL wearers in population-based studies [10,21,24,25,27,60]. CL wear was associated with a higher prevalence of severe symptoms of DED [30].

The growing interest in the relationship between DED and CL wear was explored in the TFOS International Workshop on Contact Lens Discomfort (CLD) [93]. While CLD does appear to be a discrete condition [92], this report highlighted the potential interaction between DED and CLD and although there can be some overlap in traditional signs and symptoms, specific differences are discernible. For example, there can be distinct differences between the type and chronicity of symptoms reported in each condition, symptoms are ameliorated on removal of the CL and differences in the natural history are observed. Contact lens wear impacts on normal ocular surface homeostasis [94], and while there may be overlap in clinical presentations, it is important to appreciate that CL wearers may have, or develop, concurrent DED.

4.6. Hematopoietic stem cell transplantation

Allogeneic hematopoietic stem cell transplantation is widely used as a potential curative treatment for hematologic malignancies. Despite improvement in outcomes, chronic Graft Versus Host Disease (GVHD) remains a life-threatening condition, involving various organs and tissues, including the ocular surface. The increased number of procedures performed and higher survival rates has led to a large number of patients with ocular morbidity. There are several good quality cross-sectional studies that have articulated the prevalence and presentation of DED related to ocular GVHD [95–102], confirming recipient sex mismatch, regimen intensity, history of viral infection and presence of skin, mouth and liver GVHD as associated risk factors. DED is the most common manifestation of ocular GVHD, resulting from lacrimal gland destruction from allogeneic T cells as well as from severe MGD [96], resulting in symptoms and a broad range of ocular surface manifestations. The poor accuracy of the Schirmer test used as the National Institutes of Health criteria for ocular GVHD has been criticized and is considered a limitation that must be addressed [101,103]. It is crucial to provide detailed screening and preventive strategies to avoid severe ocular discomfort as well as irreversible vision threatening complications.

4.7. Sjögren syndrome

Sjögren syndrome is a chronic autoimmune disorder characterized by exocrine gland dysfunction, which affects the salivary and lacrimal glands. Sjögren syndrome is associated predominantly with aqueous-deficient dry eye, although a higher rate of evaporative dry eye than in the non-Sjögren population has also been reported [104]. The prevalence of Sjögren syndrome is estimated to be in the order of 0.6% (0.19–1.39%) [105], although there is some variation in prevalence, based on the definition used. The incidence of physician diagnosed Sjögren syndrome in a white population in
the US has been estimated at 3.9 per 100,000 per year, with a 14x higher rate in women than men [106]. Of 1208 participants in an international Sjögren syndrome registry, 85% reported symptoms of dry eye [61]. Of individuals with significant aqueous deficient dry eye, 10% are likely to have Sjögren syndrome [62]. In a US clinical study, 26% of patients with either aqueous tear deficiency or evaporative dry eye have an underlying rheumatic condition, including Sjögren syndrome [107].

4.8. Environmental exposures

Several environmental factors have been suggested to impact DED, such as air pollution, wind, low humidity and high altitude. There has been a limited number of case-control studies performed in selected populations (such as in India, Italy and Brazil) that compared metropolitan areas with rural areas and showed associations between DED and hazardous exposure [108–111].

Fig. 8. The prevalence of DED signs by age and sex.
However, despite these data, an important gap in knowledge about how environmental factors affect DED persists. Indeed, the understanding of the impact of pollution requires the challenging integration of location-based health data and corresponding environmental data conditions.

Galor and colleagues demonstrated a higher risk of DED in metropolitan areas of the USA. Subjects with DED were identified by the International Classification of Disease (ICD-9) code 375.15. Spatial information was determined by assessing latitude and longitude coordinates of patients’ zip codes, which were correlated with meteorological data, such as temperature, wind speed, relative humidity, visibility and atmospheric pressure from National Climatic Data Center and aerosol optical depth (a marker of air pollution) extracted from National Aeronautics and Space Administration, at each point location. This large population study comprised 606,708 subjects and demonstrated the risk of DED to be 13% higher in areas where the atmospheric pressure was one standard deviation higher (incidence rate ratio (IRR) 1.13x) and in areas with a higher level of aerosol optical depth (IRR 1.13x). In addition, higher humidity and wind speed (in the presence of air pollution) were inversely associated with the risk of DED (IRR 0.92x and IRR 0.93x) [112]. A large population based study conducted in Korea compared outdoor pollution measurements collected from national monitoring stations to DED based on symptoms or a prior
4.10. Vitamin A deficiency/nutritional issues

Dietary vitamin A deficiency is recognized as a major health problem in certain parts of the world, such as the African continent, with children being more frequently affected. It is associated with a form of DED that contributes to corneal involvement, keratomalacia and preventable blindness [120]. Vitamin A deficiency also increases susceptibility to a range of illnesses and an increased risk of mortality. Worldwide vitamin A supplementation programs have significantly reduced ill health, blindness and death [121–123]. In addition, similar presentations of DED may be related to other nutritional conditions, such as eating disorders (e.g. anorexia and bulimia), bariatric surgery, vegan diet, and malabsorption syndromes [124–127].

4.11. Dietary supplementation

Accumulated evidence over the past decade has shown a potential benefit of essential fatty acid (EFA) supplementation on dry eye. There is an increasing interest in the use of nutritional supplementation or dietary modification regarding EFAs on the prevention and treatment of dry eye, based on the understanding that a balance of omega-3/omega-6 is important to perform distinct and complementary functions. EFAs may play an important role in ocular surface health and DED treatment. EFAs have been shown to display anti-inflammatory properties systemically, based on their effects on arachidonic acid metabolism, specifically the production of prostaglandins [128–130]. In the eye, EFAs enhance lipid layer retarding tear evaporation and decrease apoptosis of lacrimal gland acini and epithelial cells, also contributing to improved tear secretion [131,132].

Well-designed and appropriately powered prospective, interventional trials have evaluated the role of EFAs supplementation on dry eye signs and symptoms [133,134]. Recently, a multicenter 12-week intervention study comprising 1419 dry eye patients using oral omega 3 supplementation showed improvement in their symptoms and reported decreased use of lubricants [135]. Further evidence is outlined in the TFOS DEWS II report on management and therapy [136].

It is important to note that the role of EFAs in the treatment of DED is still not completely understood and that there is also no consensus on the dose, composition and length of treatment [137]. Increased quality evidence on the usefulness of nutritional supplements is needed to enable eye care professionals to confidently outline specific treatment recommendations for using EFAs for DED.

4.12. Refractive surgery

Laser in Situ Keratomileusis (LASIK) is the most commonly performed vision correction surgery. However, signs and symptoms of DED can occur in both early and late postoperative periods. LASIK has been proposed to result in neuropathic dry eye [138], associated with sensory nerve damage, reducing lacrimal gland secretion and

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Risk factors for dry eye disease.</th>
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<tbody>
<tr>
<td>Consistent&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Probable&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Non-modifiable</strong></td>
<td></td>
</tr>
<tr>
<td>Aging</td>
<td>Diabetes</td>
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<tr>
<td>Female sex</td>
<td>Rosacea</td>
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<tr>
<td>Asian race</td>
<td>Viral infection</td>
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<tr>
<td>Meibomian gland dysfunction</td>
<td>Thyroid disease</td>
</tr>
<tr>
<td>Connective tissue diseases</td>
<td>Psychiatric conditions</td>
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<tr>
<td>Sjogren Syndrome</td>
<td>Pterygium</td>
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<tr>
<td><strong>Modifiable</strong></td>
<td></td>
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<tr>
<td>Androgen deficiency</td>
<td>Low fatty acids intake</td>
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<tr>
<td>Computer use</td>
<td>Refractive surgery</td>
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<tr>
<td>Contact lens wear</td>
<td>Allergic conjunctivitis</td>
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<tr>
<td>Hormone replacement therapy</td>
<td></td>
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<tr>
<td>Hematopoietic stem cell transplantation</td>
<td></td>
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<tr>
<td>Environment: pollution, low humidity, sick building syndrome</td>
<td></td>
</tr>
<tr>
<td>Medications: antihistamines, antidepressants,</td>
<td>Medications: anticholinergic, diuretics, beta-blockers</td>
</tr>
<tr>
<td>anxiolytics, isotretinoin</td>
<td></td>
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<tr>
<td>Medications: multivitamins, oral contraceptives</td>
<td></td>
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</tbody>
</table>

<sup>a</sup> Consistent evidence implies the existence of at least one adequately powered and otherwise well-conducted study published in a peer-reviewed journal, along with the existence of a plausible biological rationale and corroborating basic research or clinical data.

<sup>b</sup> Suggestive evidence implies the existence of either inconclusive information from peer-reviewed publications or inconclusive or limited information to support the association, but either not published or published somewhere other than in a peer-reviewed journal.

<sup>c</sup> Inconclusive evidence implies either directly conflicting information in peer-reviewed publications, or inconclusive information but with some basis for a biological rationale.
triggering neurogenic inflammation [139,140]. The risk of dry eye after LASIK is significantly associated with preoperative conditions, such as pre-existing tear dysfunction and long-term CL wear; Asian patients have a higher incidence of dry eye after LASIK (28%) compared to Caucasian patients (5%) [141]. Operative conditions may also contribute to DED after LASIK. The impact of factors such as flap hinge location (superior versus nasal) and width on the development of DED are not well defined, as recent studies report conflicting results [142,143]. Nevertheless, higher refractive corrections and deeper ablations are associated with decreased corneal sensitivity, increased postoperative dry eye symptoms, and chronic tear dysfunction [139,144].

4.13. Diabetes

The association between dry eye and diabetes mellitus is not significant in most population-based studies [10,21,25,102]. However, a population-based survey [145] analysing the comorbidities of dry eye and several case control studies [102,146–148] found a positive correlation with complicated disease. In two of these studies, dry eye was associated with neuropathy [148] and retinopathy classified according to the early treatment diabetic retinopathy study (ETDRS) criteria [147]. In a study conducted with 199 type 2 diabetic patients, the prevalence of DED was 54.3% and dry eye positively correlated with the duration of diabetes and the presence of retinopathy [146]. Another study compared symptoms and objective signs of DED in 104 children with type 1 diabetes compared to 104 age and sex-matched controls, where 15.4% of diabetic children complained of dry eye symptoms compared with 1.9% of the controls and 7.7% of diabetic children had dry eye signs compared with 1.0% of controls. [149].

In diabetics, it is possible that the signs of DED are a consequence of the reduction in corneal sensitivity and that impaired homeostasis can occur in this population. Thus, it is conceivable that in population studies that use self-reported symptoms as an outcome measure, that the prevalence of DED may be underestimated. In the Salnes Eye Study [7] an association was found with asymptomatic but not with symptomatic MGD. However, this was the only sign found to be associated with diabetes in this general population. The associations with TBUT, corneal and conjunctival staining and the Schirmer test were not significant, in contrast to the positive correlation found in the case control studies described above.

4.14. Affective and somatoform disorders

Recent studies have shown an association between DED and several affective disorders, with anxiety and depression the most frequently reported [69,12,25,26,70,150–152]. Whether these disorders precede or arise as a consequence of DED is not known, although these circumstances are not mutually exclusive. Irrespective of the nature of the association, there are a number of factors that can confound the results of these studies or the interpretation of risk factors. For example, the role of anxiolytics and antidepressants needs to be elucidated, as these medications can also be associated with DED [15,23,57,70]. Similarly, individuals with DED report lower self-perceived health [153], which could bias the results of the questionnaires used to evaluate mental health. Stress has been associated with both dry eye and mental health and could act as a trigger in some instances [11,12,26,102]. Psychological factors and the consequent altered immune response could increase the probability of DED associated with this disorder [154].

Several chronic pain syndromes such as chronic widespread syndrome, pelvic pain and irritable bowel syndrome have also been associated with DED, as has migraine [12,25,153,155,156], suggesting that these disorders could share etiopathogenic neuropathic mechanisms with DED. Although somatisation and increased pain sensitivity may impact on the frequency of reporting of symptoms of dry eye, the extent to which this impacts the prevalence of the disease remains to be elucidated.

4.15. Heritability and genetic risk factors

In addition to environmental risk factors, genetic susceptibility is likely to be important in the etiology of DED, but relatively little is known about the role of genes. DED has been shown to be moderately heritable in one female twin study in the United Kingdom [157], with heritability of approximately 30% for symptomatic dry eye and of 40% for a diagnosis of DED by an ECP. The remaining 60–70% of the variation of DED in the population was due to environmental factors. Like most common diseases, DED is complex or multifactorial, which means it is unlikely to have a simple Mendelian inheritance pattern controlled by a single gene locus [158].

Complex interactions between genes and the environment most likely play a role, which makes genes difficult to identify. Genome-wide association studies (GWAS) identify genetic variants by looking at millions of common single-nucleotide polymorphisms and have been highly successful in common eye diseases such as myopia, glaucoma and age-related macular degeneration [159]. To date, no GWAS studies on DED have been published. Two large GWAS case-control studies on Sjögren syndrome have been performed [160,161], showing associations with immune-related genes, but not with genes encoding for salivary or lacrimal components, secretion machinery or neuronal proteins that innervate glands [162]. There have been several candidate gene studies in DED that examined a few selected polymorphisms in pre-specified genes of interest in clinic-based case-control studies. These studies suggested possible associations with pro-inflammatory cytokine genes [163], killer cell immunoglobulin-like receptor and human leukocyte antigen-C genes [164,165], the tachykinin receptor 1 gene [166] and brain-derived neurotrophic factor and vitamin D receptor genes [167]. However, it is important to note that none of these results were strong, and that they have not been (well) replicated in independent studies, and candidate gene studies are notorious for false positive results. Unravelling the interplay between genes and the environment in DED using hypothesis-free GWAS has the potential to identify new biological insights and therapeutic options and is highly encouraged by this subcommittee. It is important to note that sufficient statistical power using high sample sizes is critical to success in GWAS studies, especially in a poorly defined and multifactorial phenotype such as DED. International (gene-by-environment) GWAS collaborations using strict and similar disease definitions across cohorts are needed to obtain reliable results. A standardized, quantitative phenotype with a (near) normal distribution such as tear osmolarity may result in the highest power as per outcome measure, but high sample sizes and sufficient statistical power are most likely easier to obtain with a case-control setting using questionnaire-based disease definitions, such as the WHS questionnaire, particularly in populations that already have GWAS data available.

4.16. Summary and recommendations

This review has generated a broad summary of risk factors, categorized both based on whether factors are modifiable or non-modifiable and by the level of evidence in support of the association. However, these findings are still somewhat confounded by methodological differences between studies, the quality of studies
in terms of the power to detect differences, differences in diagnostic criteria and study population differences. The review has highlighted the need for appropriately powered hypothesis driven studies, which address the major and important risk factors. Risk factors may vary with different diagnostic criteria but also may vary based on the health service provision in different jurisdictions. It may also be useful to consider population attributable-risk percentage to prioritize risk factors based on their impact.

The Committee concluded that there were limited studies to evaluate the impact of climate change, digital device use and dry eye in youth, and that it was important to distinguish dry eye from other symptomatic conditions, including allergic disease, infectious diseases, inflammatory conditions and other chronic ocular surface diseases.

5. Goal 3. to evaluate available data on the natural history of DED and disease morbidity

5.1. Natural history of DED

Despite the significant impact of DED in the community, there are limited published studies available which describe the natural history of treated or untreated DED. Bronn and colleagues [168] proposed a theoretical model of progression based on the disease evolving through three stages 1) Initiation of DED, 2) Reflex compensation, and 3) Loss of the compensatory response. This model suggests that disease may worsen without intervention and that over time aqueous-deficient dry eye may show clinical signs of evaporative dry eye and vice versa. The disease may also plateau at a certain stage [168]. A counter view that not all DED is progressive is supported by a recent retrospective study based on resurveying 784 participants from the Women's and Physicians' Health Studies in the USA, who had previously reported a positive diagnosis of dry eye or severe dry eye symptoms [169]. This study determined the rate of, and risk factors for, an increase in dry eye discomfort, worsening vision related symptoms and greater social impact. Medical records were reviewed and a subset of participants also underwent clinical examination [169]. The average duration of DED was 10.5 years for men and 14.5 years for women. The most common perception of subjects was that there was no change in dryness symptoms (32% unchanged, 44% improved and 24% worsened), visual symptoms (52% unchanged, 19% improved and 29% worsened) or social impact (71% unchanged, 19% improved and 10% worsened) over time. The distribution of change in symptoms was not related to the type of treatment or its relative level of severity. Worsening of dryness symptoms was associated with a high monthly dollar spend for treatment, a history of severe dry eye symptoms and the use of systemic beta-blockers. A worsening of vision symptoms was also associated with a history of ocular surgery, depression and either MGD or blepharitis. A worsening of social impact was associated with older age, use of systemic beta-blockers and either MGD or blepharitis. Worsening symptoms was not related to the probability of corneal staining [169].

While recall bias in retrospective studies may confound symptom recall, these findings do support the view that DED characterized by severe dry eye symptoms at diagnosis, appears to progress irrespective of treatment. The lack of association between progression of symptoms and signs is not unexpected. Without reference to disease severity, a reduction in symptom reporting over time has been established in the Twins UK study, where 37% of subjects with symptomatic disease at baseline (using the Beaver Dam study criteria) did not report symptomatic disease when resurveyed two years later [25]. It is not clear whether these individuals were undergoing treatment or if this is representative of the waxing and waning course of the disease. A recent meta-analysis of the effects of topical 0.05% cyclopentolate and artificial tears, vehicle control or no treatment on disease signs and symptoms confirmed the overall efficacy of treatment in reducing signs and symptoms, but there was heterogeneity between studies in severity and etiology of dry eye [170].

Prospective studies are needed to determine the clinical course of all severities of dry eye, prognostic factors in disease progression, and the role of treatment in reducing signs and symptoms. The subcommittee also recommends reviewing data from available placebo/vehicle and treatment groups in randomized double-masked controlled trials of sufficient duration to determine changes in prevalence over time. Other sources of information would include registry studies and claims data, although the type and quality of data may vary.

5.2. Morbidity of dry eye

5.2.1. Economic burden of dry eye

Since the initial TFOS DEWS epidemiology report [1], an increasing number of studies have quantified the costs incurred by healthcare systems in association with DED [174–184]. Many of the large cohort and population-based studies have calculated the estimated cost of DED treatment or work productivity losses. However, cost analyses cannot provide direct conclusions regarding effective resource allocation for particular treatments or strategies. Nevertheless, cost of illness analyses provide information about the patterns of resource use for a particular condition, thereby enabling a greater understanding of the framework within which decisions about resource allocation are made. Although the medical insurance fee and health care systems vary among countries, it has been consistently reported that DED significantly increases the utilization of healthcare resources.

DED affects tens of millions of individuals and carries significant socioeconomic implications, including the expenses associated with medications and physician visits and the effects on daily social and physical functioning. Furthermore, increased time spent on treatment and the avoidance of certain environments in the workplace that aggravate dry eye symptoms can lead to a decrease in workplace productivity.

The economic burden of DED can be attributed to direct medical care spending, the impact of loss of productivity, and impact on quality of life [179,181–186]. The total annual cost for the management of DED was estimated to be USD 3.84 billion in the United States [182], and USD 0.15 million in Singapore [180]. The annual total cost for 1000 patients with DED in Europe managed by ophthalmologists ranged from USD 0.27 million in France to USD 1.10 million in the United Kingdom [175]. The total annual health plan cost per patient was estimated as USD 323 in Japan, and USD 375 in United States [183]. Annual productivity loss per patient associated with definite DED was estimated to be USD 6160 in Japan [179] and the annual cost of DED from a societal perspective, was USD 11,302 in the United States [182].
Measurement of the treatment cost of DED is challenging because the treatment options and health insurance service vary by country. The treatment utilization includes prescription medication, punctal plugs, and surgical management [182]. Fiscella and colleagues reported the mean treatment cost per patient at USD 336 for topical cyclosporine and USD 375 for punctal plugs [183]. Mizuno et al in 2012 estimated the total annual cost of prescription drug per patient to be USD 323 and the cost of punctal plugs per patient to be USD 42 [177].

Table 4 summarizes the healthcare costs by region [174–184]. A recent systematic literature review has confirmed that the largest proportion of costs are attributed to indirect costs due to reduced productivity at work [187].

While cost analyses cannot recommend resource allocation for particular treatments or strategies, cost of illness analyses provide information about the patterns of resource use for a particular condition, thereby enabling a greater understanding of the framework within which decisions about resource allocation are made. Although the medical insurance fee and health care systems vary among countries, it is widely accepted that DED significantly increases the utilization of healthcare resources. Cost savings through improved quality of life (QoL), improved productivity and reduction in healthcare utilization costs associated with effective disease treatment should also be modelled in future studies.

5.2.2. Quality of life questionnaires
The currently validated dry eye specific questionnaires, the OSDI and the Impact of Dry Eye on Everyday Life (IDEEL) are frequently used to measure disease severity (Table 5) [12,24,26,185,188–193].

The OSDI is a DED-specific instrument that includes 12 questions assessing the frequency of dry eye symptoms and their effects on vision-related function. The 12 OSDI questions comprise three different subscales, namely ocular symptoms, vision-related functions and limitations, and environmental triggers during a 1-week recall period. Each answer is scored on the basis of symptom frequency using a 4-point scale where 0 indicates no problem and 4 indicates multiple problems.

Table 4 The economic burden of dry eye disease.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Methods</th>
<th>Study Population</th>
<th>Years Studied</th>
<th>Cost Analysis</th>
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<tbody>
<tr>
<td><strong>United States</strong></td>
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<tr>
<td>Fiscella 2008 [183]</td>
<td>Retrospective administrative claims analysis</td>
<td>23,821 of dry eye patients treated with cyclosporine or punctal plugs</td>
<td>2004–2005</td>
<td>• The total health plan for topical cyclosporine, US$3.05 million (mean cost $236/patient).</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• Total health plan costs for punctal plugs procedures, $2.28 million (mean cost $175/patient).</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Systane® cost on average US$57.79/year more than Refresh Tears®.</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• Assigning a quality-adjusted life year (QALY) gain of 0.03 to responders results in an incremental cost per QALY gain of US$5373.</td>
</tr>
<tr>
<td>Wlodarczyk 2009 [184]</td>
<td>Meta-analysis, literature review and economic model for dry eye</td>
<td>Cohort of dry eye patients from two clinical trials (n = 147) treated with either Systane® or Refresh Tears®</td>
<td>2006</td>
<td>The societal perspective incremental cost-utility ratio (CUR) for cyclosporine over vehicle therapy is $34,953 per QALY and the societal perspective average CUR is $11,199 per QALY. The third-party-insurer incremental CUR is $37,179 per QALY, while the third-party-insurer perspective average CUR is $34,343 per QALY.</td>
</tr>
<tr>
<td>Brown 2009 [174]</td>
<td>Multicenter, randomized, clinical trials</td>
<td>877 of dry eye (270 had Sjogren syndrome)</td>
<td>2007</td>
<td>• Approximately 31% of severe DED patients, 40–60% loss in productivity while working; 15% experienced 70–100% loss.</td>
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<tr>
<td><strong>Japan</strong></td>
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<tr>
<td>Mizuno 2012 [177]</td>
<td>Estimated annual direct costs from outpatient medical records and survey</td>
<td>118 of prospective cohort dry eye</td>
<td>2008</td>
<td>Drug cost was US$323 ± 219/year; Clinical cost US$165 ± 101/year; Total direct costs including punctal plug treatment US$330 ± 384/year.</td>
</tr>
<tr>
<td>Uchino 2014 [179]</td>
<td>Survey</td>
<td>672 office workers</td>
<td>2013</td>
<td>The estimated cost of annual work productivity losses: US$6160/person in the definite DED group; US$2444/person in the probable DED group.</td>
</tr>
<tr>
<td><strong>Singapore</strong></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• US $1,520,797.8/year in 2009.</td>
</tr>
<tr>
<td><strong>France, Germany, Italy, Spain, Sweden, and the United Kingdom</strong></td>
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<tr>
<td>Clegg 2006 [175]</td>
<td>Systemic literature review and interviews</td>
<td>Model cohort 1000 dry eye patients</td>
<td>2003–2004</td>
<td>Annual burden of UK (~US $1100/person), Spain (~US $800/person), Italy (~US $600/person), Germany (~US $500/person), Sweden (~US $400/person), and France (~US $300/person).</td>
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</table>
indicates a significant problem. However, the OSDI has some limitations in that it does not assess the psychological and social aspects of DED, therefore, it is not widely used to evaluate the more holistic effects of DED on QoL.

The IDEEL, which is a 57-item questionnaire, comprises three modules: dry eye symptom bothersomeness; impact on daily life (including daily activities, emotional impact, and impact on work) and treatment satisfaction (both effectiveness and treatment-related bother/inconvenience). There are two items related to visual disturbance that assess the extent to which the patient is affected by blurry vision and sensitivity to light, glare, and wind. The strength of the IDEEL is that it covers all relevant domains of DED and it also distinguishes the severity of DED, however, it is not frequently used in routine clinical practice because of a long duration of testing (typically taking over 30 min).

Perhaps the most widely used questionnaires pertaining to general health and general eye health include the Short Form-36 (SF-36) and the 25-item National Eye Institute’s Visual Function Questionnaire (NEI VFQ-25), respectively. The SF-36 is used as a measure of the general health status of an individual. It includes 36 items under the following subscales: Physical Functioning, Role-Physical (role limitations due to physical problems), Bodily Pain, General Health Perceptions, Vitality, Social Functioning, Role-Emotional (role limitations due to emotional problems), and Mental Health. The VFQ-25 includes 25 items under the following subscales: Visual Activity Limitations,-role emotional, role physical, pain/discomfort, anxiety score and circulating C-reactive protein level.

Table 5

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Instruments</th>
<th>Subjects</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mertzans [188]</td>
<td>United States</td>
<td>IDEEL, SF-36</td>
<td>32 with SS, 130 with non-SS KCS, 48 controls</td>
<td>- Non-SS KCS patients had lower Role-Physical (effect size [ES] = −0.07), Bodily Pain (ES = −0.08), and Vitality (ES = −0.11) scores.</td>
</tr>
<tr>
<td>Rajagopalan [189]</td>
<td>United States</td>
<td>SF-36, EQ-5D, IDEEL</td>
<td>130 with non-SS KCS, 32 with SS, 48 controls</td>
<td>Significant differences between severity levels were found with most SF-36 scales (P &lt; 0.05), all EQ-5D scales (P &lt; 0.05), and all IDEEL scales (P &lt; 0.0001), except for Treatment Satisfaction.</td>
</tr>
<tr>
<td>Na 2015 [26]</td>
<td>South Korea</td>
<td>EQ-5D, EQ VAS</td>
<td>Korea National Health and Nutrition Examination Survey (KNHANES)(2010–2011), (N = 3285), women aged over 19 years</td>
<td>Significantly poorer functional ability in SS compared with controls across all domains; Functional impairment specifically associated in univariate analysis with physical fatigue, pain, depression, symptom burden, disability, activity, quality of life, dryness, daytime somnolence, anxiety score and circulating C-reactive protein level.</td>
</tr>
<tr>
<td>Ahn 2014 [12]</td>
<td>South Korea</td>
<td>EQ-5D, EQ-VAS</td>
<td>Korea National Health and Nutrition Examination Survey (KNHANES)(2010–2011), (N = 11,666), aged 19–95.</td>
<td>- Means of pain, discomfort/anxiety, depression dimensions, and EQ-VAS in the EQ-5D were significantly higher in the group diagnosed with DES than in the normal group (all P &lt; 0.01)</td>
</tr>
<tr>
<td>Belenguer 2005 [192]</td>
<td>Spain</td>
<td>SF-36</td>
<td>110 patients (105 women and 5 men, mean age of 56 years) with primary SS</td>
<td>Comparison between patients with primary SS and the control population showed lower scores in SS in all SF-36 scales (p &lt; 0.001)</td>
</tr>
<tr>
<td>Mizuno 2010 [193]</td>
<td>Japan</td>
<td>VFQ-25, SF8</td>
<td>158 with DED (30 with SS, 128 with non-SS)</td>
<td>- Some patients recorded extremely low VFQ-25 scores - VFQ-25 and SF-8 scores were not significantly different between the SS and non-SS patients.</td>
</tr>
</tbody>
</table>
Mental Health [194]. A 4-week recall period is used for all these subscales, except Physical Functioning and General Health, which reflect the health of the patient at the time of questionnaire completion. The NEI-VFQ-25 assesses the effects of various eye diseases on QoL [195]. The ocular pain subscale of the NEI-VFQ-25 shows the strongest overall correlation with the OSDI in individuals with Sjögren syndrome [196], leading some researchers to suggest that patients with low ocular pain scores (where a higher score reflects better function) in NEI-VFQ-25 should undergo further testing for dry eye. However, with regard to the assessment of QoL in patients with dry eye, the NEI-VFQ-25 is limited because it is not disease-specific and needs further validity and reliability testing in a dry eye cohort, lacks a specified recall period, and requires 10 min for completion. In some instances, a 14-item appendix can be administered to subjects to enhance the reliability of the various subscales. The NEI-VFQ is comprised of 39 questions with the following 12 domains or subscales: (1) general health, (2) general vision, (3) ocular pain, (4) difficulty with short distance vision activities, (5) difficulty with long distance vision activities, (6) vision-related limitations in social functioning, (7) mental health symptoms related to vision, (8) vision-related role difficulties, (9) vision-related dependency, (10) vision-related driving difficulties, (11) limitations with near vision, and (12) limitations with peripheral vision. The scores range from 0 to 100, with higher scores indicating better function.

5.2.3. Effects of dry eye on quality of life

The available evidence suggests that DED has an adverse effect on overall QoL. It causes pain and irritation and affects ocular and general health and well-being, the perception of visual function, and visual performance [12,24,26,185,188–193,197,198]. The development of methods to assess DED patients in detail enables clinicians to understand the magnitude of the effects of DED on QoL. Some available measurement tools are specific to DED or vision, some are generic, and some focus on work productivity or anxiety/depression. Pain associated with DED can have psychological and physical impacts, while blurred vision may impose restrictions in daily life activities such as reading, driving, watching television, and operating smartphones. Moreover, the cost of DED treatment and the chronicity/intractability of DED symptoms affect the social life of an individual. Collectively, all these factors affect QoL and have an impact on public health.

Utility assessments suggest that patients with mild and severe DED experience a reduction in QoL at a level similar to that experienced by patients with mild psoriasis and moderate-to-severe angina, respectively [199]. In everyday activities, such as driving, reading, carrying out professional work, using a computer, and watching television, individuals with DED are three times more likely to report difficulties [200].

5.2.4. Impact of dry eye on quality of vision

The precorneal tear film has an important optical function. Tear film instability and corneal surface irregularities due to epithelial desiccation, resulting in changes in optical quality, can be visualized and quantified using a range of techniques [200–202]. In the majority of patients with DED, the visual acuity is normal according to standard measurements, however, instability of the tear film introduces higher-order aberrations that result in a decrease in visual quality. Early studies investigated optical fluctuations using the double-pass method to assess changes in the modulation transfer function after blinking [202]. Others involved the continuous acquisition of corneal topography or videokeratoscopy images to show that fluctuations in the tear film cause increased irregular astigmatism [201]. Patients with DED often report vision-related difficulties during daily activities, resulting in a decreased QoL and these changes are often related to depression and anxiety [203].

There are two categories of vision-related QoL instruments. Generic instruments are designed for a broad spectrum of visual disorders and ocular diseases, while disease-specific instruments are designed and validated for a specific ocular disorder [196]. Generic instruments provide broader and more general vision-related information, whereas disease-specific instruments provide more sensitive results on vision-related QoL. Most studies assessing the vision-related QoL of patients with DED used both generic (e.g. NEI-VFQ-25) and disease-specific instruments (e.g. the vision-related functions and limitations subscale of the OSDI) [200–205].

5.2.5. Impact of dry eye on mental health

The effects of DED associated with Sjögren syndrome on mental health status have been widely reported, although the impact on DED more broadly has not been evaluated. Patients with Sjögren syndrome experience significant symptoms of fatigue, autonomic dysfunction, and excessive sleepiness in addition to sicca-related symptoms. The overall impact of these symptoms on the functional ability of individuals is considered to have a significant negative impact on psychological well-being [190,197,206,207]. Because most previous studies on autoimmune-related DED did not assess the burden of dry eye separately from that of other systemic symptoms and signs of Sjögren syndrome, there is limited information of the impact of DED. Hackett and colleagues reported that patients with primary Sjögren syndrome experienced greater functional impairment than controls (Improved HAQ total scores: mean ± SD 24 ± 25 for primary SS versus 9 ± 19 for controls; p = 0.0002) across all domains of activity, including physical fatigue, pain, depression, total symptom burden, systemic disease activity, quality of life, dryness, daytime somnolence, anxiety score, and C-reactive protein (CRP) level [190]. Patients with primary Sjögren syndrome showed similar scores compared with those with systemic lupus erythematosus, using the Zung Self-rating Anxiety/Depression Scales [208].

Recently, population-based studies indicated a relationship between depression/anxiety and DED [25,70,150,151,209–211]. Ocular pain and discomfort without a definitely impaired tear film may also be associated with depression, anxiety, and psychological stress [186,200,201,203,205,212,213]. DED affects vision quality through tear-related changes in aberrations, and an impaired visual performance can likewise lead to depression and impaired QoL. An awareness of such associations between dry eye symptoms and depression is important for ECP, who may serve as the starting point for medical care. Although the precise mechanisms underlying the effects of DED on mental health remain unclear, one possible explanation is that DED results in neuropathic disease, resulting in chronic pain and negatively affects the patient’s QoL, function, and daily activities and work, eventually leading to depression and/or anxiety. A further consideration is the use of medications for these conditions which may increase the risk of dry eye.

5.2.6. New methods for measurement of dry eye related QoL

Because there is no “gold standard” diagnostic test for DED, a combination of signs and symptoms is commonly used as diagnostic criteria. Most methods for assessing dry eye-related QoL are time consuming, and their ability to quantify changes in symptoms is limited. Therefore, the development of a simple, reproducible, reliable, and quantitative instrument is critical for the diagnosis, treatment, and follow-up of DED patients.

A short questionnaire based on a visual analog scale (VAS) to
quantify the frequency and severity of dry eye symptoms has been developed. This is known as the Symptom Assessment in Dry Eye (SANDE) questionnaire [214], which comprises two questions assessing the frequency and severity of dry eye symptoms. Each of these two items is assessed using a 100-mm VAS and scored from 0 to 100. The total SANDE score is calculated as the square root of the product of the two scores and ranges from 0 to 100, with higher scores indicating greater disability [214]. The SANDE questionnaire has been validated against the OSDI instrument in a clinic population and the SANDE scores have shown negligible differences from OSDI scores [215], suggesting that the SANDE may be used in clinical practice as a short, quick, and reliable measure of disease symptoms.

In 2013, the Dry Eye-Related Quality-of-Life Score (DEQS) questionnaire was developed and validated in Japan [216]. The diagnostic criteria conformed to those defined by the Japanese Dry Eye Society in 2006. The questionnaire comprises 15 items under an Overall Summary scale and two multi-item subscales, namely Impact on Daily Life and Bothering Ocular Symptoms. When the results were compared with those of the SF-8 and NEI-VFQ-25, the DEQS questionnaire was valid and reliable for evaluating the multifaceted effects of DED on the daily lives of patients, including their mental health [216]. This suggests that this instrument may be used in routine clinical practice, although the questionnaire is time consuming and the generalizability to other populations has not been reported.

5.2.7. Future research directions

With the development of electronic devices and transmission technology, monitoring symptoms and the burden of disease in individuals with DED is changing rapidly compared with existing measurement tools. Smartphone based applications, such as electronic diaries or electronic data capture systems may be used to translate and validate the prevalence of disease effect of chronicity and treatment and the effect of DED on quality of life.

6. Goal 4: review of instruments and their use/applicability in epidemiological research

Although clinical tests have shown a wide variability in their ability to detect many cases of DED [40,217,218], conducting a battery of them could provide information on risk factors in the absence of symptoms, as recent research has suggested [7,21,56]. Evaporimetry and interferometry and other investigational techniques may be useful and specific diagnostic tools, but they lack standardization and are not yet applicable to epidemiological research.

Symptoms alone or in combination with signs are present in many definitions of dry eye used in published epidemiological studies. Since the initial TFOS DEWS report, MGD or evaporative dry eye has been identified as the most common cause of dry eye [2–5] and MGD is more frequently asymptomatic than symptomatic [7], which perhaps challenges the use of current symptom instruments. The definition of dry eye in the current workshop includes both signs and symptoms, although symptoms or signs may be absent in a single subject where there is a disturbance or a lack of tear film homeostasis. There has been increasing focus on non-obvious disease, characterized by signs in the absence of symptoms [7]. The report of the TFOS DEWS II Diagnostic Methodology subcommittee [40] has described a battery of tests suitable to diagnose and monitor dry eye and the grading of disease severity includes both signs and symptoms. While the relationship between signs and symptoms may be absent in early or mild disease, the assessment of both symptoms and signs is clearly important in grading disease severity, understanding the natural history and in monitoring response to treatment.

In 2007, the initial TFOS DEWS report summarized the available instruments for DED [1]. In the previous report, the focus was on questionnaires that had been used in randomized clinical trials or epidemiologic studies [1]. This report will similarly focus on those instruments used in epidemiological studies in disease ascertainment or determination of severity.

We searched PubMed using the terms ‘dry eye’ and ‘questionnaire’ and we limited the language to ‘English’ and the use as ‘human’. We also reviewed existing data regarding validation and utility of each questionnaire. In the present report, we discuss seventeen questionnaires. The first twelve questionnaires have been validated using various methods, while the last five questionnaires have not yet been validated.

The twelve validated questionnaires are reviewed below and are summarized in Table 6. Appendix 1, available on the TFOS website (www.tearfilm.org), provides additional details of the non-validated questionnaires. The first five questionnaires (OSDI, IDEEL, NEI-VFQ, SANDE, and DEQS) are described in the quality of life section above, and the remainder are described below.

1) Ocular Surface Disease Index (OSDI) [219].
2) Impact of Dry Eye on Everyday Life (IDEEL) [189].
3) National Eye Institute-Visual Function Questionnaire (NEI-VFQ) [220].
4) Symptom Assessment in Dry Eye [214,221,222].
5) Dry Eye–Related Quality-of-Life Score Questionnaire (DEQS) [216].
6) McMonnies Dry Eye History Questionnaire [223,224].
7) Women’s Health Study Questionnaire [53].
8) Dry Eye Questionnaire (DEQ) [225].
9) North Carolina Dry Eye Management Scale (UNC DEMS) [226].
10) Subjective Evaluation of Symptom of Dryness (SESOD) [227].
11) Standard Patient Evaluation of Eye Dryness (SPEED) [228].
12) Dry Eye Epidemiology Project Questionnaire (DEEP) [222].
13) Canada Dry Eye Epidemiology Study (CANDEES) [229].
14) Salisbury eye evaluation [230].
15) Melbourne visual impairment project [52].
16) Bjerrum questionnaire [231].
17) Japanese dry eye awareness study [232].

6.1. McMonnies Dry Eye History Questionnaire

The McMonnies Dry Eye History Questionnaire consists of 12 items, of which most are dichotomous (yes/no) [223]. This questionnaire has been used for dry eye screening in dry eye clinic populations [25,27]. Items include age, sex, contact lens wear, previous diagnosis of dry eye, and triggers (environment, swimming, alcohol). It also assesses the frequency of symptoms dryness, grittiness, soreness, redness, tiredness (never, sometimes, often, constantly), and medications used (arthritis, dry mouth, thyroid status) [224].

6.2. Women’s Health Study (WHS) questionnaire

The WHS questionnaire has been used widely in population based studies of dry eye (Table 1). It consists of the following 3 items:

1) Previous diagnosis of dry eye from clinician? (yes or no).
2) How often eyes feel dry (not wet enough)? (constantly, often, sometimes, or never)
### Table 6
Summary of questionnaires.

<table>
<thead>
<tr>
<th>Number</th>
<th>Instrument Title</th>
<th>Description</th>
<th>Category</th>
<th>Number items</th>
<th>Domains sampled</th>
<th>Recall frequency</th>
<th>Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>McMonnies</td>
<td>Key questions in a dry eye history</td>
<td>Symptoms and risk factors</td>
<td>15</td>
<td>1) Symptoms; 2) Environment; 3) Review of systems</td>
<td>Not specified</td>
<td>Clinical studies</td>
</tr>
<tr>
<td>2</td>
<td>OSDI</td>
<td>The Ocular Surface Disease Index Impact of Dry Eye on Everyday Life</td>
<td>Symptoms and HRQL</td>
<td>12</td>
<td>1) Daily Activities 2) Treatment Satisfaction 3) Symptom Bother</td>
<td>1 week</td>
<td>Clinical studies Epidemiologic and clinical studies</td>
</tr>
<tr>
<td>3</td>
<td>IDEEL</td>
<td>Impact of Dry Eye on Everyday Life</td>
<td>Symptoms and HRQL</td>
<td>57</td>
<td>1) Ocular symptoms 2) History of DED 3) Symptom Bother</td>
<td>2 weeks</td>
<td>Epidemiologic studies</td>
</tr>
<tr>
<td>4</td>
<td>WHS</td>
<td>Women’s health study questionnaire</td>
<td>Symptoms</td>
<td>3</td>
<td>1) Ocular symptoms 2) History of DED</td>
<td>Not specified</td>
<td>Epidemiologic studies</td>
</tr>
<tr>
<td>5</td>
<td>DEQ</td>
<td>Dry Eye Questionnaire</td>
<td>Symptoms and bothersomeness</td>
<td>21</td>
<td>1) Prevalence 2) frequency, diurnal severity and intrusiveness</td>
<td>Not specified</td>
<td>Epidemiologic and clinical studies</td>
</tr>
<tr>
<td>6</td>
<td>UNC DEMS</td>
<td>North Carolina Dry Eye Management Scale</td>
<td>HRQL</td>
<td>1</td>
<td>Symptom bothersomeness</td>
<td>1 week</td>
<td>Clinical studies</td>
</tr>
<tr>
<td>7</td>
<td>SPEED</td>
<td>Standard Patient Evaluation of Eye Dryness</td>
<td>Symptoms</td>
<td>4</td>
<td>Symptoms (type, frequency, severity)</td>
<td>3 months</td>
<td>Epidemiological studies, clinical practice</td>
</tr>
<tr>
<td>8</td>
<td>SESoD</td>
<td>Subjective Evaluation of Symptom of Dryness</td>
<td>Symptoms</td>
<td>3</td>
<td>Symptoms</td>
<td>Not specified</td>
<td>Clinical practice</td>
</tr>
<tr>
<td>9</td>
<td>DEQS</td>
<td>Dry Eye-Related Quality-of-Life Score Questionnaire</td>
<td>Symptoms and HRQL</td>
<td>15</td>
<td>Symptoms (frequency and severity)</td>
<td>1 week</td>
<td>Clinical practice</td>
</tr>
<tr>
<td>10</td>
<td>SANDE</td>
<td>Symptom Assessment in Dry Eye</td>
<td>Symptoms</td>
<td>2 (visual analog scale)</td>
<td>Symptoms (frequency and severity)</td>
<td>Not specified</td>
<td>Clinical practice</td>
</tr>
<tr>
<td>11</td>
<td>DEEP</td>
<td>Dry Eye Epidemiology Projects</td>
<td>Symptoms</td>
<td>19</td>
<td>Symptoms (frequency)</td>
<td>Not specified</td>
<td>Screening</td>
</tr>
<tr>
<td>12</td>
<td>NEI-VFQ</td>
<td>National Eye Institute Visual Function Questionnaire</td>
<td>Visual functioning; HRQL</td>
<td>25</td>
<td>Symptoms (frequency and severity), impact</td>
<td>Not specified</td>
<td>Clinical research(^a)</td>
</tr>
<tr>
<td>13</td>
<td>CANDEES</td>
<td>Canadian Dry Eye Epidemiology Study Questionnaire</td>
<td>Symptoms</td>
<td>13</td>
<td>Symptoms severity, risk factors</td>
<td>Not specified</td>
<td>Prevalence study</td>
</tr>
<tr>
<td>14</td>
<td>SEE</td>
<td>Salisbury Eye Evaluation</td>
<td>Symptoms</td>
<td>6</td>
<td>Symptoms (frequency)</td>
<td>Not specified</td>
<td>Prevalence study</td>
</tr>
<tr>
<td>15</td>
<td>Melbourne VIP</td>
<td>Melbourne Visual Impairment Project questionnaire</td>
<td>Symptoms</td>
<td>6</td>
<td>Symptoms (severity)</td>
<td>Not specified</td>
<td>Epidemiologic studies</td>
</tr>
<tr>
<td>16</td>
<td>Bjerrum</td>
<td>Japanese dry eye awareness study</td>
<td>Symptoms</td>
<td>14</td>
<td>Symptoms</td>
<td>Not specified</td>
<td>Clinical practice</td>
</tr>
<tr>
<td>17</td>
<td></td>
<td></td>
<td>Symptoms</td>
<td>30</td>
<td>Symptoms</td>
<td>Not specified</td>
<td>Prevalence study; clinical practice (self-diagnosis)</td>
</tr>
</tbody>
</table>

HRQL – Health related quality of life.

\(^a\) Useful for group-level comparisons of vision-targeted, health-related QOL.
3) How often eyes feel irritated? (constantly, often, sometimes, or never)

An individual is considered positive for dry eye with reported rates of disease based on symptoms of dryness and irritation at least often and/or a physician’s diagnosis of dry eye, as reported by the participant. The WHS has been reported to have similar sensitivity and specificity as a 16 item instrument [233], comprising symptoms including: sandy or gritty, burning or stinging pain, itching, light sensitivity, blurry vision, tiredness, soreness, scratchiness, redness, stickiness, achy feeling watery eyes and swollen eyelids. In addition, it has been validated against a standardized clinical exam [53].

6.3. Dry eye questionnaire (DEQ)

The DEQ has 21 items and includes questions about contact lens wear, age, and sex. It includes categorical scales of prevalence, frequency, diurnal severity and intrusiveness of symptoms in a typical day over a one-week recall period. It also assesses the frequency (never, infrequent, frequent, constantly) and intensity (from 0; none to 5; very intense) of the following symptoms of comfort, frequency, diurnal severity and intrusiveness of symptoms in a typical day over a one-week recall period. It also assesses the frequency when compared with the DEQ, McMonnies questionnaire, OSDI and SESoD questionnaires [236].

6.4. North Carolina Dry Eye Management Scale (UNC DEMS)

The UNC DEMS has 1 item, which asks about the severity of dry eye symptoms (pain, burning, tearing, grittiness, feeling like something is in your eye, and sensitivity to light), and how symptoms affect daily life. The answer uses a 10-point scale over a one week of recall period. It has been validated using dry eye patients and non-dry eye patients, and appears to be highly correlated with the longer OSDI [226].

6.5. Subjective Evaluation of Symptom of Dryness (SESoD)

The SESoD consists of a three-item questionnaire to evaluate a patient’s perception of ocular discomfort related to dryness for the purpose of clinical practice. Key questions are frequency of symptoms [31], the presence of discomfort [32], and interference with activity. The SESoD assesses dry eye using a 5-point scale where 0 = no dryness to 4 = severe dryness. This questionnaire has been validated against the SPEED, OSDI, DEQ, and McMonnies Dry Eye History questionnaires [227].


The SPEED questionnaire is a four-question survey to assess the frequency and severity of patient dry eye symptoms. Specifically, it monitors diurnal and longer-term symptom changes over the course of three months. The SPEED questionnaire has been shown to exhibit good validity, unidimensionality, objectivity and consistency when compared with the DEQ, McMonnies questionnaire, OSDI and SESoD questionnaires [236].
ascertainment or determination of severity were reviewed. Future questionnaire design and development should focus on defining normative data and ensuring sufficient sensitivity to clinically significant changes in both the natural history of disease and in response to treatment, plus determining recommendations for patients for self-monitoring and in communicating with practitioners. Improved public and practitioner awareness will result in both eye and general health improvement.

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Appendix I. Questionnaires not yet validated

Canada Dry Eye Epidemiology Study (CANDEES)

CANDEES is a 13-item questionnaire. The assessment of frequency and intensity of symptoms are combined, with patients asked to rate each using the following categories: occasional and mild, occasional and moderate, constant and mild, constant and moderate, and severe. This questionnaire also evaluates medications, time of day, allergies, dry mouth, and itchy/swollen/red eyelids [229].

Salisbury eye evaluation

The Salisbury eye evaluation is a standardized 6-item questionnaire that assesses the frequency of symptoms and 3 signs (Answers: Rarely, Sometimes, Often, All of the time). This questionnaire has been used for a self-reported population-based prevalence survey in the elderly for clinical and subjective evidence of dry eye [230].

Melbourne visual impairment project

The questionnaire used in the Melbourne visual impairment project assesses self-reported dry eye symptoms elicited by an interviewer-administered questionnaire [52].

Bjerrum questionnaire

The Bjerrum questionnaire is a three-part questionnaire, which includes an ocular part with fourteen questions. It has been used to evaluate QOL due to Sjögren syndrome dry eye, diagnosis of dry eye, and the epidemiology of Sjögren syndrome [231].

Japanese dry eye awareness study

This questionnaire consists of thirty questions relating to symptoms and knowledge of dry eye. It has been used for a population-based, self-diagnosis study to assess public awareness and symptoms of dry eye [232].

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jtos.2017.05.003.

References


