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TFOS Lifestyle: Impact of lifestyle challenges on the ocular surface

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ABSTRACT

Many factors in the domains of mental, physical, and social health have been associated with various ocular surface diseases, with most of the focus centered on aspects of dry eye disease (DED). Regarding mental health factors, several cross-sectional studies have noted associations between depression and anxiety, and medications used to treat these disorders, and DED symptoms. Sleep disorders (both involving quality and quantity of sleep) have also been associated with DED symptoms. Under the domain of physical health, several factors have been linked to meibomian gland abnormalities, including obesity and face mask wear. Cross-sectional studies have also linked chronic pain conditions, specifically migraine, chronic pain syndrome and fibromyalgia, to DED, principally focusing on DED symptoms. A systematic review and meta-analysis reviewed available data and concluded that various chronic pain conditions increased the risk of DED (variably defined), with odds ratios ranging from 1.60 to 2.16. However, heterogeneity was noted, highlighting the need for additional studies examining the impact of chronic pain on DED signs and subtype (evaporative versus aqueous deficient). With respect to societal factors, tobacco use has been most closely linked to tear instability, cocaine to decreased corneal sensitivity, and alcohol to tear film disturbances and DED symptoms.

1. Introduction to lifestyle challenges

1.1. What is lifestyle? What are the challenges?

Lifestyle is defined as the way in which a person lives. Challenge can be understood as a call for demand, provocation or threat. Many changes in lifestyle in the last decades have improved quality of life and have allowed for improvements in general health and lifespan of the population around the globe. However, some lifestyle changes have been postulated to challenge the ocular surface and contribute to the increased frequency and severity of dry eye disease (DED) and other ocular surface diseases. The examination of this postulate is the purpose

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of the present work (Fig. 1), as part of the Tear Film & Ocular Surface Society (TFOS) Workshop, *A Lifestyle Epidemic: Ocular Surface Disease* which set out to establish the direct and indirect impacts that everyday lifestyle choices and challenges have on ocular surface health. The topics considered under the category of 'lifestyle challenges' include behavioral and environmental variables that often accompany the "modern lifestyle". These include variables in the domains of mental, physical, social health, as discussed in more detail below. The use of "lifestyle" in this report is intended to reflect the way we live in contemporary society and does not imply that individuals are choosing to jeopardize their ocular health through deliberate lifestyle choices.

1.2. An introduction to ocular surface disease and DED

For the purpose of this Workshop, the 'Ocular Surface' is defined as the cornea, limbus, conjunctiva, eyelids and eyelashes, lacrimal apparatus and tear film, along with their associated glands and muscular, vascular, lymphatic and neural support. 'Ocular Surface Disease' includes established diseases affecting any of the listed structures, as well as etiologically related perturbations and responses associated with these diseases.

Ocular surface disease, including DED, is frequently present in daily clinical practice and several studies have indicated that the prevalence of DED is growing in the population [1,2]. In order to interpret relationships between lifestyle challenges and the broad term "dry eye disease", it is important to consider the multifaceted nature of the condition.

DED is "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles [3]." Given the complexity within the definition, it becomes apparent that DED is in fact not a single entity , but a term describing a variety of manifestations (symptoms and signs) that can be driven by multiple contributors. Symptoms placed under the purview of DED include ocular surface discomfort/pain (often characterized as symptoms such as dryness, burning and aching) and visual complaints. Signs can include aqueous tear deficiency, tear film instability, epithelial disruption, ocular surface inflammation, and meibomian gland abnormalities. These symptoms and signs can occur in isolation or in association with a systemic disease, such as immune conditions (for example, Sjögren syndrome, graft-versus-host disease), disorders of the periocular skin (for example, rosacea, seborrheic dermatitis), chronic pain syndrome (for example, fibromyalgia, migraine), and diabetes mellitus. Importantly, manifestations vary based on comorbid conditions, with aqueous tear deficiency more common in individuals with systemic immune disorders and symptoms disproportionate to clinical signs more common in individuals with migraine [4]. In addition, other disorders that are relevant to DED are anatomical abnormalities of the eyelid and conjunctiva, which may induce or potentiate tear film abnormalities. This complexity needs to be considered when examining how different lifestyle challenges impact different aspects of DED (including symptoms and abnormalities of the eyelids, meibomian glands, tear film, and ocular surface). In this report, when possible, we break down DED into its various components and examine how facets of DED relate to the various lifestyle challenges examined.

It is important to note that other ocular surface diseases, outside the purview of DED, including allergic conjunctivitis and pterygium, have also been studied with respect to the modern lifestyle. As such, this report includes data on relationships between all ocular surface diseases and lifestyle challenges, but the predominance of the data centers around DED.

1.3. Measures used to characterize DED

1.3.1. DED symptoms

Given the heterogenous nature of DED, questionnaires have been developed to assess various aspects of patient-related symptoms such as the Ocular Surface Disease Index (OSDI, range 0–100, a higher score indicates more severe ocular symptoms), which examines pain, vision, triggers, and quality of life [5] and the 5-item Dry Eye Questionnaire (DEQ-5, range 0–22, a higher score indicates more severe ocular symptoms), which examines dryness, discomfort, and tearing [6]. Other questionnaires have specifically focused on ocular pain, such as the Numerical Rating Scale (pain only, rated on Likert scale 0–10) [7], the Neuropathic Pain Symptom Inventory modified for Eye (range 0–100, a higher score indicates more severe symptoms), which examines five dimensions of neuropathic pain complaints [8], and the Ocular Pain Assessment Survey (range 0–200), which is designed to measure ocular pain intensity in patients with eye pain of any origin [9]. In this report, we include studies that examined a wide range of DED symptoms in relationship to lifestyle challenges. However, we exclude studies that specifically focused on neuropathic ocular pain given that this entity is outside the scope of ocular surface diseases.

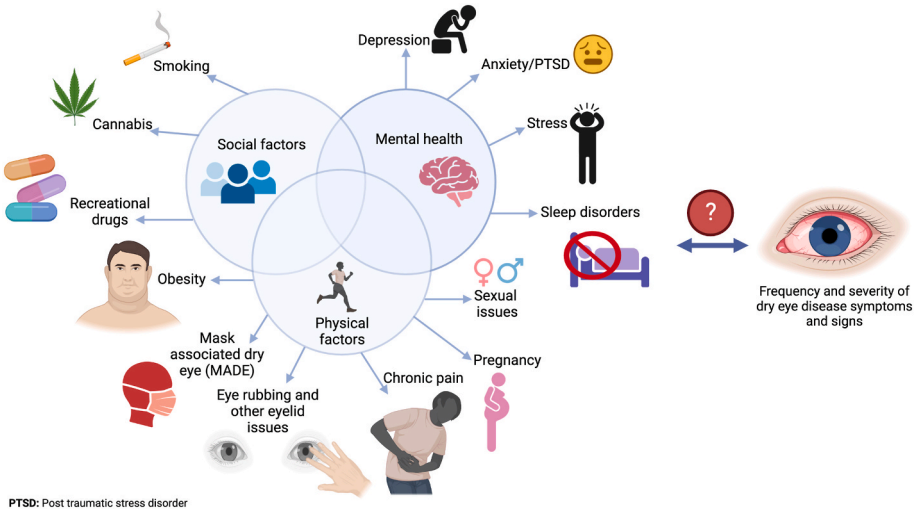

Fig. 1. Multiple daily life decisions associated with lifestyle can induce or modulate the severity of symptoms and signs of dry eye disease and other ocular surface diseases.

1.3.2. DED signs

Several tests are used to examine various aspects of ocular surface health; tests used to diagnose, monitor, and classify DED are described in the TFOS DEWS II Diagnostic Methodology report [10]. Point-of-care tests can measure tear osmolarity (for example, TearLab, San Diego, CA) and assess ocular surface inflammation (InflammaDry, a test that can indicate raised tear matrix metalloproteinase-9 levels, Quidel, San Diego, CA). Using slit lamp biomicroscopy, tear film stability can be assessed by quantifying tear breakup time and corneal and conjunctival epithelial disruption with the use of vital dyes. Tear volume can be assessed by observing the tear meniscus height and tear production by evaluating results of the Schirmer test. Anatomic abnormalities of the eyelids and eyelashes (such as anterior blepharitis, meibomian gland atrophy, meibum quality), conjunctiva (such as conjuctivochalasis, pterygium, papillary changes), and cornea (such as epithelial basement membrane dystrophy) can also be noted. Two tests that can be used to assess somatosensory function are corneal sensitivity testing (for example, qualitatively assessed with a cotton tip applicator or dental floss and rated as 0 = none; 1 = reduced; 2 = normal; 3 = increased or using a Cochet-Bonnet or non-contact corneal esthesiometer) and the anesthetic challenge (assessment of ocular pain after topical anesthetic instillation; non-resolution of pain suggests a central or non-ocular cause of pain) [11].

1.3.3. Relationships between DED signs, corneal nerves, and DED symptoms

One reality in DED is that its symptoms (e.g., ocular surface pain described as “dryness”, “burning”, “aching”, and/or “tenderness” often do not align with signs of disease (e.g., tear production, stability) [12,13]. DED symptoms can be out of proportion to DED signs, as is often the case in individuals with co-morbid migraine and fibromylagia, or DED signs may be out of proportion to DED symptoms, as is often the case in individuals with co-morbid diabetes mellitus. One explanation for the discordance is that corneal nerves transmit information on ocular surface status (with concomitant pain symptoms with their activation) and corneal nerve status is not equal across individuals [14]. Patients with reduced corneal sensation often present with neurotrophic keratitis, with corneal staining noted on examination. Patients with increased corneal sensation often present with features of neuropathic pain, and often complain of burning pain and evoked pain to wind and light [7,15]. Abnormal nerve status can exist in isolation or can co-exist with all DED sub-types (e.g., aqueous tear deficiency and evaporative DED). In this review, we focus on DED symptoms and signs as they relate to lifestyle challenges but do not discuss neuropathic ocular pain as it is outside the scope of this work.

1.4. Overview of review

In this report, we review literature that examines associations between various lifestyle challenges and various aspects of DED and other ocular surface diseases. We split the report into 3 main sections: mental health (depression, anxiety, coping, stress, sleep), physical factors (inactivity, obesity, eye rubbing, sexual issues, pregnancy, chronic pain, and physical interventions), and social factors (tobacco, cannabis, other recreational drugs). Within each section, we focus on epidemiological studies, but also include mechanistic studies, as available. Under the physical factors section, we take a more in-depth look at the connection between DED and pain outside the eye with a systematic review and meta-analysis examining associations between chronic primary pain disorders and DED (section 4.6.6) [16].

2. Methods

The goal of this review is to summarize knowledge on associations and mechanisms that link various lifestyle challenges to various aspects of DED and other ocular surface diseases. Articles for this review were collected from the National Library of Medicine MEDLINE database and Google Scholar using a non-systematic literature search strategy. Authors examined retrieved articles and selected literature most relevant to the review. As our goal was not to exhaustively cover all articles, where multiple studies were available on the same topic, the goal was to focus on those with the most robust methodology. All published scientific articles were considered, including original research, meta-analyses, and systematic reviews. All searches were limited to the English language.

Keywords used to search articles included a mix of the following: “dry eye”, “dry eye disease”, “ocular surface”, “ocular surface disease”, “meibomian gland dysfunction”, “aqueous tear deficiency”, “keratoconjunctivitis sicca”, “Sjögren’s”, “graft versus host disease, “tears”, “cornea”, “conjunctiva”, “pterygium”, “keratoconus”, “ocular allergy”, and “floppy eyelid syndrome” combined with terms such as “depression”, “anxiety”, “post-traumatic stress disorder”, “stress”, “coping”, “sleep”, “insomnia”, “obesity”, “inactivity”, “eye rubbing”, “mask wear”, “pain”, “chronic fatigue syndrome”, “fibromyalgia”, “sexual issues”, “pregnancy”, “smoking”, “smoke”, “tobacco”, “caffeine”, “cannabis”, “cannabinoids”, “marijuana”, “cocaine”, “opioids”, “hallucinogens”, and “alcohol”.

As for the other *TFOS Lifestyle Workshop* reports, the Evidence Quality Subcommittee provided a comprehensive database of appraised systematic review (Level 1) evidence that had been judged to be of potential relevance to the report; this database was considered when writing the narrative review. Wherever possible, the report authors sought to refer to outcomes from high quality systematic reviews, and the reliability of cited systematic reviews was factored into their description in the narrative review.

In addition, a systematic review was undertaken as part of this report, to evaluate the association between chronic pain conditions and DED by following a prespecified protocol (CRD42021296994). The systematic review methodology broadly aligned with that applied in the other systematic reviews performed as part of the *TFOS Lifestyle Workshop* [16] and results are reported in Section 4.6.6.

3. Mental health

3.1. Depression

3.1.1. What is depression?

Depression is a chronic mood disorder that causes a constant feeling of sadness and loss of interest. Depressive patients often present with physical symptoms, such as loss of energy, insomnia and unexplained pain, gastrointestinal symptoms and headache [17,18]. Patients with somatic problems often seek the help of medical physicians rather than psychiatrists [19], and, as such, the diagnosis of depression is often missed, with subsequent improper treatment.

3.1.2. Clinical assessment tools

There are many clinical assessment tools for quantifying depressive symptoms. Some of the instruments used to examine associations between depression and DED include Beck Depression Inventory [20], the Patient Health Questionnaire-9 [21,22], and the Symptoms Check List −90 (SCL-90). The Patient Health Questionnaire-9 is a self-administered questionnaire that consists of nine questions based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for depressive disorders. It is used to diagnose depression and also to quantify and monitor depression severity. It has been validated in many settings including primary health care clinics [23]. The Symptom Checklist-90 is a psychopathological scale applied in psychiatric and medical outpatient settings. In its entirety, it comprises 90 items representing various symptoms, and each item has five answer choices relating to severity (1–5 scale). The diseases under evaluation include somatization, obsessive-compulsive disease, interpersonal sensibility, depression, anxiety, hostility, phobic anxiety, paranoid thoughts, psychotic and additional symptoms [24–26].

3.1.3. Depression and DED

3.1.3.1. Depression and ocular surface symptoms. Depression is a common finding in individuals with eye diseases. In a 2017 study that examined the prevalence of depression or depressive symptoms across 28 studies (10 in the United States (US), 8 in Asia, and 7 in Europe), the overall pooled prevalence of depression in people with eye diseases was 25% (1502/6589 individuals, 95% confidence interval (CI) 0.20–0.30). Across different eye diseases, depression prevalence was found to be highest in DED (29%, 95% CI 0.17–0.40; diagnosed variably across five studies), followed by glaucoma (25%, 95% CI 0.18–0.32), age-related macular degeneration (24%, 95% CI 0.18–0.30), and cataracts (23%, 95% CI 0.07–0.40) [27]. A meta-analysis published in 2021 found a depression prevalence of 40% (95% CI 0.29–0.52) in DED patients, which was 1.81 times higher odds than controls (95% CI: odds ratio (OR) 1.61–2.02; DED was variably defined across the 31 studies). Depression scores were also higher in patients with DED than in controls, and DED symptom scores were associated with depression severity in several studies [28].

A number of studies have examined the associations between depression and DED using large databases. In a case-control study of US veterans (2,454,458 patient records examined) a DED diagnosis (based on International Classification of Disease (ICD) edition 9 code) was present in 462,641 individuals and absent in 1,991,817 individuals. After adjusting for age and sex, both depression (OR 1.92, 95% CI 1.91–1.94) and post-traumatic disorder (OR 1.92, 95% CI 1.91–1.94) remained associated with a DED diagnosis. Overall, 22% of the population carried a diagnosis of depression, with a higher frequency in those with than without a DED diagnosis (24% versus 18%) [29]. Another population-based study in North Carolina, which was not included in the meta-analyses above, also found a significant association between depression and DED (OR 2.9, 95% CI 2.7–3.1) [30]. In this study, from 460,611 records examined, 7207 had DED and 30,100 had depression based on ICD-9 codes.

Corroborating the findings from US-based studies, a large population-based study in the Netherlands involving 79,866 participants, which was also not included in the meta-analyses above, also found an association between self-reported depression and DED (OR 1.52, 95% CI 1.42–1.62), after correcting for 48 comorbidities, including other psychiatric disorders and demographic factors. The authors also evaluated the association between DED and depression assessed using the validated MINI-interview and found similar ORs to those from self-reported depression diagnoses (OR 1.5, 95% CI 1.4–1.6). Furthermore, there was a significant association between DED and depression even in people who did not take any anti-depressant medications (OR 1.6, 95% CI 1.4-1.8), suggesting that this association was independent of antidepressant medication use [31].

Studies have also evaluated this question by examining DED frequency in individuals with psychiatric disease. In a Taiwanese database study (n = 75,650), 4.84% of individuals with psychiatric disease had a DED diagnosis (n = 3665) [32]. In this population, the prevalence of depression was higher in individuals with than without a DED diagnosis (32.3% versus 23.6%; OR 1.54, 95% CI 1.43–1.65, $p < 0.001$) [32]. Higher estimates for the presence of DED in individuals with psychiatric diseases were obtained when symptoms were prospectively assessed. In 472 individuals who presented for treatment of depressive and/or anxiety disorders in Shanghai, 81% of individuals who were questioned reported at least one DED symptom and 60% exhibited both a DED symptom and sign [33]. After adjusting for age and sex, significant associations were found between DED and longer duration of psychiatric disorders (DED versus no DED: 54 ± 59 versus 39 ± 39 months), longer duration of antianxiety or antidepressant medication use (17 ± 25 versus 10 ± 18 months), and use of selective serotonin reuptake inhibitors [33].

Other studies examined relationships between depression and DED symptoms in non-hospitalized populations. Data from the fifth Korea National Health and Nutrition Examination Survey (16,408 participants) found that individuals who reported a DED diagnosis had a higher prevalence of depression (assessed via interview, OR 1.32; 95% CI 1.11–1.57), compared to those not diagnosed with DED. In a similar manner, the presence of DED symptoms was associated with depression (OR 1.5, 95% CI 1.30–1.73) [34].

Other studies have examined relationships between depression and DED symptom severity. In a Hungarian population, depressive symptoms were evaluated (with the Shortened Beck Depression Inventory) in individuals with a) DED symptoms alone, b) DED symptoms and signs, and c) no DED symptoms (without or without signs). Shortened Beck Depression Inventory scores were higher (more abnormal) in symptomatic versus asymptomatic individuals, with a correlation coefficient (r) of 0.31 ($p < 0.01$) between Ocular Surface Disease Index and shortened Beck Depression Inventory scores [35]. In particular, some studies have found that specific DED symptoms are associated with depressive symptoms. In a Singaporean study of 96 adults visiting an ophthalmology clinic, depression scores (Center for Epidemiologic Studies Depression Scale) were significantly associated with visual blurring, but not irritation, in individuals with a low tear breakup time [36]. However, findings have not been uniform across studies. In a Shanghai population, burning was the symptom most frequently reported by individuals with generalized anxiety disorder compared to other psychiatric disorders [33]. It is possible that DED symptoms vary by the type of psychiatric disorder.

3.1.3.2. Depression and ocular surface signs. Studies have examined associations between depression and ocular surface signs in non-hospitalized populations. In one study, 657 Korean elders (≥65 years) were randomly selected from an official household registration database in Yongin, Korea and profiled for depressive symptoms and DED symptoms and signs. Overall, DED symptoms, but not signs, were associated with depression (assessed via the Geriatric Depression Scale—Short Form). In fact, the correlation between depression and DED symptoms was stronger in individuals with normal versus abnormal tear production (Schirmer>5 mm: OR 3.08; 95% CI 1.93–4.93; $p < 0.001$; Schirmer<5 mm: OR 1.52; 95% CI 0.70–3.30; $p = 0.29$) [37]. These results reinforce the idea that the connection between DED symptoms and depression does not seem to be driven by DED signs. Another population-based study conducted in Beijing (n = 1957) had the same conclusion, noting that depression score (via the Chinese depression scale adapted from the Zung self-rated depression scale) was weakly, but significantly, correlated with DED symptoms ($r = 0.07$; $p = 0.01$), but not with DED signs, including tear breakup time ($p = 0.18$), Schirmer test score ($p = 0.37$), corneal staining ($p = 0.30$) and meibomian gland dysfunction ($p = 0.93$) [38]. A study from the Netherlands further supported these findings as, in a study of 648 individuals with DED, the presence of depression was a risk factor for having a disconnect between DED symptoms and signs, with symptoms outweighing signs [13]. However, some studies did not find relationships between depression severity and either DED symptoms or signs. A German study reported that while the mean Beck Depression Inventory score (11.95 ± 8.46) was significantly higher in individuals with DED (variably defined) versus controls ($p < 0.0001$), depression severity (via the Beck Depression Inventory) was not correlated with severity of symptoms (via Ocular Surface Disease Index) or signs (tear breakup time, Schirmer, epithelial staining) [39]. Overall, depressive symptoms have been associated with DED symptoms in several studies covering diverse populations.

However, a few studies did report differences in tear parameters that related to depression status. In a Turkish study of individuals with newly diagnosed depression (n = 40) or anxiety (n = 35), compared to 37 controls, both the depression and anxiety study groups had lower Schirmer test scores (7.24 ± 6.02, 6.58 ± 4.9 and 18.79 ± 4.9 mm

wetting respectively, $p < 0.05$), lower tear breakup time (5.6 ± 3.5, 5.62 ± 3.1,13.37 ± 1.7 s respectively, $p < 0.05$) and higher corneal staining scores (Oxford scale: 1.9 ± 0.7, 2.1 ± 0.6 and 0.7 ± 0.4, respectively, $p < 0.001$) compared to controls [40]. The ocular surface was also imaged with anterior segment optical coherence tomography (AS-OCT). Similar to observations at the slit lamp, tear parameters on AS-OCT (tear meniscus height, tear meniscus depth and tear meniscus area) were more abnormal in individuals with depression and anxiety compared to controls ($p < 0.05$) [40]. Similar findings were noted in another Turkish study of 36 individuals with newly diagnosed depression compared to 32 controls, where Schirmer test, tear breakup time, and Oxford staining scores were more abnormal in individuals with depression [41]. Finally, a population-based study of 312 participants living in New Zealand reported that improved self-perceived health status was significantly associated with decreased odds of aqueous tear deficiency and meibomian gland dysfunction [42].

Overall, while several studies have reported a significant relationship between depression and DED symptoms, some hospital and population-based studies have also found that individuals with depression display more abnormal DED signs than those without depression, although mean values were often within the normal range in both groups.

3.1.3.3. Depression and tear biomarkers. Several pro-inflammatory cytokines have been found to be elevated in the tear fluid of individuals with depression. For example, increased levels of tear pro-inflammatory cytokines (interleukin-6, interleukin-17 and tumor necrosis factor-α) (all $p < 0.001$) were noted in 32 individuals with depression (treated with antidepressants) as compared to 34 controls [43]. However, this finding was not replicated in a larger multicenter study ($n = 535$) where levels of a number of inflammatory markers did not differ by depression status [44]. In another study, tear levels of matrix metalloproteinase 9 (MMP-9), a protease involved in degradation of the extracellular matrix and leukocyte migration, was significantly increased in patients with depression ($n = 10$) compared to controls ($n = 21$) [45].

Other researchers have focused on examining tear biomarkers collected longitudinally during the treatment of stress. Specifically, 23 stressed participants (21–53 years old) underwent relaxation response training and levels of cortisol, nerve growth factor and brain-derived neurotrophic factor were quantified over time in saliva and tears. Brain-derived neurotrophic factor levels were found to be significantly elevated and nerve growth factor levels non-significantly decreased in tears after the last training session relative to before training [46].

3.1.4. Mechanisms

Many animal models of depression exist, but the link between depression and DED has not been robustly investigated in animal models and may be an important direction for future research. Well-established models of depression in animals include reserpine-induced depression (which depletes catecholamines in blood) [47], the learned helpless model, the chronic mild stress model, and the social defeat stress model [48]. Brain-derived neurotrophic factor has been examined with respect to tear secretion as brain-derived neurotrophic factor knockdown mice exhibit decreased tear secretion compared to controls, providing another clue that brain-derived neurotrophic factor may be a mechanistic link between depression and symptoms associated with DED [49].

3.1.5. Depression and anti-depression medication

Whether depression, antidepressant medications, or both contribute to the link between depression and aspects of DED, is unknown [50]. A number of studies, compiled in the report of the TFOS Dry Eye Workshop (DEWS) published in 2007, reported an association between antidepressants and DED [51]. Selective serotonin reuptake inhibitors are a commonly prescribed medication for depression. Their mechanism of action is to inhibit serotonin transport and increase extracellular 5-HT levels.

Comparing ocular surface changes in individuals on selective serotonin reuptake inhibitor, one study examined 36 individuals with treated depression or anxiety whose symptoms were in remission and 36 controls. Tear breakup time (7.05 ± 4.86 versus 12.53 ± 4.75 s, $p < 0.001$) and Oxford staining score (0.78 ± 0.76 versus 0.11 ± 0.32, $p < 0.001$) were more abnormal in individuals on a selective serotonin reuptake inhibitor compared to controls. However, the clinical significance of these findings is unclear as values were within normal range in both groups. Interestingly, DED symptoms (assessed via the Ocular Surface Disease Index) significantly differed between the groups, with higher symptom scores in individuals with treated depression and anxiety (32.07 ± 19.08 versus 16.31 ± 14.28, $p < 0.001$) compared to controls [52].

Tear production has also been examined in individuals on selective serotonin reuptake inhibitors as compared to controls. In 54 patients newly on an antidepressant and 57 controls, individuals on an antidepressant had lower mean Schirmer test scores compared to controls (10.4 ± 5.8 versus 12.3 ± 0.7 mm wetting), again with overall normal means in both groups. However, more individuals on the selective serotonin reuptake inhibitor had a Schirmer score<5 mm wetting as compared to individuals on an serotonin-norepinephrine reuptake inhibitor (35% versus 18.8%), suggesting that selective serotonin reuptake inhibitors may have a greater effect on tear production than serotonin-norepinephrine reuptake inhibitors [50].

The effect of selective serotonin reuptake inhibitor treatment on serotonin levels in tears has also been examined. In one study, 20 individuals on a selective serotonin reuptake inhibitor had higher serotonin levels detected in tears and more serious inflammation and cell apoptosis detected on the ocular surface compared to 20 controls (on placebo) [53]. This question was concomitantly examined in a rat model of depression. After treatment with a selective serotonin reuptake inhibitor (paroxetine) for 6 weeks, tear serotonin levels increased, as did ocular surface expression of inflammatory cytokines (tumor necrosis factor-α, interleukin-1b, and interleukin-10) and cell apoptosis genes [53]. Despite these possible mechanistic explanations, no relationship was identified between DED and antidepressant medication use in a human study where symptoms and signs were assessed in one eye of each individual [44].

Contrary to these findings, a large population-based study in the Netherlands ($n = 79{,}606$) found no association between DED symptoms and any of the major antidepressive medication classes after adjusting for more than 50 comorbidities and demographic factors [54]. This study, using a hypothesis-free approach, investigated the association between DED and the most commonly prescribed medication classes. In patients with a diagnosis of depression, the use of selective serotonin reuptake inhibitors was found to be associated with a decreased risk of DED (OR 0.87, 95% CI 0.77–0.98). Based on these findings, the authors concluded that the positive effects of antidepressants on the depression itself potentially outweighs the risk on DED of potential anticholinergic side-effects, and emphasized the importance of correcting for underlying disorders in future studies investigating this relationship.

3.1.6. Treatment implications

There are no standard guidelines regarding how to best treat depression in individuals with DED symptoms and signs, or how best to treat DED in individuals with depression. However, longitudinal examination of both DED symptoms/signs and depressive symptoms (assessed via the Mental Component Summary of the 36-Item Short Form Health Survey) was undertaken in the secondary data analysis of a randomized controlled trial. In this study, while DED symptoms and signs improved over time in the omega 3 and placebo treatment groups, depressive symptoms remained unchanged, suggesting that in at least one study with its own limitations, improving DED symptoms and signs did not directly translate to improved depression scores [44]. A qualitative study using semi-structured face-to-face interviews explored the main causes of anxiety and depression in 47 individuals with DED

recruited from a University hospital in China. Three main causes were identified: hospital, daily life, and social-related factors. The investigators concluded that psychological interventions to address these causes are needed when treating DED patients with anxiety and depression [55].

3.1.7. Future directions and gaps

In summary, several studies have linked depression to DED in different populations and using various study methods. Most reports found a stronger association with DED symptoms rather than with signs. The mechanisms underlying the noted associations are unclear, and there is a lack of guidelines on how best to approach the combined therapy of DED and depression. More studies are needed to understand the mechanistic links between depression and DED, the contribution of antidepressant medications (with a clear time course), the DED phenotypes that most closely relate to depression, confounders (such as pain or sleep) that may contribute to the association, as well as optimal treatment approaches.

3.2. Anxiety and post-traumatic stress disorder

3.2.1. What is anxiety and post-traumatic stress disorder?

Anxiety is an emotional state characterized by feelings of tension, intrusive or worried thoughts, and in some cases physical changes (tachycardia, hypertension). While anxiety is experienced fairly ubiquitously at some level, it can also exist in a more debilitating and chronic form as an anxiety spectrum disorder (including generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, social anxiety disorder, and specific phobias) [56]. As many as 33.7% of the population may be affected by an anxiety spectrum disorder during their lifetime, making these conditions a significant source of morbidity in the population [56,57]. Post-traumatic stress disorder, which occurs after experiencing a traumatic situation (such as a natural disaster, serious accident, violence, amongst others) leading to intense intrusive thoughts related to that experience that can last long after its resolution, is one such condition that has been linked to DED frequency and severity [58]. Uncontrolled anxiety has been implicated in worsening and refractory symptoms in systemic and ocular chronic pain disorders [29,30,59–61]. Assessing for the existence of an underlying anxiety disorder, and for an individual's ability to cope with anxiety, are important when examining patients with DED [62,63].

3.2.2. Clinical assessment tools

Anxiety and its spectrum disorders are routinely assessed in the clinical setting via symptom assessments and questionnaires. The Symptom Checklist-90 can be used to assess psychological distress as a function of nine specific psychological symptom dimensions [somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism; range 1–5, higher score indicates more severe symptoms] [64]. Post-traumatic stress disorder-related symptoms can also be assessed using a number of questionnaires. Specifically, the Post-Traumatic Stress Disorder Checklist: Military Version (17-item, range 17–85, higher score indicates more severe symptoms) has been used to evaluate symptoms of post-traumatic stress disorder in veterans [65]. Use of these and other clinical assessment tools allows providers to diagnose anxiety disorders and monitor change in symptom severity with therapeutic intervention [66].

3.2.3. Anxiety, post-traumatic stress disorder and DED

Anxiety and its related disorders have been related to various aspects of DED (symptoms more than signs) [30,67,68].

3.2.3.1. Anxiety and post-traumatic stress disorder and a DED diagnosis. Several studies have examined the relationship between anxiety and a DED diagnosis using large databases. One study examined this relationship in 16,862 South Florida veterans– of these, 12% had a DED diagnosis (n = 2056). A higher proportion of individuals with DED also had a diagnosis of post-traumatic stress disorder (19% versus 11%), with a post-traumatic stress disorder diagnosis increasing the odds of a DED diagnosis approximately 2-fold (OR 1.97, 95% CI 1.75–2.23). A similar pattern was seen with major depressive disorder (17% versus 10%), with such a diagnosis increasing the odds of a DED diagnosis ~2-fold (OR 1.91, 95% CI 1.73–2.10). When examining post-traumatic stress disorder and major depressive disorder along with other variables, including demographics and concomitant medications, both post-traumatic stress disorder and major depressive disorder remained significantly associated with a DED diagnosis (post-traumatic stress disorder OR 1.40, 95% CI 1.22–1.60, $p < 0.0001$; major depressive disorder OR 1.31, 95% CI 1.14–1.50, $p < 0.0001$) [60]. This question was re-examined in a larger veteran population (n = 2,454,458), encompassing individuals seen in any eye clinic across the US. In this analysis, 18% of veterans had a diagnosis of DED (n = 462,641) and several conditions increased the odds of a DED diagnosis, including post-traumatic stress disorder (OR 1.92, 95% CI 1.91–1.94), depression (OR 1.92, 95% CI 1.91–1.94), antidepressant use (OR 1.97, 95% CI 1.79–2.17), and anxiolytic use (OR 1.74, 95% CI 1.58–1.91). On multivariable regression modeling, all of these variables remained significant predictors of a DED diagnosis, with the use of anxiolytics being the strongest predictor, overall [29]. In addition, in a population-based study in the Netherlands (n = 79,866) self-reported agoraphobia (OR 1.9, 95% CI 1.5–2.4), self-reported panic disorder (OR 1.4 (95% CI 1.3–1.6)), and generalized anxiety disorder assessed by the validated MINI interview (OR 1.6, 95% CI 1.4–1.8), were all associated with DED (assessed by the Women's Health Study questionnaire) indicating that potentially all types of anxiety disorders are associated with DED [31]. Post-traumatic stress disorder is frequently co-morbid with traumatic brain injury, and this relationship was examined in the three conditions (post-traumatic stress disorder, traumatic brain injury, and DED) among 3,265,894 veterans. Overall, individuals with a diagnosis of traumatic brain injury (n = 124,820) were more likely to have a DED diagnosis (37.2% vs. 29.1%, $p < 0.0005$), a post-traumatic stress disorder diagnosis (54.3% versus 22.5%, $p < 0.0005$), and a depression diagnosis (69.0% vs. 42.0%, $p < 0.0005$) compared to individuals without a diagnosis of traumatic brain injury [59]. In summary, large-scale studies have found that a diagnosis of post-traumatic stress disorder increases the odds of having a DED diagnosis, raising the possibility of a potential pathophysiological link between the two disorders. However, these relationships have been noted in veterans and further studies in other populations are needed to examine the generalizability of findings.

3.2.3.2. Anxiety and post-traumatic stress disorder and ocular surface symptoms. Relationships between anxiety/post-traumatic stress disorder and ocular surface symptoms have been examined in hospital-based studies. In a study of 136 South Florida veterans (mean 5-item Dry Eye Questionnaire score of 11 ± 5.2, 87% with a score of ≥6 consistent with mild or greater DED symptoms), positive relationships were noted between DED symptoms (5-item Dry Eye Questionnaire and Ocular Surface Disease Index) and symptoms of anxiety (Post-Traumatic Stress Disorder Checklist: Military Version: $r = 0.45$ and 0.58 respectively, $p < 0.05$) and depression (Patient Health Questionnaire-9: $r = 0.42$ and 0.55 respectively, $p < 0.05$). On multivariable modeling, along with non-ocular pain intensity (assessed with a numeric rating scale), post-traumatic stress disorder symptoms associated with DED symptoms severity (5-item Dry Eye Questionnaire: B = 0.07, SE 0.02, $p < 0.0005$; Ocular Surface Disease Index: B = 0.60 SE 0.10, $p < 0.0005$). Of note, DED signs did not remain in the model that examined their association with DED symptoms [58]. Similar results were noted in 248 South Florida veterans, as individuals with a post-traumatic stress disorder (n = 22) and/or depression (n = 40) diagnosis had higher 5-item Dry Eye

Questionnaire scores (13.4 ± 1.1 and 12.0 ± 0.8, respectively) compared to individuals without these conditions (n = 186; 9.8 ± 0.4; p < 0.01 and p = 0.02, respectively). On multivariable modeling, a post-traumatic stress disorder diagnosis (OR 4.08, p = 0.04) and use of a selective serotonin reuptake inhibitor (OR 2.66, p = 0.05) significantly associated with DED symptom severity (via 5-item Dry Eye Questionnaire). No significant differences in DED signs were found among the three groups [69].

To better understand the relationship between post-traumatic stress disorder and DED symptoms vs. signs, a study of South Florida veterans examined factors associated with DED discordance. In 326 individuals, a DED discordance score was calculated by assigning a normalized ratio that incorporated symptoms (Ocular Surface Disease Index) and six signs (osmolarity, tear breakup time, corneal staining, Schirmer score, eyelid vascularity, meibum quality). The DED discordance score ranged from −1 (representing individuals with severe signs and minimal symptoms) to 1 (representing individuals with severe symptoms and minimal signs). Anxiety (Symptom Checklist-90, r = 0.41, p < 0.005), post-traumatic stress disorder (Post-Traumatic Stress Disorder Checklist: Military Version, r = 0.46, p < 0.0005) and depression (Patient Health Questionnaire-9, r = 0.41, p < 0.0005) scores all positively related to the DED discordance score, suggesting a relationship between more severe anxiety and depression and a DED phenotype where symptoms outweigh signs. On multivariable modeling, post-traumatic stress disorder (Post-Traumatic Stress Disorder Checklist: Military Version; correlation coefficient (B) = 0.21, standard error (SE) 0.02, p = 0.05) and depression (Patient Health Questionnaire-9; B = 0.01, SE = 0.005, p = 0.03) scores remained significantly predictive of discordance, and post-traumatic stress disorder scores remained significantly predictive of DE symptoms (5-item Dry Eye Questionnaire: B = 0.28, SE = 0.19, p < 0.001; Ocular Surface Disease Index: (B = 0.24, SE 1.35, p = 0.02) [70]. In an earlier study in a tertiary dry eye clinic in the Netherlands, including 648 dry eye patients and using similar methodology, depression was also associated with greater symptoms compared to signs [13].

Similar findings have been reported in non-veteran populations. One study examined 233 individuals who were profiled for DED symptoms (5-item Dry Eye Questionnaire) and symptoms suggestive of neuropathic ocular pain (ocular pain that occurs due to somatosensory abnormalities in nerves connecting the ocular surface/periocular regions to the brain), including burning pain and evoked pain to wind and light [7,8]. First, DED symptoms (5-item Dry Eye Questionnaire) correlated with neuropathic ocular pain measures (r = 0.37 for burning, r = 0.37 for sensitivity to wind; r = 0.34 for sensitivity to light, p < 0.001). Second, DED symptom intensity (5-item Dry Eye Questionnaire) correlated with both anxiety (Symptom Checklist-90; r = 0.21, p = 0.001) and depression (Patient Health Questionnaire-9: r = 0.34, p < 0.001) scores [71]. These findings were replicated in a study of South Florida veterans that examined individuals with DED symptoms (5-item Dry Eye Questionnaire≥6) with or without neuropathic ocular pain features (burning, sensitivity to wind and light). Overall, individuals with neuropathic ocular pain features (n = 51) scored higher on post-traumatic stress disorder (Post-Traumatic Stress Disorder Checklist: Military Version: 53 ± 21 vs. 36 ± 17, p < 0.0005) and depression (Patient Health Questionnaire-9: 13.5 ± 8.1 vs. 7.6 ± 7.2, p < 0.0005) questionnaires than individuals with DED symptoms but without a symptoms profile consistent with neuropathic pain [72]. This suggests that specific symptoms associated with DED, specifically burning, and sensitivity to wind and light, are closely linked to post-traumatic stress disorder.

Less information is available on relationships between anxiety and visual quality as a symptom of DED. One Chinese study of 87 individuals with a DED diagnosis assessed patients with the National Eye Institute Visual Function Questionnaire (range 0–100 higher score indicating better function; 12 domains including short distance and long-distance visual quality) as well as for anxiety and depression symptoms (Zung Self Rating Anxiety and Depression Scales, range 20–80, higher score indicates more severe anxiety). Overall, visual function (National Eye Institute Visual Function Questionnaire) negatively correlated with self-rated anxiety and depression scores, indicating that higher anxiety/depression scores was associated with reduced visual function. Both near (r = −0.31 and r = −0.33, p < 0.05 for both) and distance (r = −0.24 and r = −0.27, p < 0.05 for both) visual acuity were negatively correlated with the self-rated anxiety score and self-rated depression score, respectively [73].

Long-term sequelae of anxiety disorders, such as suicidal ideation, have also been examined with respect to DED. In particular, a large-scale Korean study of 15,864 participants found that in men diagnosed with DED, those experiencing DED symptoms reported significantly higher levels of stress (28.7% vs. 24.0%, p = 0.03), depression (9.3% vs. 6.1%, p = 0.003), and suicidal ideation (12.0% vs. 9.0%, p = 0.04) compared to men without symptoms. Near identical patterns were noted in women (stress: 35.7% vs. 28.1%, p < 0.001; depression: 23.2% vs. 17.5%, p < 0.001; suicidal ideation: 22.0% vs. 16.6%, p < 0.001). On regression modeling, a DED diagnosis (OR 1.24, 95% CI 1.05–1.48) and/or DED symptoms (OR 1.47, 95% CI 1.27–1.70) remained associated with suicidal ideation [34].

Overall, studies are generally uniform in reporting a relationship between DED symptoms and anxiety, with more severe symptoms associated with more severe anxiety. Further studies are needed consolidate the reported associations, especially with regard to visual function. It is important to note that many of these associations have been examined in a specific patient population, namely veterans, and more studies are needed to evaluate relationships in other populations.

3.2.3.3. Anxiety and post-traumatic stress disorder and ocular surface signs. Results have been less uniform in examining relationships between anxiety and DED signs, such as tear film stability, tear production, and epithelial cell disruption [74,75]. In the Chinese study of 87 individuals with a DED diagnosis, self-reported anxiety scores were not correlated with ocular surface signs including tear breakup time (right and left eyes: r = 0.09, p = 0.38 and r = 0.01, p = 0.92), Schirmer test score (r = 0.04, p = 0.72 and r = −0.08, p = 0.45), or staining score (r = −0.03, p = 0.77 and r = 0.04, p = 0.70) [73]. In contrast, a Turkish study found significant differences in ocular signs in patients with anxiety relative to those without anxiety. Specifically, when comparing 35 individuals with newly diagnosed anxiety (Beck Anxiety Inventory, range 0–64) and 37 controls without anxiety, Schirmer test results (7.24 ± 6.02 versus 18.79 ± 4.9 mm wetting, p < 0.001) and tear breakup time (5.62 ± 3.1 versus 13.37 ± 1.7 s, p < 0.001) were significantly lower in those with than without anxiety, while staining was significantly higher (Oxford scale: 1.9 ± 0.7 versus 0.7 ± 0.4, p < 0.001) [40].

3.2.4. Mechanisms

Several studies have examined connections between anxiety disorders and DED at a molecular level. A pathophysiology linking anxiety and DED is the common association with inflammation [69]. In particular, patients with post-traumatic stress disorder and depression have been found to have higher serum inflammatory markers including elevated CD4:CD8 ratios, C-reactive protein, intercellular adhesion molecule-1, tumor necrosis factor-α, and pro-inflammatory cytokines such as interleukin-1 and interleukin-6 [69]. Individuals with DED have similarly been shown to have increased inflammatory markers in the tears and conjunctiva, including increased CD4 lymphocytes [76], and several pro-inflammatory cytokines [77,78], akin to those observed in the serum in post-traumatic stress disorder and depression. In a Korean study of 133 individuals with DED (defined by a combination of symptoms, Schirmer test score, tear breakup time, staining), concentrations of tear interleukin-1β, interleukin-16, transforming growth factor-α, fractalkine, macrophage inflammatory protein-1δ, and epithelial neutrophil-activating peptide-78 increased with increasing DED grade, suggesting a positive correlation between tear inflammatory markers and clinical disease severity [78]. Other studies have reported near

identical results in participants with newly diagnosed DED [79] and in patients with DED secondary to Sjögren syndrome [80]. Given these findings, one area of potential future study includes examining whether tear inflammatory profiles vary according to the presence of anxiety/post-traumatic stress disorder.

3.2.5. Treatment implications

No studies have prospectively examined how treatment of uncontrolled anxiety affects DED. One study has, however, examined the reverse relationship – with concomitant anxiety symptoms improving after treatment of DED. In particular, this study examined 45 patients reporting to an ocular clinic for DED symptoms (assessed with the University of North Carolina Dry Eye Management Scale; scale 1–10). Anxiety was quantified with the Generalized Anxiety Disorder 7-item scale (each item scored 0–3; total score 0–21). Patients with moderate-to-severe DED symptoms were treated with an individualized protocol (which included one or more of the following: lubricants, fish oil, lid scrubs, warm compresses, tetracycline derivatives, topical corticosteroids, topical cyclosporine, punctal plugs) for a period of 3–6 months. At baseline, the average Dry Eye Management Scale score was 5.8 ± 1.8 (with 78% scoring ≥5, indicating moderate or greater symptoms) and the average 7-item Generalized Anxiety Disorder scale was 5.6 ± 5.5. On follow-up (mean 13.8 ± 4.9 weeks), significant improvements in both dry eye (to 4.6 ± 2.2, $p = 0.01$) and anxiety (to 3.3 ± 4.6, $p = 0.05$) scores were seen, suggesting a positive relationship between improvement in DED symptoms and improvement in anxiety symptoms after treatment of DED [81]. Interestingly, in a study of individuals with rheumatoid arthritis (a condition often co-morbid with DED), individuals with baseline depression/anxiety symptoms had less improvement in joint symptoms with treatment compared to individuals without symptoms of depression/anxiety at baseline [82]. This suggests that baseline anxiety symptoms may influence treatment response in a range of situations, including treatment of DED. More studies are needed to investigate these relationships.

3.3. Coping & resiliency

3.3.1. What are coping and resiliency?

Coping has been defined as "the cognitive and behavioral efforts used to manage external or internal demands appraised as taxing or exceeding an individual's resources [83]." While definitions of psychological resiliency vary considerably, resiliency may be generally understood as the ability of a person to "resist disturbance caused by sudden changes" and return to a normal state of mental function [84]. Albeit closely linked, deficiencies in coping and resiliency are distinct from anxiety or anxiety-related disorders, however, a person's failure to demonstrate strong mental resilience or utilize positive coping mechanisms in the face of a psychological disturbance have been shown to negatively impact DED [85].

3.3.2. Clinical assessment tools

Like with anxiety, a number of scales have been developed to measure coping and resiliency. Coping can be categorized as healthy/active (reliance on oneself to function despite pain, e.g., task persistence or positive self-statements when in pain) or dysfunctional/passive/maladaptive (allow daily life to be changed by pain and thus leading to a sense of helplessness, e.g., relying on external aid during painful tasks, pain avoidance, and catastrophizing). Coping is commonly examined by assessing for reliance on maladaptive coping strategies, such as catastrophizing (which includes rumination (e.g., "I can't stop thinking about how much it hurts"), magnification (e.g., "I'm afraid something serious might happen"), and helplessness (e.g., "There is nothing I can do to reduce the severity of my pain") [62]. Examples of coping questionnaires include the Coping Strategies Questionnaire (rates severity of 8 maladaptive strategies - diverting attention, reinterpreting pain sensations, coping self-statements, ignoring pain sensations, praying or hoping, catastrophizing, increased behavioral activities, and increasing pain behavior; each scored on 0–7 scale, higher scores indicate more maladaptive coping [86]) and the Pain Catastrophizing Scale (rumination, magnification, and helplessness assessed via 13 items, scale 0–52, higher scores indicate more catastrophizing [87]). Related to this, assessment of daily interference (quality of life loss) can be assessed with the Interference Subscale of the West Haven-Yale Multidimensional Pain Inventory (9 items, scale 0–6 each, higher scores indicate more pain-related activity interference [88]). Resiliency can be assessed with the Connor-Davidson Resilience Scale (25 items, scale 0–4 for each, with higher scores reflecting greater resilience [89]), among others.

3.3.2.1. Coping, resiliency, and DED. Coping has been examined in relationship to DED. In a study of 194 South Florida veterans with a DED diagnosis or DED-related symptoms, the connection between catastrophizing and ocular symptoms was examined. Catastrophizing (Pain Catastrophizing Scale) was positively correlated with DED symptoms (5-item Dry Eye Questionnaire: $r = 0.41$, $p < 0.0005$; Ocular Surface Disease Index, $r = 0.49$, $p < 0.0005$) and pain-specific ocular symptoms (numeric rating scale: $r = 0.48$, $p < 0.0005$; Neuropathic Pain Symptom Inventory-Eye: $r = 0.48$, $p < 0.0005$). Similarly to anxiety, tear parameters were not associated with catastrophizing intensity; signs that were associated with catastrophizing included corneal sensitivity (Belmonte ethesiometry: $r = -0.17$, $p = 0.02$; indicating a higher level of catastrophizing was related to *lower* mechanical threshold or *higher* sensitivity) and ocular surface inflammation (InflammaDry: $r = -0.16$, $p = 0.02$; indicating that higher catastrophizing levels related to less ocular surface inflammation). On multivariate modeling, the Pain Catastrophizing Scale score predicted DE symptom and ocular pain severity, linking catastrophizing to more severe ocular symptoms [62], but not to signs. Outside the eye, studies on low back pain [90], pain after surgical repair of the anterior cruciate ligament [91], and postoperative cardiothoracic pain [92] have reported similar magnitude correlations between the Pain Catastrophizing Scale score and pain severity.

Resiliency was also examined in relationship to DED, specifically in individuals with primary Sjögren syndrome. Resilience was assessed using the 14-item Resilience Scale in 74 women with primary Sjögren syndrome and 74 controls. Individuals with primary Sjögren syndrome had similar levels of resilience (median 78.5) compared to controls. While an inverse relationship was found between resilience and mood disorders such as anxiety ($p = 0.038$) and depression ($p < 0.001$), no significant relationships were noted with regard to disease activity. However, DED metrics specifically were not examined in the study [93].

3.3.3. Mechanisms

Most of the data on the biologic plausibility for a connection between maladaptive coping and resilience and DED symptom severity comes from data on pain conditions outside the eye. Potential shared mechanisms may include alterations in diurnal cortisol levels, elevated pro-inflammatory cytokine levels [94,95], inability of the central nervous system to modulate incoming pain signals leading to heightened pain perception [96], and aberrant activity in brain cortices involved with pain anticipation [97]. In fact, functional magnetic resonance imaging (MRI) studies have suggested that dysfunction in certain brain areas may underlie both DED and psychiatric symptoms [98]. However, studies are lacking that examine potential markers, such as interleukin-6, in various compartments, in individuals with maladaptive vs. healthy coping strategies and resilience, to examine these questions more deeply.

3.3.4. Treatment implications

Given the potential link between DED and mental health, ancillary treatments targeting mood-related dysfunction may be useful in individuals with various DED phenotypes. While no studies have examined this question in patients with DED specifically, studies have shown the value of mental health therapies as adjuvant treatments in other

chronic pain conditions. For instance, a British randomized controlled study separated 598 adults with low-back pain into cognitive behavior therapy (n = 399) and control (n = 199) groups and found that individuals receiving cognitive behavior therapy had greater improvements in pain levels compared to controls at 12 months (Von Korff pain scale, scale 0–100%; mean decrease 13.8% versus 5.4%, $p < 0.0001$) [99]. Other therapies that have also been examined in a similar manner for various chronic pain conditions include acupuncture, exercise, and massage [15,100]. An important area for future investigation is to examine how strategies that target coping mechanisms and resilience will impact various aspects of DED.

3.4. Stress

3.4.1. What is stress?

Psychological stress is defined as "a particular relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her well-being" [101–103]. It occurs when an individual perceives that their environmental demands tax or exceed their adaptive capacity. Rapid social and cultural changes as well as globalization have resulted in profound transformation of our social organizations, and in some cases, new challenges have caused psychological stress for some individuals. Psychological stress can occur across multiple domains including but not limited to occupational stress, socioeconomic stress, and stress associated with depression and anxiety [101–104].

3.4.2. Clinical assessment tools

The physiological impact of stress is different for each individual. Thus, stress monitoring systems need to consider both the physiological and psychological impacts of stress and translate these assessments into an accurate quantitative metric. Several methodologies have been developed in this regard, including subjective report and quantification of objective physiological and biochemical measures. Self-reported questionnaires have been predominantly used when examining stress as it relates to eye disorders [42,101–106]. Participants in previous studies were often asked to self-rate psychological stress burden using a 3-point scale (1, minimal stress burden, 2, moderate stress burden, 3, high stress burden), a 4-point Likert scale (1, low, 2, moderate, 3, severe, and 4, very severe), or the Perceived Stress Scale 4 [37,42,101–104,106–108].

3.4.3. Stress and DED

3.4.3.1. Stress and ocular surface symptoms. There are level 3 population-based studies that report positive associations between DED and psychological stress. In one study, 1125 visitors who were attending an exhibition in London, England (707 females, age, 33 ± 21) were asked to complete questionnaires regarding demographics and lifestyle challenges. Concomitantly, information on DED symptoms (5-item Dry Eye Questionnaire) and signs (using the OCULUS Keratograph, which quantifies conjunctival hyperemia, non-invasive tear breakup time, and facilitates evaluation of meibomian gland atrophy, tear meniscus height, and lipid layer grade) was collected. Multivariate modeling demonstrated that poorer self-perceived health status and increased psychological stress were associated with an increased odds of both aqueous deficient and evaporative DED, defined using Keratograph metrics [109].

Similar findings were reported in a cross-sectional study of 312 community residents living in New Zealand (178 females, 134 males) where DED symptoms and signs were profiled. Multivariate modeling, adjusting for age, sex, ethnicity, and contact lens wear, demonstrated that better self-perceived health status was associated with a decreased odds of DED (OR 0.61, 95% CI 0.43–0.86), aqueous tear deficiency (OR 0.54, 95% CI 0.34–0.85), and meibomian gland dysfunction (OR 0.63, 95% CI 0.45–0.88). On the other hand, a higher self-reported psychological stress burden positively associated with DED (OR 1.98, 95% CI 1.29–3.04), aqueous tear deficiency (OR 2.28, 95% CI 1.14–4.49) and MGD (OR 1.87, 95% CI 1.20–2.89) [42].

Other studies have evaluated patient populations at high risk for stress. One study examined the association between DED and psychological stress in 232 paramedical workers in Korea. DED symptoms were assessed using a 9-item questionnaire, and DED was defined symptomatically as reporting one or more symptom, often or all the time. Psychological stress was measured using a visual analog scale for stress and using the Perceived Stress Scale 4. The frequency of DED in the population was 42.7% (99/232). Female sex, prolonged computer use, and higher stress scores on visual analog scale and Perceived Stress Scale 4 were significantly associated with DED. In multivariate modeling, female sex and stress score on visual analog scale remained associated with DED [107]. The same group also examined this question in 208 medical students. On multivariate modeling, Perceived Stress Scale 4 scores (representing higher stress levels) remained associated with DED (OR 1.17, 95% CI 1.03–1.33; $p = 0.014$) [110].

Other authors have focused on examining this question in healthy populations. For example, the association between DED and psychosomatic symptoms was examined in healthy young adults (16–35 years old). In the study, 211 individuals filled out the Ocular Surface Disease Index, short version of the depression, anxiety, and stress scale, and dry eye quality of life score questionnaires and underwent an ocular surface exam to quantify meibomian gland expressibility, tear breakup time, corneal staining, and Schirmer test score. DED symptoms severity (Ocular Surface Disease Index) was correlated with dry eye quality of life ($r = 0.67$, $p < 0.001$), anxiety ($r = 0.45$, $p < 0.001$), depression ($r = 0.54$, $p < 0.001$), and stress ($r = 0.44$, $p < 0.001$) scores, with higher DED symptoms correlating with worse function and stress [111].

Similar findings were noted in a population-based study using data from the fifth annual Korea National Health and Nutrition Examination Survey (2010–2011, 6655 women aged 19 years or older). Participants with a DED diagnosis had a higher likelihood of reporting severe psychological stress (OR 2.5, 95% CI 1.6–4.0), depressive mood (OR 1.5, 95% CI 1.1–2.0), anxiety/depression (OR 1.5, 95% CI 1.1–2.0), and a history of psychological counseling (OR 1.8; 95% CI 1.0–3.1) compared to those without a diagnosis. Similar patterns were noted when the analysis was repeated considering the presence or absence of DED symptoms [108].

Given the cross-sectional nature of these studies, it is not possible to examine the direction of association and imply causality. However, it has been postulated that DED symptoms could impact visual function, quality of life, and work productivity, which might negatively influence self-perceived health status and psychological stress. On the other hand, psychological stress may also exacerbate pre-existing ocular surface homeostatic disturbances through modulation of immune, hormonal, and neurosensory systems [109]. Longitudinal studies that examine psychological stress as a consequence of change in DED symptoms (and vice versa) are currently lacking.

3.4.3.2. Stress and ocular surface signs. Most studies have not reported associations between stress and ocular surface signs. However, in the clinic-based study of young, healthy adults, meibomian gland expressibility was associated with the anxiety subscale score of the short version of the depression, anxiety and stress scale ($r = 0.15$, $p = 0.026$). No additional significant associations were noted between other DED signs and anxiety, depression, and stress subscales scores on this scale [111]. Overall, these results suggest that DED symptoms are more closely related to stress than to clinical signs.

3.4.3.3. Stress and tear biomarkers. There are no human studies that describe an association between stress and tear biomarkers, highlighting this as a potential avenue for future study.

3.4.4. Mechanisms

3.4.4.1. Stress models and ocular surface symptoms. There is evidence that psychological stress provokes depression-like behaviors through inflammation, oxidative, apoptotic and anti-neurogenic mechanisms [112]. Two animal models of external stress are the chronic mild stress model and the learned helplessness model [113,114]. The chronic mild stress model paradigm involves exposure to a series of mild and unpredictable stressors such as isolation, crowded housing, alterations to the dark–light cycle, and restricted food [115]. The learned helplessness model is induced through application of uncontrollable and unpredictable aversive stimuli, such as an electric foot shock or tail shock or loud acoustic sounds [101]. Psychological stress has been found to increase proinflammatory factors such as tumor necrosis factor-α [112] that have relevance in DED. However, the pathophysiology underlying the noted association between psychological stress and DED is unclear and causal relationships are not conclusive. However, several mechanisms have been suggested including that psychological stress may affect pain perception and somatization [116], which may make individuals more susceptible to DED symptoms. Psychological stress can increase systemic inflammatory activity by promoting production of inflammatory cytokines [117], which may trigger ocular surface inflammation. Depression resulting from stress may be a confounding factor, as depression has also been linked to DED, as outlined above.

3.4.4.2. Stress models and ocular surface signs. Enriched environments have been reported to relieve disease symptoms and progression in Alzheimer's disease, Parkinson's disease, and cancer [118]. Changes in brain-derived neurotrophic factor activity in the brain have been reported to be the major mechanism by which an enriched environment provides beneficial effects on health. Additionally, brain-derived neurotrophic factor has been reported to be involved in stress-related symptoms, and a brain-derived neurotrophic factor gene polymorphism has been associated with DED in humans [119]. In one model, psychological stress resulted in decreased brain-derived neurotrophic factor expression while an enriched environment resulted in increased expression of brain-derived neurotrophic factor. These findings were further examined using knockdown mice. Brain-derived neurotrophic factor knockdown mice showed decreased basal tear secretion and loss of stress tolerance [49]. These results suggest that brain-derived neurotrophic factor may be one link between stress and tear production as a key aspect of DED [49,107].

3.4.5. Treatment implications

Psychological stressors, particularly those that are persistent, are well recognized by clinicians as apparent triggering factors in the initiation of fibromyalgia, which is defined as "a sense of unease" because of the chronic effects of pain, fatigue, and psychologic distress on functioning [120]. It is plausible that stress can similarly trigger aspects of DED, and this is a subject in need of further study. However, treatment studies are lacking that examine the impact of treating stress on DED outcomes and vice versa, the impact of treating DED on stress levels.

3.4.6. Future directions and gaps

Many questions remain regarding the noted link between stress and DED. Cross-sectional studies have demonstrated associations between the two, but longitudinal studies, including treatment studies, are lacking. Such studies need to account for potential confounders, such as other mental health conditions and medication use. Furthermore, animal models of psychological stress may be helpful to more robustly examine mechanisms that cannot easily be gleaned from human studies.

3.5. Sleep disorders

3.5.1. What is a sleep disorder?

Sleep is an essential physiological process that affects bodily functions in a profound way, including impacting immune, metabolic, aging, psychiatric and cardiovascular metrics [121].

Insomnia is a heterogeneous disorder with many different phenotypes or subtypes, characterized by difficulty falling asleep or difficulty staying asleep. Sleep disorders can manifest as insomnia, disorders of a stage of sleep (parasomnia) or excessive daytime sleepiness (hypersomnolence). Another class within sleep disorders is circadian rhythm sleep–wake disorders, where the timing of the main sleep episode is earlier or later than desired. This type of disorder is relevant in shift workers and people suffering from jet lag [122]. Even in expert hands, these disorders are difficult to differentiate from sleep disorders related to medical conditions (sleep apnea, for example) and psychological disorders [123].

Overall, sleep disorders are common. Excessive daytime sleepiness was noted to affect more than one tenth of Australian and Korean adults [124]. In addition, sleep disorders are related to negative outcomes including poor health, accidents, dementia, and mortality [124]. The frequency of both sleep and mental health disorders were found to increase following the COVID-19 pandemic [125].

3.5.2. Clinical assessments

Clinical assessments of sleep disorders can be divided into objective sleep recordings and patient-reported outcomes (with instruments such as the Pittsburgh Sleep Quality Index, Insomnia Severity Index, and the Epworth Sleepiness Scale). Although subjective assessments are faster and less expensive to administer, objective measures of sleep (for example, actigraphy, in-laboratory and in-home polysomnography, and the Multiple Sleep Latency Test) are needed to arrive at a formal diagnosis. Questionnaires are not without utility, however, and are more feasible to administer as part of clinical and population-based screenings. For example, the Berlin questionnaire has shown utility in screening individuals for sleep apnea, whereas the Insomnia Severity Index and Pittsburgh Sleep Quality Index have shown utility in quantifying insomnia symptoms and monitoring response to intervention. Since questionnaires have been developed to serve different purposes, there is no consensus on the single best questionnaire for universal use [126].

3.5.3. Sleep disorders and DED

3.5.3.1. Sleep disorders and ocular surface symptoms and signs. A systematic review and meta-analysis including 19 articles found that, compared to controls, DED patients have poorer sleep quality, spend less time asleep, experience more sleep disturbances, and may have increased prevalence, incidence, and severity of sleep disorders [127]. Another systematic review found that individuals with primary Sjögren syndrome reported greater sleep disturbances and demonstrated more night awakenings and pre-existing obstructive sleep apnea than controls [128]. However, it is important to consider that in Sjögren syndrome, another associated organic health problem (such as urinary incontinence) may influence sleep (for example, sleep interruption due to the need to urinate frequently) whereas this may be less likely to occur in individuals with non-Sjögren syndrome DED. Thus, it is best to consider these two populations separately.

3.5.3.1.1. Sjögren syndrome. Studies have linked primary Sjögren syndrome to sleep disorders, using both database [129] and clinic-based methodologies. Sleep disorders were quantified in a variety of ways, including: assessing day time sleepiness and sleep onset latency [130], quantifying sleep efficiency by calculating the percentage of time asleep when in bed, and examining daytime fatigue [131]. Some studies have used validated questionnaires, including the Epworth Sleepiness Scale

[132], Improved Health Assessment Questionnaire [133], Pittsburgh Sleep Quality Index [134], and 10-point Mini Sleep Questionnaire [135]. Other studies have used objective tests, such as polysomnography to evaluate muscular tension and restless legs [136]. One study assessed sleep in a longitudinal manner, using the 15-item Dutch questionnaire to rate sleep quality [137]. While a limitation of these studies is that they did not examine DED symptoms or signs in the Sjögren syndrome population, the studies overall confirmed that individuals with Sjögren syndrome have a higher frequency and severity of sleep disorders compared to controls.

3.5.3.1.2. Non-Sjögren syndrome DED

3.5.3.1.2.1. Sleep disorders and DED in major population-based surveys

Several large population-based studies from Asia and the Netherlands have examined the relationship between sleep disorders and DED. Most studies considered DED symptoms rather than signs. Sleep disorders was assessed using a variety of metrics, most frequently the Pittsburgh Sleep Quality Index (Table 1).

A Singaporean study included 3303 participants aged 40 years and above from two large population-based cohorts, the Singapore Malay Eye Study-2 (n = 1,191, 2011–2013) and the Singapore Indian Eye Study-2 (n = 2,112, 2013–2015). DED symptoms were defined as experiencing one of six symptoms often or all the time (using the Salisbury Eye Evaluation Survey). Of 3303 participants, 6.4% reported excessive sleepiness (Epworth Sleepiness Scale), 20.5% were deemed at high risk for sleep apnea (Berlin and STOP-Bang questionnaires), 2.7% had insomnia (Insomnia Severity Index), and 7.8% had <5 h of sleep. These sleep factors were associated with DED symptoms. After adjusting for relevant demographic, medical, and social factors, excessive sleepiness (OR 1.77, 95% CI1.15-2.71), high risk of sleep apnea (Berlin questionnaire: OR 1.55, 95% CI 1.17–2.07; STOP-Bang Questionnaire: OR 2.66, 95% CI 1.53–4.61), insomnia (OR 3.68, 95% 2.17–6.26) and <5 h of sleep (OR 1.73, 95% 1.17–2.57, reference sleep duration 5–9 h) were associated with DED symptoms. This study is unique in that data on two different ethnic groups were presented, and that four independent sleep questionnaires were used [138].

In the China Hangzhou Study, the Ocular Surface Disease Index was used to assess DED symptoms, and individuals were divided into no, mild, moderate or severe DED symptom groups. The Pittsburgh Sleep Quality Index, customized and validated in Chinese, was used to assess sleep quality. Several aspects of sleep (poor subjective sleep quality, long sleep latency, short sleep duration, poor habitual sleep efficiency, sleep disturbance, and daytime dysfunction) were associated with increased DED symptom severity. These associations remained significant after accounting for potential confounders [139].

In the Japanese study, DED was defined as the presence of clinically-diagnosed DED or severe symptoms. Difficulty falling or staying asleep and waking up tired were significantly related to DED in both men and women ($p < 0.001$). Compared to obtaining 8 h/day of sleep, shorter sleep duration was also associated with DED in both sexes, although DED frequency was increased among men who slept ≥10 h/day. By comparing participants with the greatest vs. the least difficulty in falling asleep, the multivariate-adjusted ORs were 2.23 (95% CI 1.99–2.49) for men and 1.91 (95% CI 1.76–2.07) for women. When analyzed separately, the magnitude of each relationship was stronger with those reporting severe DED symptoms than clinically-diagnosed DED [140].

In the Korean study of 4185 participants aged ≥65 years, sleep duration ≥9 h/day was associated with a lower odds of DED symptoms (adjusted OR 0.52, 95% CI 0.33−0.83, adjusted for gender, cataract, suicidal ideation, and hypercholesterolemia). Of note, DED symptoms were determined based on the response to "Until now, have you ever had a symptom of dry eye, for example, a sense of irritation or dryness of the eyes?" If the participants responded as having experienced dry eye symptoms 'persistently,' they were categorized as having DED symptoms. However, if the participants reported symptoms 'sometimes', 'occasionally', or 'never', they were categorized as not having DED symptoms [141].

A large population-based study in the Netherlands (71,761 participants), also evaluated the association between DED and sleep quality assessed using the Pittsburgh Sleep Quality Index [142]. From 8.9% of the study cohort with DED (defined as clinically diagnosed or having severe symptoms), the odds of having poor sleep quality was still higher in DED after correcting for >50 comorbidities (OR 1.20, 95% CI 1.11–1.28). A relationship was present across all age categories (from 20 to 30 years to 70+) and sexes, and for all subcomponents of the Pittsburgh Sleep Quality Index (e.g., sleep latency, sleep duration, habitual sleep efficiency, and daytime dysfunction). Of those with highly symptomatic DED (either 'constant' or 'often' symptoms of both ocular irritation and dryness), 44.9% had poor sleep quality, similar to disorders such as obstructive sleep apnea and osteoarthritis.

In conclusion, large population-based studies have consistently reported an association between DED symptoms and sleep abnormalities. A similar relationship was observed after adjusting for potential confounders, indicating the importance of correcting for associated comorbidities in assessing this question.

Table 1
Population-based studies on sleep and dry eye disease (DED).

Author, year	Study design	Participants	Comparator(s)	Outcomes	Key findings
Hanyud, 2021 [140]	Cross-sectional study	Adults aged 40–74 years from the Japan Public Health Center-based Prospective Study for the Next Generation (total n = 106,282; n = 25,864 with DED)	Participants without clinically diagnosed DED and participants without severe DED.	Frequency of difficulty falling/staying asleep, Waking up tired, Hours of sleep	Poor sleep quality and quantity associated with DED
Magno, 2021 [142]	Cross-sectional study	Adults aged 19–94 years from the Lifeline cohorts, Netherlands (n = 71,761)	Absence of DED (assesed using the Women's Health Study DED questionnaire, clincal diagnosis, and highly symptomatic DED)	Sleep quality evaluated using the PSQI	Sleep quality was significantly reduced in people with DED
Kim, 2019 [141]	Cross-sectional study	Adults aged >65 years (Fifth Korea National Health and Nutrition Examination Survey 2010–2012] (n = 4185; n = 806 had DED symptoms)	Absence of DED symptoms	Hours of sleep	Duration of sleep>9 h reduced odds of having DED symptoms
Lim, 2019 [138]	Cross-sectional study	Adults aged >40 years from the Singapore Malay Eye Study-2 2011–2013 (n = 1191) and the Singapore Indian Eye Study-2 2013–2015 (n = 2112; total n = 3303)	Participants without DED symptoms	ESS, Berlin, Stop-Bang, Insomnia Severity Index, Hours of sleep	Poor sleep quantity and quality associated with significant DED symptoms
Yu, 2019 [139]	Cross-sectional study	Adults aged 18–80 years from Hangzhou, China in 2016–2017 (n = 3070)	Normal OSDI	Sleep quality evaluated using the Chinese PSQI	PSQI associated with mild, moderate, and severe DED (odds ratios: 1.07, 1.13, 1.14, all $p < 0.001$)

DED: dry eye disease, OSDI: Ocular Surface Disease Index, PSQI: Pittsburgh Sleep Quality Index, ESS: Epworth Sleepiness Scale.

3.5.3.1.2.2. Sleep disorders and DED in clinic-based surveys and cross-sectional studies

Clinic-based survey and cross-sectional studies have reported similar findings to the large population-based studies above. These studies used subjective, rather than objective, metrics to examine sleep quality.

A Japanese study identified 301 individuals with clinically diagnosed DED. The mean Pittsburgh Sleep Quality Index score was 6.4 ± 3.2 in individuals deemed to have severe DED (n = 146) and 5.5 ± 3.3 in individuals with mild DED (n = 155). Although the difference was significant between these two groups, the study did not evaluate healthy controls [143].

In China, a multi-hospital (n = 94) cross-sectional study found that DED (n = 17,937, 57.6%) diagnosed with McMonnies Questionnaire was associated with use of sleeping tablets (multivariate OR 1.21, 95% CI 1.09–1.34) and with use of tranquilizers (OR 1.60, 95% CI 1.40–1.82). This study, however, did not include other sleep-related outcomes [144].

A US-based study using national insurance claims data (from military personnel and their families) found that the frequency of insomnia and sleep apnea was significantly higher in the DED compared to the non-DED group [145]. Similarly, a Korean study, using claims data, found that sleep disorders were positively associated with a DED diagnosis [146].

A website survey of 2000 Japanese people asked participants to answer a questionnaire on DED, sleep quality and happiness. The results showed that individuals self-reporting DED also reported longer sleep latency, shorter sleep duration and worse sleep efficacy, compared to non-DED participants [147].

Obstructive sleep apnea has also been associated with DED and conjunctival hyperemia [148]. Interestingly, obstructive sleep apnea has also been associated with meibomian gland dropout and other changes [149]. Interference with activities of daily living (including sleep) has been associated with worse DED symptoms [150].

Sleep disorders have been studied in relation to specific aspects of DED, including ocular pain. In a study of US veterans, two-step clustering was performed to separate individuals into high and low ocular pain groups. A greater proportion of individuals in the high ocular pain group (61%) experienced at least moderate insomnia (Insomnia Severity Index score≥15) relative to the low ocular pain (41%) and control (18%) groups ($p < 0.0005$ for all). Furthermore, DED symptom severity (5-item Dry Eye Questionnaire, OR 1.1; 95% CI 1.01–1.2) was associated with insomnia (Insomnia Severity Index score≥15) after controlling for potential confounders [151], suggesting that higher levels of ocular pain are associated with worse insomnia symptoms.

In conclusion, hospital-based studies support the associations noted in the population-based studies, regarding sleep abnormalities and DED, most often defined by symptoms. Longitudinal studies are needed to further understand whether a change in one domain has the potential to influence a change in the other.

3.5.3.2. Sleep disorders and keratoconus. Other studies have focused on relationships between sleep and other anterior segment diseases, beyond DED. In a recently published meta-analysis, data from four hospital-based case-control studies and one large population-based cohort study were pooled. Most of the studies assessed obstructive sleep apnea using the Berlin Questionnaire. Obstructive sleep apnea was significantly associated with keratoconus (pooled OR 1.84, 95% CI, 1.16–2.91) [152].

3.5.4. Mechanisms

The relationship between DED and sleep has been investigated in a mouse model: "the stick over water"sleep deprivation-induced dry eye model. In the stick over water sleep deprivation model, epithelial disruption, lipid accumulation, microvilli morphological changes, and decreased tear production were noted to occur after 10 days of sleep deprivation [153]. Resting for 14 days after sleep deprivation reversed the observed changes [154]. As an intervention, the addition of topical palmitoylethanolamide during sleep deprivation preserved corneal barrier function and improved DED clinical signs [155].

This study demonstrated that sleep deficiency in mice resulted in induced ocular surface alterations and objective reduction of tear secretion that mirrors DED signs in humans. This is important because human studies have failed to demonstrate a strong link between DED signs and sleep disorders. Furthermore, the reversibility of these signs and the knowledge gained in regard to molecular alterations may be useful in future sleep-based interventional research.

3.5.4.1. Shared physiological pathways. Several potential mechanisms have been proposed that link sleep disorders to DED. First, the effect may be driven by alterations in hormones (Fig. 2). Sleep deprivation can reduce androgen levels [156,157], impair circadian rhythms [158], and increase levels of stress hormones (norepinephrine and cortisol) that could impact tear secretion [159]. Androgens impact lacrimal and meibomian gland function, and low androgen levels have been linked to DED [160]. Lacrimal secretion has been shown to follow a circadian rhythm [161], and as a result, sleep disturbances also may disrupt its regulation. Poor sleep quality, mood disorders, and DED are inextricably linked and all three may be impacted by hormonal changes (serotonin, norepinephrine, and dopamine imbalances) and alteration of the hypothalamic-pituitary axis [162].

Another potential link between sleep disorders and DED is via autonomic nervous system dysfunction. Sleep deprivation has been shown to decrease parasympathetic activity, and reduced innervation can lead to rapid reduction in tear flow [163]. Sleep deprivation has been linked to reduced brain-derived neurotrophic factor, which could be another link with DED [49,164]. Interestingly single nucleotide polymorphism within the brain-derived neurotrophic factor gene have been linked to DED in a clinic-based study of 64 DED cases and 51 controls. DED was diagnosed based on: (1) symptoms: burning sensation, irritation, grittiness or foreign body sensation, light sensitivity, pain, dryness, soreness, or discomfort in the eye; (2) a Schirmer test value of <10 mm/5 min; or (3) positive corneal staining and/or Rose Bengal corneal and conjunctival staining of ≥1. It was demonstrated that 18% of cases and 9% of controls had the minor allele A of Val66Met (rs6265) single nucleotide polymorphism in the brain-derived neurotrophic factor gene ($p = 0.05$), with an OR of 2.22 [119].

Furthermore, sleep deprivation can reduce tear secretion and increase tear film instability, with percentage time of eye open versus closed at night impacting this finding. In a prospective interventional study involving 20 healthy males, 10 participants were deprived of sleep in an experimental setting and compared to the control group, that was not sleep-deprived. DED signs were evaluated at 2 p.m., 10 p.m., and 6 a.m. and 2 p.m. the following day. At 6 a.m. (after deprivation), a higher tear osmolarity level, lower tear breakup time, and lower tear secretion rate were noted as compared to the non-sleep deprived control group [165].

Finally, insufficient sleep may also result in reduced repair processes on the ocular surface. Tears from closed eyes have been found to have immunosuppressive properties and it is hypothesized that antiproteases may be released into tears during sleep [166]. CD66b positive neutrophils have been recovered from the tears of individuals with DED, and thus, a homeostatic mechanism that occurs during sleep may play a role in preventing degranulation of these neutrophils [167]. Furthermore, collection of tears from a closed eye followed by 16s ribonucleic acid (RNA) sequencing revealed differences in the microbiome of individuals with DED compared to controls. Individuals with DED had higher abundance of genera such as Streptococcus and Pseudomonas, and at the phylum level of Proteobacteria [168]. Although supporting evidence is currently lacking, it is possible that sleep disorders alter the microbiome, contributing to an abnormal tear microenvironment and subsequent

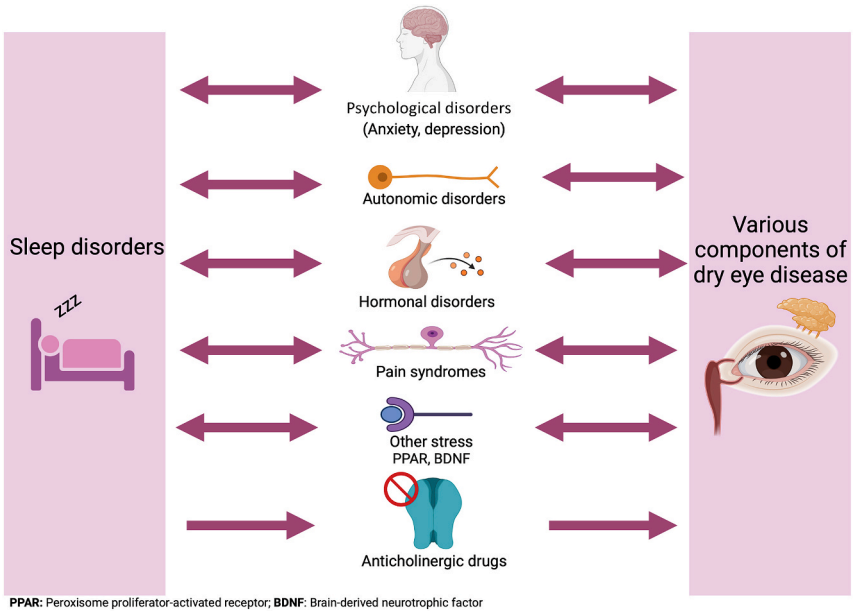

Fig. 2. Potential mechanisms that may underlie the association between sleep disorders and dry eye disease symptoms and signs.

DED. Further studies are needed to examine this question.

3.5.4.2. Molecular pathways. Beyond brain-derived neurotrophic factor, clinical signs and microscopic findings in animal studies suggest that peroxisome proliferator-activated receptors may underlie the link between sleep disorders and DED [153].

3.5.5. Treatment implications

There have been no randomized controlled trials reported in this field. An interesting pilot study was conducted on the chronobiology of sleep after DED treatment with eye drops. Seventy-one patients with a clinical diagnosis of DED underwent evaluation using the Pittsburgh Sleep Quality Index and Hospital Anxiety and Depression Scale. Photophobia and chronotype (a person's natural inclination with regard to the times of day when they prefer to sleep or when they are most alert or energetic: morningness/eveningness) were also evaluated with representative questions (from the National Eye Institute Visual Function Questionnaire-25 and Morningness/Eveningness questionnaire). Follow-up evaluation was conducted by interview or mail 3–10 months after the initial evaluation. Sleep evaluation included sleep diary, actigram, and medical interviews. It was found that patients with newly diagnosed DED exhibited a greater improvement in sleep after DED treatment compared to patients with established DED. Interestingly, improvement in Pittsburgh Sleep Quality Index score ($p < 0.05$) was strongly correlated with improvement in Hospital Anxiety and Depression Scale score ($p < 0.05$) for new patients, but not for patients with established DED. This study suggests that interventions initiated at the onset of disease may be more beneficial than those initiated later in a disease process, i.e. that there may be "a window of opportunity" in modulating sleep in individuals with DED.

In an open label study of 15 patients with DED and neuropathic pain symptoms, the impact of a topical transient receptor potential cation channel subfamily M (melastatin) member 8 (TRPM8) agonist was examined with relation to sleep. Sleep quality (as measured by subjective report) was improved at one week, but this was not adjusted for improvement of other parameters, as both ocular pain and tear production also improved at one month after treatment [169].

In a crossover study using ocular gels, the quality of sleep was evaluated with a visual analog scale and found to be improved with hyaluronic acid/trehalose-based formulations. However, this study had no untreated parallel control group [170].

There have been no sleep intervention studies that have explored corresponding improvement in DED metrics. However, there is indirect evidence that interventions that impact sleep could alter DED. The prevalence and incidence of DED increased more than in the general population up to 3 years after starting continuous positive airway pressure (CPAP) and nasal masks [171]; however, without a control arm, it is difficult to interpret such findings conclusively.

Melatonin has been shown to improve the onset, quality and quantity of sleep, and help synchronize circadian rhythms [172]; however, it has not been studied specifically in relation to DED.

Overall, the effect of DED on sleep disorders may not be easily distinguishable from its association with psychological disorders. In fact, sleep disorders may be largely due to psychological disorders. In a practical setting such as in a DED clinic, it is preferable to treat both sleep disorders and psychological disturbances rather than to focus on only one of these conditions. Some suggestions that have not been tested in trials include blue-light-shield eyewear, blue-light therapy lamps, relaxation, cognitive rehabilitation and mindfulness therapies [173]. These approaches need to be more robustly tested [174].

3.5.6. Future direction and gaps

While both DED and sleep disorders are heterogeneous conditions, various aspects of DED (symptoms, including ocular pain) have been linked to various aspects of sleep disorders (insomnia and sleep-wake cycle disorders). The contributions of possible confounders, such as anxiety and depression, on these relationships need to be considered in further studies. Other co-morbidities warrant consideration are pain conditions outside the eye, such as migraine headaches, which have been associated with both sleep disorders [175] and DED [176]. Menopause and andropause, mental health status, and changes associated with aging [177] should also be considered. In addition to epidemiological studies, few interventional studies on sleep and DED have been undertaken. Randomized controlled studies are needed to assess sleep intervention on DED, and DED intervention on sleep characteristics. These studies should monitor for pain and psychological symptoms as covariates. Basic studies are also needed to determine molecular processes that underpin DED in sleep deprivation. Such studies may lead to new interventions, such as in peroxisome proliferator-activated receptors or brain-derived neurotrophic factor pathways.

4. Physical factors

4.1. Physical inactivity and obesity

4.1.1. What is physical inactivity and obesity?

Physical inactivity is a term used to identify people who do not get the recommended level of regular physical activity. The American Heart Association recommends 30–60 min of aerobic exercise three to four times per week. Physical inactivity is an epidemic in modern society. The average body mass index has increased in recent decades in many countries, and this has led to an increased prevalence of medical conditions, such as obesity, hypertension, diabetes, and obstructive sleep apnea, among others [178]. Obesity is commonly defined using the Body Mass Index metric. For adult men and women, a body mass index between 18.5 and 24.9 kg/m^2 is considered healthy. A body mass index of between 25.0 and 29.9 kg/m^2 is deemed overweight, and of 30 kg/m^2 or higher is considered obese [178,179].

4.1.2. Associations between obesity, DED, and ocular surface diseases

There have been mixed reports on the relationship between obesity and DED [180]. Several population-based studies found that a high body mass index is associated with a lower frequency of DED. In a Dutch population-based cohort study (n = 79,866, of which 59% were women and 9.1% had DED), both higher body mass index (adjusted OR 0.985, 95% CI 0.979–0.991) and higher waist circumference (adjusted OR 0.995, 95% CI 0.992–0.997) were negatively associated with DED prevalence [31]. Another cross-sectional questionnaire-based survey study of 85,264 Japanese men and women aged 40–74 years who participated in the Japan Public Health Center-based Prospective Study also found an inverse relationship between body mass index and DED prevalence. In this study, DED was defined by the presence of severe symptoms or a clinical diagnosis. Overall, the prevalence of DED was 23.4% (n = 19,985; 6289 men, 13,696 women). Higher body mass index was correlated with a lower prevalence of DED in a dose-response fashion, with an adjusted OR of 0.98 (95% CI 0.97–0.99) for DED per kg/m^2 increment of body mass index for men and 0.97 (95% CI 0.97–0.98) for women [181]. However, in 305 adults presenting to optometry clinics in Australia, a moderate correlation was noted between body fat percentage and DED symptoms (evaluated using both the short form Dry Eye Questionnaire $r = 0.34$, $p = 0.003$ and the Ocular Comfort Index $r = 0.32$, $p = 0.004$) [182]. This study also found an interaction between body fat percentage and sex on DED symptoms (in a multivariate model with age and contact lens wear); body fat percentage was only significantly correlated with higher DED symptom score in females, but not in males.

Tear film parameters have also been evaluated in individuals with elevated body mass index. In a single center study of 40 males, half with elevated body mass index (median 31.8 kg/m^2) and half with normal body mass index (median 20.5 kg/m^2), individuals with elevated body mass index had a lower non-invasive tear breakup time compared to those with normal body mass index (mean 8.5 versus 14.7 s, $p < 0.05$). Similarly, tear ferning scores in obese patients were found to be abnormal compared to the normal body mass index group (2.0 ± 1.1 versus 0.7 ± 0.6 kg/m^2, $p < 0.05$). No significant differences in tear meniscus height and phenol red thread test scores were noted between the groups [183], indicating that the effects of obesity on tear film stability are unrelated to changes in tear production.

Obesity has also been associated with alteration in meibomian gland architecture. One study of 175 US-based children, aged 4–17 years, reported a mean meiboscore of 0.82 ± 0.94 (range 0–4) and mean gland tortuosity score of 0.53 ± 0.70 (range 0–2) in the study population [184]. Most individuals (56%) showed evidence of gland atrophy (meiboscore>0) and 29% had a gland tortuosity score of 1. Mean body mass index was 20.5 ± 4.86 kg/m^2 with 39.4% of patients (n = 69) above the 85th percentile. While body mass index percentile was not found to be a significant predictor of meiboscore, it was found to be a significant predictor of gland tortuosity score (OR 1.01, 95% CI 1.00–1.02). Patients with body mass index percentiles between 41 and 60 were 3.79 times more likely to have a gland tortuosity score greater> 0 compared to individuals with percentiles between 0 and 20 (OR 3.80, 95% CI 1.17–12.24) [184].

DED, meibomian gland dysfunction, and floppy eyelids have also been associated with obstructive sleep apnea, a disease co-morbid with obesity. In a study of 80 hospital-based patients with moderate to severe obstructive sleep apnea patients living in Egypt, conjunctival hyperemia and DED, defined by clinical examination, was more likely in individuals with obstructive sleep apnea compared to controls (OR 3.7 and OR 4.4, respectively) [148]. Additionally, tear breakup time was reduced in 45% of all individuals with sleep apnea, which again indirectly links obesity with meibomian gland abnormalities. This relationship has also been examined in relationship to obstructive sleep apnea severity. In a study of 36 individuals with severe obstructive sleep apnea and 24 with mild sleep apnea living in Turkey, foamy tear film, meibomian gland plugging, and meibomian gland duct distortion were all significantly more prevalent in individuals diagnosed with severe compared to mild obstructive sleep apnea. The total meiboscore was also much higher in patients with severe disease as well. A postulated mechanism in the study was that pro-inflammatory cytokines, such as interleukin-1, interleukin-6, interleukin-8 and tumor necrosis factor-α, underlie the association, as they have been reported to be elevated in obstructive sleep apnea and DED, though this hypothesis was not directly tested in the study [149]. Together, these studies lend more support to a link between obesity and meibomian gland abnormalities.

Floppy eyelid syndrome has also been linked to obesity, likely due to a weakened tarsus. The prevalence of floppy eyelid syndrome in patients with obstructive sleep apnea has been reported to be as high as 32% [185]. Tarsal weakness can lead to trauma of the tarsal conjunctiva from unnecessary exposure of the lid to rotational forces that allow easy opening of the lids and nocturnal trauma from a pillow or bedding. The treatment of obstructive sleep apnea, with a continuous positive airway pressure device, may also confound this relationship. Patients with obstructive sleep apnea and floppy eyelid syndrome, who wear a continuous positive airway pressure device to treat obstructive sleep apnea, can have their weakened eyelids forced open by the airflow of the device which further increases stress on the ocular surface. In a study using Medicare claims data to identify adults with known obstructive sleep apnea and continuous positive airway pressure device use, DED prevalence (by International Classification of Diseases, edition 9 or 10 coding) was higher in continuous positive airway pressure device users compared to the general population; DED prevalence was 6.2%, 10.0%, and 13.0% at 12, 24, and 36 months, respectively, in continuous positive airway pressure or nasal mask therapy device users. However, individuals with obstructive sleep apnea often have co-morbid conditions that in themselves may increase the risk of DED and, as such, the findings may be driven by factors other than obstructive sleep apnea alone [171].

4.2. Physical interventions

4.2.1. What are physical interventions?

In the context of this report, physical interventions are defined as devices used for the purpose of influencing, modifying, or preventing disease. Herein, we focus on continuous positive airway pressure as a means to modify sleep apnea and mask wear as a protective measure against transmission of airborne diseases.

4.2.2. Continuous positive airway pressure (CPAP)

The role of interventions to treat obesity related complications must be considered when discussing the connection between obesity and DED. As above, continuous positive airway pressure devices used to treat patients with conditions such as obstructive sleep apnea and chronic obstructive pulmonary disease have been found to cause or worsen DED

[186,187]. Continuous positive airway pressure device masks can subject the eye to mechanically generated air causing excessive drying of the ocular surface. Ocular manifestations of continuous positive airway pressure device users have been reported in as high as 50–70% of individuals [185,187] and include floppy eyelid syndrome, decreased tear breakup time, and increased Schirmer scores [188].

Multiple studies have shown that continuous positive airway pressure device use is associated with DED. A study of 350,420 individuals (age 53.1 ± 11.8 years, 63.3% male) reported a DED prevalence (over 36 months) of 13.0% in continuous positive airway pressure device users compared to 6.7% in the general US population [2,171]. Additionally, female continuous positive airway pressure device users had a higher prevalence of DED than male users (14.9%, 95% CI 14.7–15.2 vs. 7.7%, 95% CI 7.6–7.9). Another study of 72 individuals with obstructive sleep apnea and continuous positive airway pressure device use reported a DED frequency of 67%, based on an Ocular Surface Disease Index score of ≥13 and the presence of one or more clinical sign. Floppy eyelid syndrome was the most common clinical DED sign, found in 26 patients (54%) diagnosed with DED [187]. The impact on continuous positive airway pressure device initiation was also examined in 40 individuals (age 52.48 ± 9.5 years, 80% male) diagnosed with obstructive sleep apnea and no prior continuous positive airway pressure device use. The incidence of ocular irritation was found to increase after continuous positive airway pressure therapy (42.5% pre- and 57.5% post-continuous positive airway pressure device use, $p = 0.031$) [188], linking symptoms to the use of this device.

Constant airflow around the eyes is one potential contributor to ocular surface irritation in continuous positive airway pressure device users. Continuous positive airway pressure devices are available in multiple forms, ranging from full face masks to nose-coverage only. Ensuring best mask type and fit is patient specific and can help prevent air leakage towards the eyes. Providers should pay special attention to educating patients on proper mask fit and nighttime artificial tear or topical emollient use to mitigate the potentially negative effects of the device.

4.2.3. Mask-Associated Dry Eye disease

Another intervention that has been related to DED exacerbation is mask wear. Face masks have become an ever-increasing part of daily life since the pandemic era. Patients are often required to wear masks for extended periods of time while at work or outside the home. Both patients with and without a prior diagnosis of DED have reported new or worsening symptoms with mask wear [189,190]. The term "MADE" (Mask-Associated Dry Eye) was first coined during the early COVID-19 pandemic, as many clinicians anecdotally described an increase in patient-reported DED. In a survey study of 3605 people, mask-associated DED symptoms were found in 68% of responders, 27% of whom stated their symptoms were exacerbated when wearing a mask [190]. Individuals with pre-existing DED may have a higher likelihood for symptom exacerbation with mask wear than individuals without baseline symptoms.

The length of mask wear has also been examined in relation to DED. Individuals wearing masks for ≥6 h per day, 5 days per week reported a greater increase in DED symptoms (on the Ocular Surface Disease Index) from pre-pandemic scores compared to individuals who wore masks less frequently [191]. This suggests that DED symptoms are more likely with extended mask wear. Destabilization of the tear film is thought to underlie these symptoms although the exact mechanism is unknown. Some postulate that air flow is directed towards the eyes in non-form-fitting mask wear, and that, in addition, alteration in local temperature and humidity occurs at the level of the ocular surface when wearing a mask.

The clinical implications of mask wear have also been studied. Consistent use of a facemask for 3 months was found to worsen DED signs, including reducing tear breakup time and increasing ocular surface staining (in 66 patients with DED and 62 controls). In addition, subclinical markers of inflammation, in the form of corneal dendritic cell density and human-leukocyte-associated antigen DR expression has been noted [192]. These changes were particularly notable in patients using a facemask more than 6 h per day. Of interest, worsening of DED signs was noted both in individuals with DED and controls; however, the changes were more pronounced in individuals with DED, suggesting that these individuals are at greater risk of the adverse effects of mask wear. Certain populations may also be at greater risk of DED with mask wear, including women and individuals who wear facemasks for long durations [193], which suggests that some populations may be susceptible to DED after shorter durations of mask wear. In addition, other ocular surface diseases have been found to increase with mask wear, most notably the frequency of chalazion [194].

4.3. Eye rubbing

4.3.1. What is eye rubbing?

Eye rubbing can be described as the act of applying firm pressure to the eyelids and using a repeated back and forth motion. Pressure is often applied using the fingertips or knuckles, in an attempt to relieve itchy and/or uncomfortable sensations originating at the ocular surface or surrounding orbital structures [195]. While no standardized definition of eye rubbing exists, eye rubbing is commonly characterized as normal or pathological. Normal eye rubbing is a relatively benign activity that occurs sporadically on waking, prior to sleep, as well as throughout the day in response to fatigue or some occasional form of eye itch or irritation; in comparison, rubbing becomes abnormal when it is performed overly frequently, too vigorously, and/or when rubbing habits have been established over a long period of time [196].

Eye rubbing is a physiological response aimed to relieve uncomfortable sensations at the ocular surface [197]. Pruritus (e.g., itchiness) is a complex and unpleasant sensory experience that is a frequent stimulus for eye and scratching [198]. The afferent arm of eye rubbing originates as a consequence of stimulation of sensory nociceptors at the ocular surface (e.g., nociceptive-pruriceptive innervation), thus overlapping with mechanisms of nociceptive and neuropathic ocular pain (including peripheral and central abnormalities) [199,200]. Rubbing itself is the efferent response to this sensation, triggered by detection of an offending agent at the affected surface [201,202]. Pruritus, like many other somato-sensorial experiences related to pain, has complex processing involving behavioral, emotional, and motivational components; as such, multiple brain regions are involved in the sensory experience, including the amygdala and GABAergic and dopaminergic neurons of the ventral tegmental area [203].

4.3.2. Eye rubbing, DED, and keratoconus

Current literature suggests that vigorous or prolonged eye rubbing can modify the ocular surface and its related structures, and thus predispose to the development or exacerbation of pathological ocular conditions such as DED and keratoconus [195]. Multiple ocular conditions have been linked to pathological eye rubbing, including corneal ectasia, conjunctivitis, glaucoma, iris prolapse, iridoschisis, rupture of the posterior capsule and intraocular lens dislocation, retinal detachment, and extrusion of implanted silicone oil, among others [197]. Ocular allergies have also been linked to eye rubbing, but this may be due to an association between such conditions and keratoconus (known to be associated with eye rubbing), although findings have been contradictory. A systematic review and meta-analysis was undertaken evaluating the association between keratoconus and allergic eye diseases, but this article was retracted in 2022 [204]. However, other cross-sectional studies have reported a positive associations between keratoconus and allergic eye diseases. One study of 61 patients with diagnosed ocular allergy (vernal keratoconjunctivitis) and corneal ectasia observed a high frequency of keratoconus (n = 53 of 61) within the population, and also remarked on the high frequency of pathologic eye rubbing in this group [205]. Interestingly, other ocular conditions have been linked to allergic conditions, such as DED with allergic

conjunctivitis [206] and asthma in children [207], which may lend support to a potential link between ocular allergy and keratoconus.

Besides underlying disease, direct ocular surface irritation, such as with contact lens wear or exposure to chemical irritants, are also known causes of eye rubbing, as these insults directly stimulate ocular surface nociceptors [[208,285]]. Contact lens use is associated with removal-relief eye rubbing [209], and may partially explain why DED is more frequent in long-term contact lens wearers [210,211]. Interestingly, eye rubbing has also been linked with non-ocular systemic conditions, particularly psychiatric conditions associated with chronic fatigue or stress [209]. While little literature on the topic exists, in one study of 212 institutionalized patients (Trisomy 21, n = 30, neonatal asphyxia, n = 15, and pregnancy-related infection, n = 9), 7.5% (n = 16) individuals were diagnosed with keratoconus and were more likely to engage in eye rubbing [212] compared to individuals without keratoconus (p = 0.008), representing a substantially higher frequency than in the general population [196].

A 2021 systematic review that pooled findings from six case-control studies reinforced findings from isolated reports as a strong association was noted between eye rubbing and keratoconus (OR 6.46, 95% CI 4.12–10.1); however, included studies were deemed to be heterogenous with limited methodological quality. This review highlighted the need for greater standardization in methodology across studies in measuring the frequency, force, and technique of eye rubbing [213].

4.3.3. Mechanisms

As discussed above, keratoconus and DED are two common ocular conditions that have been linked to eye rubbing, with significantly more literature existing for the association with keratoconus than with DED. Eye rubbing has been reported in as many as 40–70% of patients with keratoconus [214] and is also a symptom associated with ocular allergy. Pathophysiologically, when vigorous rubbing forces are applied on the peripheral cornea, the thinner or weakened cone apex may be exposed to high intraocular pressure distending forces, which can promote corneal ectasia and eventually lead to keratoconus [215]. Furthermore, changes in tear inflammatory mediators due to rubbing may also contribute to development of keratoconus - rubbing reportedly leads to observable increases matrix metalloproteinase-13, interleukin-6 and tumor necrosis factor-α in human tears, and this increase in protease, protease activity, and inflammatory mediators after eye rubbing may promote progression to keratoconus, a finding that has been supported by other similar studies [216–218]).

Studies on keratoconus and eye rubbing have almost universally reported eye rubbing as a risk factor for, and behavioral symptom of, keratoconus. In a study of 244 individuals with keratoconus seen in a practice setting, 65.5% had a history of pathological eye rubbing [219]. Another prospective study of 200 patients with keratoconus and 100 controls found that 48% of subjects reported significant eye rubbing as a symptom of their disease (p = 0.02 compared to controls on visual analog scale [220]). A third study of 1027 healthy volunteers found a prevalence of keratoconus of 2.5% (n = 26; 95% CI 1.6–3.5) and in multivariate modeling, family history (OR 1.4, 95% CI 2.5–51.3) and eye rubbing (OR 6.3, 95% CI 1.6–24.3) were the only factors significantly associated with keratoconus [221]. Supporting the link between pathological eye rubbing and keratoconus, studies have found that patients with keratoconus apply more strength on eye rubbing than healthy individuals. In particular, a reliance on knuckle rubbing (which creates a strong compressive globe indentation force (>4.5kg/2.54 cm)) has been commonly observed in individuals with keratoconus [198]. One study of 57 individuals with keratoconus studied rubbing patterns and found that while most patients relied on their fingertips (n = 51%, 4.3 ± 3.1 N of force [measured as a mimic movement on a surface of a high-precision balance scale right after performing an eye rub]), nearly as many individuals utilized the much stronger knuckle instead (n = 44%, 9.6 ± 6.3 N), followed lastly by fingernails (n = 6%, 2.6 ± 3.3 N) [222]. Interestingly, besides eye rubbing, other mechanical stimulus factors such as sleep position have also been implicated in keratoconus [223,224].

For DED, pathological rubbing may alter the mechanobiology of the ocular surface and surrounding epithelium and predispose to disease development [225,226]. Previously described as the 'concept of attrition in DED' [226], mechanical shear forces as a result of rubbing challenge the ocular surface with friction, stretching, and compression; constant or repeated challenges in this manner may trigger mechanoreceptors of the ocular surface and evoke pain, recruiting neuroinflammatory mediators simultaneously. Over time, chronic inflammation due to unchecked force application may progress to DED [226]. Supporting this hypothesis, a preclinical rat study (one eye rubbed, control eye unrubbed) found that numbers of mast cells, degranulated mast cells, and proinflammatory cells (neutrophils, macrophages) from conjunctival samples of the upper eyelids were increased after rubbing, demonstrating a link between eye rubbing and ocular surface inflammation, a known risk factor for DED [227]. Unfortunately, no studies examined how measurable signs or symptoms of DED change depending on eye rubbing patterns in humans. Of note, one British study of 49 healthy individuals found that in healthy eyes, tear breakup time significantly decreased after only 2 min of rubbing (15.3–13.9 s, p = 0.0001). On the other hand, tear breakup time was mostly stable in the contralateral non-rubbed eye (15.3–14.8 s, p = 0.096) [228].

4.3.4. Treatment implications

Generally, eye rubbing alone does not warrant therapeutic intervention, unless there are signs of an untreated underlying disorder. Awareness of the consequences of eye rubbing (such as short term increases in intraocular pressure, deformation of the cornea with resultant ectasia in susceptible patients, creation of tear film abnormalities) and avoidance of common triggers should be of utmost consideration. Special attention should be placed on patients at risk for developing chronic rubbing behaviors, such as those with ocular allergies or ocular inflammatory syndromes, healthy individuals who wear contact lenses, and even children with myopia (interestingly, both eye rubbing and DED have been associated with myopia in children [229]). Education on regular lid hygiene practices, ocular surface care, and avoidance of common allergens and chemical irritants are beneficial strategies for those at risk [196]. In refractory cases, in which rubbing behavior is maintained and there is risk for potential long term eye damage, the physician should consider recommending other management strategies, such as cognitive behavioral therapy.

Allergy and atopy are common underlying disorders associated with eye rubbing [196], and the impact of anti-allergic medications on the ocular surface is reviewed in the *TFOS Lifestyle: Impact of elective medications and procedures on the ocular surface* report [230]. Screening and treatment for other ocular pathologies not appreciated on gross exam should be considered for additional provocative factors, such as dryness of the eye, corneal deformation, anterior blepharitis, meibomian gland dysfunction. Ocular massage combined with elevation in corneal temperature (e.g., warm compresses for treating meibomian gland dysfunction) could also induce rubbing-related deformation [198]. In a similar manner, for some patients, rubbing and scratching can produce a hedonic experience and, thus, facilitate pathological scratching behaviors and lead to an itch-scratch cycle [203]. In patients with evidence of psychogenic rubbing and tissue damage without an actual underlying cause, counseling may not be enough, and screening for undiagnosed psychiatric disorders may be necessary [209].

In summary, eye rubbing is a normally benign practice that can become pathological for a variety of reasons. New cases of pathological rubbing should be worked up, as it often exists because of an underlying ocular disorder and can lead to harmful long-term consequences like DED and keratoconus if left unchecked. While education and awareness on triggers are the main courses of intervention, further studies that shed more light on the neuro-inflammatory pathophysiology of eye rubbing and its relation to disorders such as DED and keratoconus [199,217,218]

may provide better diagnostic and therapeutic guidance in the future.

4.4. Sexual issues

Sexual dysfunction and DED are both frequent findings in the general population [231,232].

4.4.1. What are sexual issues?

Sexual issues are defined as dysfunction in one or more aspects of the active and reproductive sexual life and involve developmental, functional, endocrine, obstetric, sociocultural, and psychological domains [233] (Table 2).

4.4.2. Association between sexual issues and dry eye disease

Sexual issues have been surveyed with self-completed questionnaires in the North American, British, and Asian populations, and a similar frequency of problems was detected, with 37–43% of the female and 31–33% of the male adult populations reporting one or more sexual issues [242–245]. Although possible relationships between sexual issues and DED have been studied at the cellular and molecular level for decades (especially with regard to the role of sex hormones and DED), the TFOS DEWS II report, published in 2017, highlighted relevance of the subject, the lack of high level data, and the need for further understanding of how sexual issues associate with DED [160].

There are several reasons to understand relationships between sexual issues and DED. Both conditions are frequent in the population; many ocular surface diseases have sex-based biases (often more prevalent in females), and the frequency of DED and sexual issues increase with age. Both are associated with health impairment and chronic diseases. In women, the most common sexual problem is vaginal dryness, as self-reported by a postal questionnaire survey addressed to a sample of the general population of England [243]. Sex hormones may underlie aspects of both DED and sexual issues [160]. Important to consider is that while individuals with DED symptoms often consult medical professionals for help, only a small proportion of the individuals with sexual dysfunction seek professional care [2,242,243,246].

Table 2
Sexual issues commonly investigated in the medical literature and possible relationships with dry eye and ocular surface diseases.

Type	Description	Relationship with Dry eye and ocular surface diseases	Reference
Gynecological	Vaginal dryness, dyspareunia and chronic or recurrent genital infections	Observational studies and description in diseases associated with dry eye disease (Sjögren syndrome and graft-versus-host disease)	[234]
Andrological	Erectile dysfunction, premature ejaculation	Concomitant descriptions in diseases as Sjögren syndrome, amyloidosis and human T-lymphotropic virus 1	[235–237]
Female sexual dysfunction	Hypoactive sexual desire, arousal, pain/discomfort, inhibited orgasm	Relationships not investigated. Hypothesis: sexual hormone imbalance, peripheral neuropathies.	[232]
Male sexual dysfunction	Hypoactive sexual desire and lack of sexual satisfaction	Relationships not investigated. Hypothesis: sexual hormone imbalance, peripheral neuropathies.	[232]
Fertility	Infertility	Relationships not investigated. Hypothesis: sexual hormone imbalance.	[238]
Gender dysphoria	Psychological sense that the individual gender does not match with the gender assigned by the genital observation at the birth.	Relationships not investigated. Hypothesis: Gender identity affirmation with sexual hormone therapy. Induction of sex hormone therapy side effects.	[239]
Hormonal	Sex hormones imbalance, menopause, andropause	Clinical medical literature describing the association between sexual hormone imbalance and dry eye disease	[160]
Environment influences	Synthetic anabolic hormone abuse and endocrine disruptors exposure	Anecdotal evidence for anabolic hormone and case-control study for endocrine disruptor exposure inducing disease.	[240,241]

4.4.2.1. Polycystic ovary syndrome. Polycystic ovary syndrome is a common disease in women, frequently associated with infertility, hyperandrogenism, and influenced by lifestyle, including diet [247,248]. Previous observational case series and case-control studies in Turkey and Italy investigated DED in small groups of patients with polycystic ovary syndrome and detected higher frequency of DED symptoms, lower tear breakup time, meibomian gland dysfunction, and ocular surface epitheliopathy, including metaplasia [249–253], relative to controls. An Italian study identified 62 women with an ultrasonographic diagnosis of polycystic ovary, of which 16 had clinical and biochemical signs of hyperandrogenism (polycystic ovary syndrome). The majority (15/16) of women with polycystic ovary syndrome had DED symptoms and signs. In fact, DED symptoms were more frequent in women with polycystic ovary syndrome, compared to those with polycystic ovary alone, and controls, with more reports of dryness and itching. DED signs were also more abnormal with lower tear breakup time and higher percentage of goblet cell number noted [246,251]. Polycystic ovary syndrome patients also typically have elevated levels of luteinizing hormone (which may decrease androgen receptor and 5 alpha-reductase levels [254]), decreased insulin sensitivity (they are at risk for developing Type 2 diabetes [255]), and a heightened response to luteinizing hormone-releasing hormone (which may induce increased aldosterone secretion [256]). All of these factors may impact the ocular surface and the development of DED [160]. More studies are needed to examine the relationship between polycystic ovary syndrome and DED, taking account variable manifestations and hormonal findings in individuals with polycystic ovary syndrome.

4.4.2.2. Complete androgen insensitivity syndrome. Complete androgen insensitivity syndrome induces female phenotype in 46, XY individuals due to mutations in the androgen receptor gene. Complete androgen insensitivity syndrome has been linked to DED in several studies [257,258]. A study that compared 9 individuals with complete androgen insensitivity syndrome to 10 age-matched women found that 78% of individuals with complete androgen insensitivity syndrome complained of DED symptoms compared with 14% of controls. In addition, individuals with complete androgen insensitivity syndrome had a higher frequency of tear meniscus abnormalities and meibomian gland dysfunction based on slit-lamp observations of lid keratinization, meibomian gland metaplasia, and secretion viscosity [258]. It is likely that these findings are driven by androgen receptor impairment, given that treatment of individuals with anti-androgens results in analogous sequelae [259]. DED may also be exacerbated by the estrogen supplementation that is prescribed to ensure the development of secondary sexual characteristics and bone mass development [257,258], given that estrogen administration is a risk factor for DED [231].

4.4.2.3. Graft-versus-host disease and Stevens-Johnson syndrome. Sexual issues are also addressed in the literature in specific conditions associated with DED, such as Sjögren syndrome, graft-versus-host disease, and Stevens-Johnson syndrome but not in DED in general [260–263]. Stevens-Johnson syndrome is a condition which results from an adverse effect of a drug or infection, where an inflammatory detachment of epidermis and mucosa is followed by fibrotic scar. Stevens-Johnson syndrome causes DED, ocular surface damage, and genital scars [263]. Although the association of DED and sexual issues in Stevens-Johnson syndrome has never been investigated, the concomitance of those problems in Stevens-Johnson syndrome is likely common and caused by the anatomical sequelae of the mucocutaneous fibrosis.

4.4.2.4. Sjögren syndrome. Sjögren syndrome is an immune disorder closely linked to aqueous deficient DED. Sjögren syndrome has been noted to negatively impact sexual activity. An Italian study of 24 females with Sjögren syndrome and 24 healthy controls found that sexual satisfaction (via questionnaire) was lower in both pre and post-menopausal women with Sjögren syndrome, with significant differences in the frequency of dyspareunia, lubrication, desire, and arousal between the groups. Older age and anxiety, but not gynecological changes (anatomy, cellular alterations on swabs and Pap smear) were also contributing factors [261]. A study conducted in Turkey, with 68 women with primary Sjögren syndrome and 135 controls, confirmed these observations, including an adverse impact of aging, menopause, and anxiety on sexual satisfaction, but also observed a higher frequency of genital atrophy in primary Sjögren syndrome compared to controls. In fact, clinically confirmed vaginal dryness and genital atrophy were inversely correlated with Female Sexual Function Index scores, indicating that this anatomic factor was related to sexual dysfunction in primary Sjögren syndrome [264]. The relationship of vaginal and eye dryness has also been examined in a study of 199 women with Sjögren syndrome living in the Netherlands. Vaginal dryness was found to be correlated with oral and ocular dryness, as rated on a 0–10 numeric rating scale for all three parameters. Vaginal dryness scores also inversely correlated with unstimulated whole salivary flow (mL/min) and positively with peripheral neuropathy identified by the Sjögren syndrome disease damage index, suggesting that dryness and neuropathy may underlie the noted associations [234]. Low androgen levels may underlie the noted associations between Sjögren syndrome, sexual activity, and aspects of DED [265]. Low androgen levels in women may also be associated with reduced sexual desire [266].

4.4.2.5. Hematopoietic stem cell transplantation. Hematopoietic stem cell transplantation has also been associated with gynecological issues, including hemorrhagic episodes and premature ovarian failure. Graft-versus-host-disease, a common complication of hematopoietic stem cell transplantation, is a known cause of skin and mucosal dryness (including ocular surface dryness) and introital stenosis [105,264,267]. The causes are multiple and include total body irradiation, chemotherapy, and graft-versus-host-disease in the genital organs. A study conducted in Seattle, with 161 individuals who underwent hematopoietic stem cell transplantation compared to controls, revealed that sexual activity declined differently between women and men and recovered differently after hematopoietic stem cell transplantation. After 5 years, sexual dysfunction was self-reported by 80% of females and 46% of males after hematopoietic stem cell transplantation, and 21% of controls [268]. A literature review comprising articles from 1982 to 2014 reported that genital graft-versus-host-disease can cause sclerotic changes in the genital organs of women that may seriously affect sexual function. The review recommended routine gynecological consultation even in asymptomatic women who have undergone hematopoietic stem cell transplantation, to allow early diagnosis and preventive therapy as needed [105]. Despite both ocular graft-versus-host-disease and DED being very common after hematopoietic stem cell transplantation, further clinical studies need to be undertaken to better examine the nature of this association.

4.4.3. Relevance of sexual issues to dry eye disease

The sexual issues mentioned above, in diseases commonly associated with DED, are frequent, and relevant for patient quality of life. As a result, recent guidance has been published, noting that attention should be given to preventive and therapeutic approaches for gynecological, obstetric, and sexual issues in Sjögren syndrome, Stevens-Johnson syndrome and graft-versus-host-disease [263,269,270].

Mucous tissue dryness affects sexual activity itself, fertility, and obstetric outcomes. However, the sexual issues associated with DED are likely not limited to gynecological problems attributed to sexual hormone imbalances, as inferred by the complex mechanisms associated with polycystic ovary syndrome, endometriosis, menopause, and refractory genital infections, including herpes simplex virus and others, which could affect the genital organs and also the ocular surface throughout systemic and inflammatory pathways [160,271,272]. The mechanisms of female and male sexual dysfunctions and their potential associations with DED mechanisms deserve more in-depth investigation (Table 3).

4.4.4. Future directions and gaps

Future studies are needed to advance the understanding of the relationships between sexual issues, aspects of DED, and other ocular surface diseases on epidemiological, functional, neural, immune, and psychosocial levels. This effort will help clarify common mechanisms, develop better diagnostic tools, and identify novel potential preventive and therapeutic strategies for these frequent and oftentimes under-recognized conditions.

4.5. Pregnancy

4.5.1. What is pregnancy?

Pregnancy is the condition between conception (fertilization of an egg by a sperm) and birth, during which a fertilized egg develops in the uterus. In humans, pregnancy lasts about 288 days and is split into 3 trimesters (first, second, and third).

4.5.2. Pregnancy and the ocular surface

A controversial issue in the medical literature is the association between pregnancy and ocular surface disorders, including DED. A longitudinal study conducted in Nigeria with 134 pregnant women reported that DED symptoms and signs worsened in the third trimester of pregnancy and recovered 6 weeks after delivery [278]. Using thresholds of >10 mm on the Schirmer test, >10 s for tear breakup time, and >13 on the Ocular Surface Disease Index, the frequency of DED in pregnant women was as high as 78% [278]. Using a similar diagnostic criteria (Ocular Surface Disease Index score of ≥13 and either tear breakup time <10 s or Oxford staining ≥3), a cross-sectional study conducted in Ghana also found that the frequency of DED was associated with increasing gestational age [273]. In this study, the overall prevalence of DED among pregnant women was 41% (from n = 201 pregnant women).

Applying a Schirmer test threshold of 5 mm, prolactin and testosterone levels and parity number were not found to influence tear production [278]. This link has been examined in pregnant women with gestational diabetes mellitus. One study compared 46 women with diabetes mellitus to 36 controls and found similar mean levels of tear flow, tear breakup time, tear film osmolarity, and Ocular Surface Disease Index scores, thus concluding that diabetes mellitus did not adversely affect the tear film or ocular surface during pregnancy [279].

The association between parity and gravidity (the number of times a woman has been pregnant and delivered a baby, respectively) were investigated in relationship to DED in a few studies [264,270]. The supporting hypothesis for examining this link is that frequent hormonal

Table 3
Medical conditions associated with sexual issues and dry eye or ocular surface diseases, where both conditions can interfere with lifestyle, and the relationships between the sexual issues and ocular surface problems are not well understood.

Medical condition	Sexual issues	DED and ocular surface disease	References
Genetic conditions			
Complete Androgen Insensitivity Syndrome	Infertility and hormonetherapy	Meibomian gland dysfunction	[258]
Mirage Syndrome	Hypovirilization, genital problems	Lacrimal gland hypoplasia and cornea anesthesia	[271]
Gynecological and Obstetric conditions			
Polycystic Ovary Syndrome	Infertility and hyperandrogenism	DED signs and symptoms	[253]
Pregnancy	Metabolic and hormonal changes	DED signs and symptoms	[273]
Refractory and chronic genital infections	Herpes simplex virus genital diseases	Ocular surface scar and corneal anesthesia	[272,274]
Psychological conditions			
Depression	Sexual dysfunction and side effects of antidepressants	DED (See section 3 of this chapter for details).	[29,275,275]
Post-traumatic stress disorder	Sexual dysfunction	DED	[29,276]
Systemic conditions and therapies			
Hematopoietic stem cell transplantation	Infertility and mucosal dryness	Ocular surface scar, neovascularization and DED	[277]
Sjögren syndrome	Dyspareunia, mucosal dryness and genital atrophy	DED	[234]
Stevens-Johnson syndrome	Mucocutaneous inflammation and fibrosis	Ocular surface scar, neovascularization and DED	No reported associations

DED = Dry eye disease

changes and the traffic of cells between the fetus and mother (microchimerism), potentially inducing autoimmunity (such as Sjögren syndrome) may lead to DED [280]. However, number of pregnancies and microchimerism were not found to be associated with DED or with Sjögren syndrome [264,273,280].

Assisted reproductive technology for infertile couples uses hormone modulation to attempt a pregnancy. One study found that of 117 women who underwent assisted reproduction (32 underwent childbirth), the number with a Schirmer test of <10 mm in at least one eye significantly increased at the third trimester ($p = 0.02$) and three months post-partum ($p = 0.04$), whereas in the rest of the phases, tear production levels were comparable to baseline ($p > 0.05$) [281]. Comparative and more detailed studies are necessary to determine whether pregnancy via assisted reproductive technology impacts tear parameters in a different manner from naturally-occurring pregnancy.

Many factors including lifestyle parameters, weight change, comorbid diseases, and environmental exposure may impact DED symptoms and signs during preganancy [279,282–284]. Exposure to environmental contaminants at work have been investigated in relationship to pregnancy [285]. A study of 200 pregnant women in China found that women with gestational diabetes mellitus had higher blood levels of phthalate compared to women without diabetes [286], similar studies are needed to examine environmental factors that may increase the risk of DED during pregnancy.

Conventional therapy with artificial tears has been reported as safe in pregnancy, as observed in a study of 4808 individuals, where 936 received sodium hyaluronate 0.1% and rates of congenital abnormalities were 14.9% versus 12.3% in the unexposed women. Similar results were observed in the diquafosol and 0.3% sodium hyaluronate groups [282]. Other therapeutic approaches, including systemic medications for DED and adjuvant inflammatory diseases, may present concern during pregnancy.

In conclusion, studies examining the relationships between pregnancy, number of deliveries, and supporting therapies for DED exhibit a lack of uniformity in their definition and classification of DED. In general, DED clinical parameters have been found to worsen with advanced pregnancy [273], but there are no reports of permanent damage, and artifical tear therapy has been demonstrated to be safe for mother and baby [282,287].

4.6. Chronic pain

4.6.1. What is chronic pain?

Pain is defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage". When pain persists or recurs for longer than three months, despite successful management of the condition that initially caused it, or because the underlying medical condition cannot be treated successfully, it is defined as chronic. In these cases, pain can become the prevalent or sole clinical problem [288–290]. Chronic pain conditions are common in the general population, with estimates that 20% of adults are affected [291–295]. Robust evidence suggests that chronic pain disorders are associated with aspects of DED. On a pathophysiological basis, chronic pain and DED symptoms share a number of similarities [296].

Evidence from observational studies on the relationship between chronic pain and DED are discussed herein, and section 4.6.6 presents findings from a systematic review and meta-analysis examining associations between chronic primary pain disorders and DED [16].

A survey conducted on a large population of US veterans (n = 3,265,894) demonstrated that DED (defined using International Classification of Diseases, Edition 9 codes) is comorbid with a number of chronic pain conditions, including headache, migraine, temporomandibular joint dysfunction, central pain syndrome, fibromyalgia, osteoarthritis and post-herpetic neuralgia [297]. Patients with traumatic brain injury also had been found to have a higher frequency of DED, both when considering tear film insufficiency and pain categories (again assessed via International Classification of Diseases-9 codes) [59].

Similar findings were detected in a cross-sectional study performed in the Netherlands on 425 patients with DED (diagnosed based on Ocular Surface Disease Index and various signs) with 17% of DED patients having at least one chronic pain syndrome (for example, fibromyalgia, chronic pelvic pain, irritable bowel syndrome), assessed by questionnaire. The presence of chronic pain syndromes was associated with increased DED symptom severity (on all Ocular Surface Disease Index domains, with 10 items being statistically higher in the pain group) but not with DED sign severity. Specifically, patients with chronic pain symptoms had significantly less corneal staining and higher Schirmer scores than their counterparts without pain [298].

4.6.2. Fibromyalgia and DED

A large Dutch cross-sectional study, with 79,866 participants, identified fibromyalgia to be associated with DED [31]. In this study DED was diagnosed symptomatically via questionnaire and noted as present in 9.1% of the cohort. This association was also found in a population-based UK female twin study of more than 3000 participants, where fibromyalgia was among one of the strongest risk factors for DED [299].

A Taiwanese database study also identified fibromyalgia as being related to DED (via International Classification of Diseases-9 codes), In this study, 25,777 individuals had fibromyalgia and 103,108 were

controls. The overall incidence of DED was 7.37/10,000 and 4.81/10,000 in the two groups, respectively. Both male and female patients with fibromyalgia had a higher incidence of DED compared to controls, with a 1.39-fold increased odds for males and a 1.45-fold increased odds for females to have DED, after adjustment for confounding factors. Age younger than 50 and psychiatric comorbidities also influenced this relationship [300]. Other, smaller studies measured DED signs in individuals with and without fibromyalgia. Specifically, a case control study, which enrolled 34 individuals with fibromyalgia and 42 controls, reported higher Ocular Surface Disease Index scores and lower tear breakup times in individuals with, compared to without, fibromyalgia [301].

Overall, these studies suggest that fibromyalgia is associated more with DED symptoms than with signs. Future larger case control studies are needed to test if relevant DED clinical measures, such as Schirmer test are reduced in fibromyalgia patients.

Mechanisms linking DED symptoms and signs to fibromyalgia are under scrutiny. One possible link is via corneal sensitivity, as individuals with fibromyalgia have been found to have increased corneal sensitivity, compared to controls, even in the absence of DED signs. In a case control study, which enrolled 36 individuals with fibromyalgia, corneal sensitivity was measured with the Cochet Bonnet aesthesiometer. The authors detected increased corneal sensitivity at multiple corneal locations, and found that corneal sensitivity was correlated with Ocular Surface Disease Index score ($r = 0.44$, $p = 0.007$, for central corneal sensitivity) [302].

4.6.3. Migraine and DED

Several population-based studies have shown strong significant associations between DED and migraine [31,176,299,303]. Migraine has been associated with DED symptoms more so than with signs. However, limitations of prior studies include reliance on self-reporting and on International Classification of Diseases coding to diagnose migraine. Most clinical studies assessed a combination of DED symptoms and signs [304–306]. As an example, in a Turkish study, 50 individuals with migraine were compared to 50 controls. Individuals with migraine had more DED symptoms via Ocular Surface Disease Index than those without (45.21 versus 26.59 respectively, $p = 0.001$). While DED signs were different between the groups, the means of both groups were close to normal limits (Schirmer test score 14.39 versus 21.63 mm wetting, $p = 0.001$; tear breakup time 9.54 versus 14.96 s, $p = 0.001$) [286].

The treatment of migraine may also influence DED presentation. For instance, botulinum toxin is an approved treatment for chronic migraine. Individuals receiving botulinum toxin for chronic migraines noted improvements in photosensitivity and DED symptoms (in those with baseline symptoms), that were independent of baseline tear volume (5-item Dry Eye Questionnaire scores decreased from 15.4 to 13.8 (95% CI 3.02 to −0.19) in individuals with baseline 5-item Dry Eye Questionnaire score $\geq$12). While the exact mechanism for this effect remains unclear, the authors postulated that modulation of trigeminal neural pathways may be involved [307].

Overall, existing literature suggests that migraine may be associated with aspects of DED. However, heterogeneity across studies, which is a consequence of multiple approaches used to diagnose DED and migraine, demands the conduct of additional and larger studies to consolidate this finding.

4.6.4. Chronic pain syndrome (CPS) and DED

DED and chronic widespread pain syndrome are closely related. Specifically, a population-based study on 1635 female UK twins found that elevated general pain sensitivity and reduced pain tolerance, was associated with DED. Patients were considered affected with DED if they had a prior DED diagnosis made by a physician, or they had been prescribed artificial tears, or they had symptoms of DED. A subset of patients was also administered the Ocular Surface Disease Index. Finally, pain sensitivity to heat was measured at the level of the forearm [308].

A cross-sectional study on 181 patients with DED symptoms, ocular, and non-ocular pain (quantified vis questionnaires) found that individuals with higher neuropathic ocular pain scores had more severe chronic pain disorders. For instance, 20% of individuals with high ocular pain scores, but only 7% of those with limited ocular symptoms, presented with a central pain syndrome [72].

A twins study performed on 8,564, predominantly female, twins suggests that genetic factors may underlie the link between CPS and DED [309]. Based on differences in pairwise phenotypic correlations between chronic pain syndromes in monozygotic versus dizygotic twin pairs, this study found evidence that shared genetic factors underlie the clustering of chronic widespread pain, pelvic pain, irritable bowel syndrome and DED in individuals.

Chronic pain is also a common feature in Sjögren syndrome, specifically ocular pain with neuropathic features [310]. In a case control study that enrolled 108 individuals with primary Sjögren syndrome, chronic pain was identified in patients both with seropositive and seronegative Sjögren syndrome (65% and 75% of cases, respectively).

4.6.5. Mechanisms

Development of neuropathic pain within the trigeminal somatosensory system may underlie the link between chronic pain conditions and DED (Fig. 3).

4.6.5.1. Peripheral sensitization. Corneal nerve terminals are constantly exposed to the outside environment and therefore prone to damage. Extensive and/or repeated injury to corneal nociceptors can result in profound rearrangement of the nociceptor physiology, which is associated with maladaptive neuroplasticity, hypersensitivity, ultimately leading to neuropathic pain [311].

Such a complex process is subtended by a number of biological modifications, including altered ion channel expression/functioning, hyperexcitability, and participation of nearby nociceptors beyond those that are injured. Proinflammatory mediators, abundantly released after tissue damage, contribute significantly to peripheral sensitization and pain generation [311–314].

Cold thermoreceptors, which are abundantly distributed on the ocular surface, constantly monitor corneal wetness. They are thought to develop maladaptive responses as those described above in case of chronic overstimulation in DED, which seems to be at least in part responsible for DED symptoms [315].

4.6.5.2. Central sensitization. Central sensitization generally follows prolonged damage to peripheral nerve terminals, which is associated with persistent inflammation. This is followed by a deep rearrangement of neural pathways in the central nervous system. Principal biological mechanisms parallel those acting in peripheral sensitization (described above), but their prolonged activation results in generation of pain even without peripheral stimulation and/or after peripheral injury has resolved. Such a disconnect between pain sensation and the peripheral stimuli could provide a common rationale for comorbidity of ocular and systemic chronic pain [311,316–321]. Interestingly, recent evidence suggests that selective injury to corneal nerves results in pro-inflammatory cytokine expression in the trigeminal ganglion, where corneal nerves originate [322]. This hypothesis is further corroborated by the observation that direct damage to the central nervous system can initiate chronic pain (for example, in traumatic brain injury) [318,323].

Central sensitization of trigeminal neurons has been demonstrated in animal models of DED [324]. Moreover, substance P, a mediator of pain for both acute and chronic pain, has been demonstrated to control ocular surface pain and inflammation in pre-clinical models [314,325]. Clinically, C-reactive protein, a specific biomarker of systemic inflammation, has been associated with increased evoked cold-pain sensitivity [326].

Vitamin D deficiency may also play a role in DED symptoms, namely ocular pain, as deficiency has been associated with altered corneal nerve

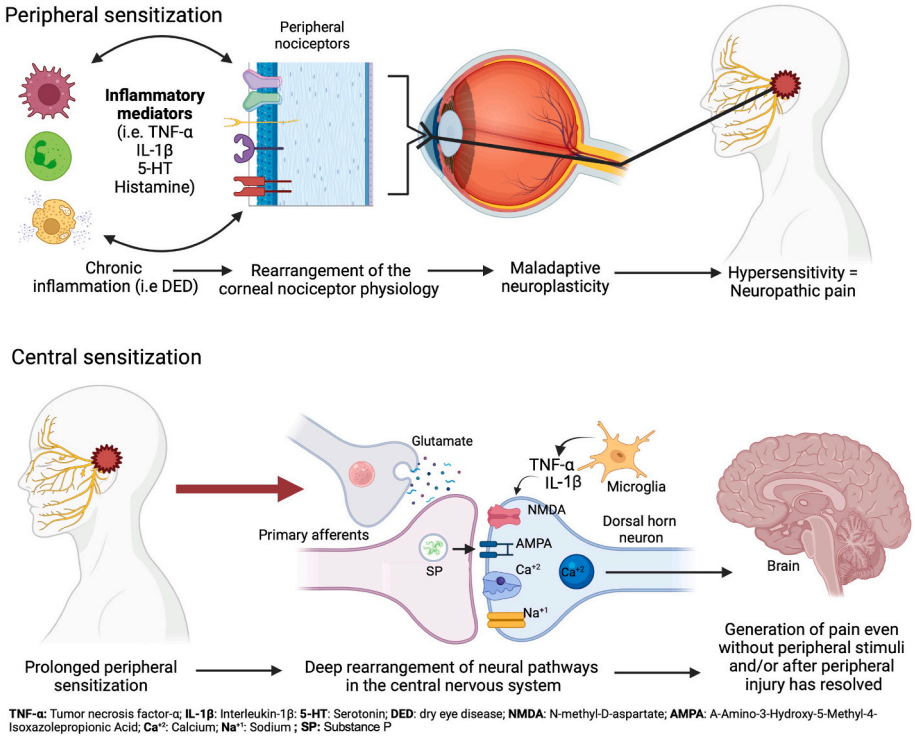

Fig. 3. Mechanisms that underlie peripheral and central sensitization and that may contribute to the development of ocular surface discomfort.

morphology, recruitment of dendritic cells and pain in chronic DED, suggesting a role for vitamin imbalance in the generation of pain [327].

Overall, the existing literature supports the existence of link between chronic pain conditions and aspects of DED, with a stronger connection between pain and DED symptoms. However, substantial heterogeneity in study design, methodology, and populations suggests that additional studies are needed. It is recommended that in future studies, DED is examined by quantification of multiple symptoms and signs, so that aqueous deficient vs evaporative DED diagnoses can be examined. In addition, standardization of pain measurement systems, following suggestions of the International Association for the Study of Pain, would significantly add to the quality of prospective studies.

4.6.6. Association between chronic primary pain disorders and dry eye disease: a systematic review and meta-analysis

4.6.6.1. Introduction. The relevance of pain and neurosensory abnormalities has been acknowledged in the updated definition of DED published in TFOS DEWS II [3]. While ocular pain and nerve abnormalities have been extensively reported, the nature of the association between systemic pain and DED is not clear.

As reviewed above, several studies have reported that DED is associated with systemic chronic pain disorders, including migraine [328], fibromyalgia [329,330] and irritable bowel syndrome [331,332], suggesting that these conditions could share similar neuropathic mechanisms with DED. Increased pain sensitivity may impact the frequency of reporting of symptoms of DED. However, the extent to which systemic pain conditions are associated with DED has not been thoroughly evaluated. It was therefore deemed valuable to investigate the clinical evidence, using systematic review methodology and meta-analysis, to address the question: *Are chronic primary pain disorders associated with dry eye disease?* in order to shed light on the relationship between DED and pain conditions outside the eye.

The objective of this systematic review was to comprehensively identify, appraise, and synthesize studies evaluating DED in individuals with chronic primary pain disorders.

4.6.6.2. Methods. This systematic review was reported in accordance with the PRISMA 2 guidelines [333]. The protocol was prospectively registered on PROSPERO (CRD42021296994).

4.6.6.2.1. Study eligibility criteria

4.6.6.2.1.1. Study design

Published systematic reviews and observational studies, including case-control, cohort, cross-sectional, and epidemiology studies, were eligible for inclusion. Both retrospective and prospective studies were included. Only studies in English were included. We excluded conference abstracts, case reports, case series, preclinical studies, and non-systematic reviews.

4.6.6.2.1.2. Participants

Studies evaluating DED in adults (aged 18 years and over) with primary pain disorders, compared to a control population from within the same study, were eligible for inclusion.

Primary pain disorders were defined as pain in one or more anatomical regions that persists or recurs for longer than 3 months and the symptoms are not better accounted for by another diagnosis [334]. We accepted studies that assessed pain disorders using an objective diagnostic criterion, by a clinician, using International Classification of Diseases codes from clinical records, or self-reported by the participant.

Individual pain conditions according to the International Association for the Study of Pain classification of chronic pain for International Classification of Diseases-11 [334] were considered, including chronic widespread pain, complex regional pain syndrome, chronic primary headache or orofacial pain, chronic primary visceral pain, and chronic primary musculoskeletal pain. We excluded populations with secondary pain due to another cause (e.g., diabetic neuropathy, post-surgical or post-traumatic pain).

4.6.6.2.1.3. DED diagnosis

Studies that diagnosed DED from clinical symptoms and/or signs, participants' self-reported diagnosis, or using International Classification of Diseases codes from clinical records, were included.

4.6.6.2.1.4. Outcome measures

The outcome for this review was the odds of DED, expressed as an OR with 95% CIs.

4.6.6.2.2. Search methods for identification of studies. Ovid Medline and Ovid Embase were searched from inception to 9 December 2021, with no date or language restrictions (Search strategy provided in Appendix A). Reference lists of the included articles were additionally searched to identify potentially relevant studies.

4.6.6.2.3. Study screening. Each study was independently screened by two of the three review authors (ACBJ, MW, GF), using a two-step process, in Covidence. Both reviewers screened titles and abstracts of all articles identified from the searches and identified articles that were eligible or potentially eligible for inclusion. Full text reports were then retrieved and classified as 'include' or 'exclude'. For all articles excluded at the full text screening stage, the reason(s) for exclusion were recorded. Any disagreements between reviewers regarding the potential eligibility of studies were resolved by discussion and consensus.

4.6.6.2.4. Data extraction. Data extraction was performed independently by two reviewers (ACBJ and MTMW). Disagreements were resolved by discussion and consensus. The following data were extracted: article details; study date and setting; study methods (design and recruitment); numbers and characteristics of participants within each study group (age, gender, comorbidities); pain condition(s) and assessment method(s); DED assessment(s) and diagnostic criteria; sources of funding; and conflicts of interest.

We also extracted outcome data as the number of cases of DED in each study group and OR for DED. Outcome data were extracted from the included articles. Where possible, adjusted ORs were extracted to minimize the potential impact of confounding [335]. Study authors were not contacted for further information.

4.6.6.2.5. Risk of bias assessment. Risk of bias assessments were performed independently by two reviewers (ACBJ and MTMW), who were blinded to each other's decisions. The assessments were performed using the AMSTAR-2 tool for systematic reviews and the Newcastle-Ottawa scale (case-report studies) for observational studies. AMSTAR-2 comprises 16 domains [336], including seven that are considered to critically affect the validity of a review and its conclusions. This Newcastle-Ottawa scale considers study quality across three domains: selection, comparability, and outcomes [337]. The maximum score is nine stars. Disagreements were resolved by discussion and consensus.

4.6.6.2.6. Data synthesis. Statistical analysis was performed using R Project for Statistical Computing (R Foundation, Vienna, Austria) [338].

4.6.6.2.6.1. Meta-analysis

Where there were at least three studies with outcome data for the same primary pain disorder, study results were combined in a meta-analysis and ORs and 95% CIs, for the association between DED and the pain disorder, calculated. The unit of analysis was the participant. As not all studies reported data on the number of DED cases in each study group, pre-calculated binary effect sizes were pooled by log transforming ORs and their 95% CIs. A random-effects inverse variance model was used. Where pre-calculated ORs were not available, dichotomous data on the number of cases of DED within each study group was converted to ORs and included in the synthesis.

4.6.6.2.6.2. Assessment of heterogeneity

Clinical and methodological heterogeneity were assessed by examining differences in the participant characteristics and the criteria used within individual studies to define DED. Only data from the same pain conditions were pooled. Statistical heterogeneity between studies was examined by inspecting the forest plots and using the I^2 and τ^2 statistics. Both the magnitude and direction of the effects of individual studies, and the strength of evidence for heterogeneity, were considered in assessing heterogeneity. An I^2 statistic of 60% or more was considered to be consistent with a moderate level of statistical heterogeneity [335].

If there was considerable heterogeneity but the effect estimates from individual studies were in the same direction, data were pooled. A prediction interval is presented where there were more than ten studies included in the meta-analysis [335]. Otherwise, a descriptive results summary is provided.

4.6.6.2.6.3. Sensitivity analysis

If there was significant heterogeneity (>60%), sensitivity analyses evaluating treatment effect were performed by limiting eligibility criteria based on the method of DED diagnosis by excluding studies that did not diagnose DED using clinical signs or symptoms (i.e., excluding studies where DED was diagnosed by self-reporting or retrospectively records/disease coding). Sensitivity analysis was performed if there were at least three studies included in the synthesis.

4.6.6.2.6.4. Subgroup analysis

It had been intended to perform subgroup analyses by DED subtype (aqueous deficient or evaporative) if sufficient data were available; however, an insufficient number of studies reported data on DED subtypes.

4.6.6.2.6.5. Reporting bias

If at least 10 studies were included in a meta-analysis, a funnel plot was used to assess for any potential publication bias. Funnel plots were assessed for asymmetry by visual inspection.

4.6.6.2.7. Certainty of the evidence. The certainty of the body of evidence for each synthesis was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach [339]. The reason(s) for the certainty estimates are reported in Supplementary Table S1.

4.6.6.3. Results

4.6.6.3.1. Description of studies. The electronic searches yielded 1570 records (Fig. 4). After removing duplicates, review authors independently screened 1417 studies, of which 23 studies were eligible for inclusion.

One systematic review and 22 observational studies were included, comprising 16 prospective cross-sectional studies, two retrospective case-control studies, and three retrospective chart reviews. Study characteristics are described in Table 4. Excluded studies and their main reason for exclusion are shown in Supplementary Table S2. Sources of funding for included studies are summarized in Table S3.

4.6.6.3.1.1. Populations

Study sample sizes ranged from 38 to 3,265,894 people. Most studies

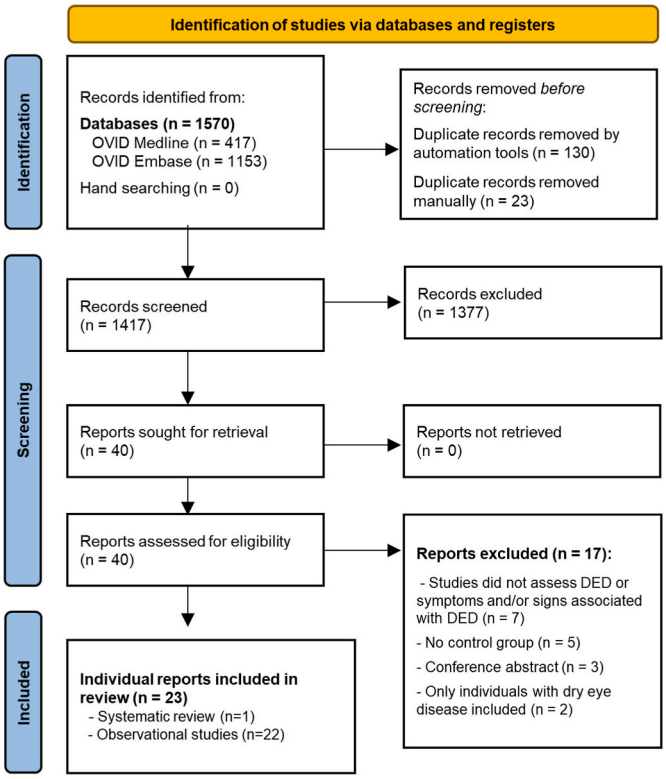

Fig. 4. PRISMA Study flow chart. Abbreviations: DED, dry eye disease.

Table 4
Characteristics of studies included in the systematic review exploring the relationship between DED and pain conditions outside the eye.

Study, Author year	Study design	Country	Population	Pain condition diagnostic criteria	DED diagnostic criteria	DED outcomes assessed
Multiple pain conditions						
Chang 2018 [71]	Prospective cross-sectional study	USA	n = 233 recruited (mean age 46.3 + 13; 68% female), including pain conditions: Migraine (n = 37); Fibromyalgia (n = 2); Back pain (n = 56); Muscle Pain (n = 35); Headaches (n = 55); Tendonitis (n = 12); Trigeminal neuralgia (n = 1); TMJ pain (n = 6).	Self-reported and classified using classification proposed by Yunus [340]	DEQ-5≥6	DEQ-5
Lee 2017 [297]	Retrospective chart review	USA	Charts from n = 3,265,894 (mean age 69.4 + 12.9; 59% female), including pain conditions: Migraine (n = 232,946); Fibromyalgia/ muscle pain (n = 299,627); IBS (n = 101,341); Back pain (n = 1,675,818); Chronic pain or syndrome (n = 317,497); Central pain syndrome (n = 1701); Tension headache (n = 53,989); TMJ dysfunction (n = 77,478); abdominal pain (n = 806,859); pelvic pain (n = 48,287).	ICD-9 coding in database	ICD-9 code for sicca syndrome, keratoconjunctivitis sicca, tear film insufficiency, visual discomfort, or pain in or around the eye	None
Vehof 2014 [299]	Prospective cross-sectional study	UK	n = 3824 females (age not specified), including pain conditions: Migraine (n = 883); IBS (n = 765); Chronic widespread pain syndrome (n = 294); Pelvic pain (n = 547). DED diagnosis data were reported in n = 3538.	Self-reported medical history	Self-reported diagnosis of DED	Self-reported diagnosis of DED, and DED symptoms was assessed with a separate symptom question.
Vehof 2021 [31]	Prospective Cross-sectional survey as part of a cohort study	Netherlands	n = 79,866 people (mean age 50.4, range 20–94; 59% female), with reported pain conditions: Migraine (n = 15,865); IBS (n = 9042); Fibromyalgia (n = 3402); Back pain (n = 1650).	IBS diagnosed using ROME III; fibromyalgia, back pain, migraine were self-reported	Women's Health Study dry eye questionnaire, of self-reported dryness and irritation	Women's Health Study dry eye questionnaire
Migraine						
Celikbilek 2015 [341]	Prospective cross-sectional study	Turkey	n = 99 people recruited, including n = 58 with migraine (mean age 29.4 + 6.1 years; 95% female) and 41 controls (mean age 28.3 + 7 years; 93% female)	Diagnosis was made according to International Classification of Headache Disorders II diagnostic criteria	At least 2 of 3 of: Schirmer test value < 10 mm/5 min, TBUT shorter than 10s, and OSDI value higher than 33	OSDI; Schirmer test, TBUT; tear meniscus height, depth, and area; Meibography
Ismail 2019 [176]	Retrospective case-control study	USA	Total population: n = 72,969 patient records (age not reported), of which 5352 had migraine (79% female) and n = 67,617 without (56% female). Study subgroup excluding confounders (use of specific medications, a history of rheumatoid arthritis, Sjögren disease, or lupus, and a history of cata- ract or refractive surgery): n = 39,306 (n = 1013 with migraine)	ICD-9 and ICD-10 coding of migraine on database	ICD-9 and ICD-10 coding of dry eye disease	None
Koktekir 2012 [306]	Prospective cross-sectional study	Turkey	n = 66 people recruited, including n = 33 with migraine (mean age 31.15 + 10.62; 79% female) and n = 33 without (mean age 36.63 + 9.94; 67% female)	Clinician diagnosed	NA (intergroup comparison)	OSDI; Schirmer (with anesthesia); TBUT (NaFl); conjunctival LG staining
Kostev 2020 [342]	Retrospective case-control study (letter to the editor)	Germany	n = 87,354 on IQVIA database (mean age 42.3 + 15.9), including n = 43,677 with migraine and n = 43,677	People with an ICD-10 code of migraine on database	ICD-10 coding of dry eye disease	None

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Table 4 (*continued*)

Study, Author year	Study design	Country	Population	Pain condition diagnostic criteria	DED diagnostic criteria	DED outcomes assessed
			without (25% female in each group; age not specified)			
Paulsen 2014 [343]	Prospective cross-sectional examination of Beaver Dam Offspring (cohort) Study	USA	n = 3275 participants (mean age 49, range: 21–84), including migraine (number in each group not reported)	Self-reported questionnaire of medical history	Symptoms using a 4-item questionnaire	4-item symptom questionnaire
Sarac 2017 [304]	Prospective cross-sectional study	Turkey	n = 96 people, including n = 46 migraine (mean age 34.43 + 8.39; 80% female) and n = 50 controls (mean age 32.6 + 7.1; 80% female)	Not reported	NA (intergroup comparison)	OSDI; Schirmer (without anesthesia); TBUT (NaFl); corneal NaFl grading
Shetty 2017 [344]	Prospective cross-sectional study	India	n = 60 people, including n = 30 migraine (mean age 24.93 + 4.54; 63% female) and n = 30 without (mean age 26.8 + 6.16 male; 73% female)	Clinician diagnosed according to International classification of headache disorders criteria	NA (intergroup comparison)	Schirmer (without anesthesia); TBUT (NaFl); lipid interferometer (Lipiview)
Wang 2012 [67]	Retrospective review of health care database	Taiwan	n = 48,028 charts reviewed (overall mean age 52.4 + 17.5; 73% female), including n = 1301 with migraine and n = 46,727 without	Comorbidity recorded in medical record, classified using the Elixhauser comorbidity index	ICD-9 coding of tear film insufficiency	None
Wang 2020 [345]	Prospective cross-sectional study	New Zealand	n = 372 community residents recruited (mean age 39 + 22; 60% female), including n = 33 with migraine and n = 339 without (gender and age not reported)	Self-reported medical history	Clinical examination and using TFOS DEWS II criteria for dry eye disease	OSDI; DEQ-5; NIBUT; tear osmolarity; lipid layer grade; tear meniscus height; corneal staining; conjunctival staining; lid margin staining; meibography
Yang 2017 [303]	Cross-sectional survey	Korea	n = 14329 recruited, including n = 3473 migraine (mean age 43.4 ± 41.68; 28% female) and n = 10,856 without migraine (mean age 45 ± 31.26; 20% female)	Self-reported questionnaire	Self-reported diagnosis by an ophthalmologist	Self-reported diagnosis. DED symptoms are also assessed with a separate symptom question
Fibromyalgia						
Chen 2016 [300]	Retrospective review of health care records	Taiwan	n = 128,885 records, including n = 25,777 with fibromyalgia (mean age 47.6 + 15.3; 52% female) and 103,108 controls (mean age 47.1 + 15.5; 52% female)	ICD coding on database	ICD-coding	None
Erkan Turan 2018 [301]	Prospective cross-sectional study	Turkey	n = 76 females recruited, including n = 34 with fibromyalgia (mean age 45.1 + 6.8) and n = 42 controls (mean age 42 + 8.5)	ACR 1990 and 2013 criteria	NA	OSDI; TBUT with fluorescein; LG staining; Schirmer I; Corneal mechanical sensitivity; IVCM
Gallar 2009 [329]	Prospective cross-sectional study	Spain	n = 38 recruited, including n = 20 fibromyalgia (mean age 51.9 + 2.3; 90% female) and n = 18 controls (mean age 51.7 + 2.4; 84% female)	Not clear	Symptoms of discomfort or dryness (specific criteria not stated)	4-item Discomfort and ocular dryness questionnaire; Lissamine green staining; Schirmer test
Klitsch 2019 [346]	Prospective cross-sectional study	Germany	n = 194 females recruited, including n = 134 fibromyalgia (mean age 51; range 21–74) and n = 60 controls (mean age 50; range 22–64)	ACR 1990 criteria	Positive Schirmer test >5 mm and OSDI >12 points	OSDI; Schirmer
Türkyilmaz 2013 [347]	Prospective cross-sectional study	Turkey	n = 106 people recruited, including n = 53 fibromyalgia (mean age 43.6 + 7; 74% female) and n = 53 controls (mean age 41.3 + 8.2; 64% female)	ACR 1990 criteria	NA	OSDI; TBUT (NaFl), tear osmolarity, Shirmer (with anesthesia)
Irritable bowel syndrome (IBS)						
Barton 1999 [348]	Prospective cross-sectional study	UK	n = 92 people recruited, including n = 42 with IBS (mean age 44; range 20–79; 83% female) and 46 controls (age and gender not reported)	Rome criteria and ACR classification criteria	Abnormal Schirmer (criteria not specified)	Self-reported symptoms of dry eyes and dry mouth; Schirmer Test; Rose Bengal staining
Asproudis 2016 [331]	Prospective cross-sectional study	Greece	n = 371 recruited, including n = 95 IBS (71% female age 49.8 + 15.36 years and 29%	Rome III criteria	3 out of 6 positive responses in 6-item dry eye questionnaire.	6-item dry eye questionnaire; TBUT (NaFl); Schirmer Test

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Table 4 (*continued*)

Study, Author year	Study design	Country	Population	Pain condition diagnostic criteria	DED diagnostic criteria	DED outcomes assessed
Uçar 2021 [349]	Prospective cross-sectional study	Turkey	male mean age 58.28 + 15.47 years) and n = 276 control (67% female age 51.9 + 16.64 years and 33% male mean age 55.8 + 19.25 years) n = 66 recruited including 29 with IBS (mean age 45.28 ± 10.15, 69% female) and 37 controls (mean age 44.95 ± 9.76, 66% female).	Rome IV criteria	NA	OSDI; TBUT (NaFl); Schirmer test I with anesthetic

Abbreviation: ACR, American College of Rheumatology; IQVIA, IQVIA Holdings, Inc, DED; dry eye disease; DEQ-5, 5-item Dry Eye Questionnaire; IBS, irritable bowel syndrome; ICD, International Classification of Diseases; LG, lissamine green; NA, not applicable; NaFl, sodium fluorescein; OSDI, Ocular Surface Disease Index; TBUT, tear breakup time; TMJ, temporomandibular joint.

included both males and females; the proportion of females ranged from 24% to 94% in these studies (Table 4). One population-based study [299] and two studies on fibromyalgia [301,346] included only females in their study cohort.

Four studies included study cohorts across a range of pain conditions, including migraine [31,71,297,299], fibromyalgia [31,71,297,299], irritable bowel syndrome [31,297,299], back pain [31,71,297,299], as well as temporomandibular joint pain [71,297], pelvic pain [297,299], other types of headaches [71,297], central pain syndrome [297], abdominal pain [297], muscle pain [71] tendonitis [71] and trigeminal neuralgia [71], and general chronic pain or syndrome [297]. Nineteen studies reported data on participant populations in which only one primary pain condition was evaluated, including 11 studies on migraine [67,176,303–306,328,341–343,345], five on fibromyalgia [300,301,329,346,347], and three on irritable bowel syndrome [331,348,349].

Eleven of the 23 included studies included information on other comorbidities in the study population [31,67,71,176,297,299,303,342,343,345,347], and six studies included data on concomitant medications [176,297,301,343,346,347].

4.6.6.3.1.2. DED assessments

Eleven of the 22 observational studies assessed DED using symptoms and signs [301,304,306,329,331,341,345–349]; five evaluated only DED symptoms [31,71,299,303,343], one evaluated only DED signs [344], and five used International Classification of Diseases coding from clinical records or databases (Table 4) [67,176,297,300,342]. Of the studies that evaluated symptoms of DED, eight used the Ocular Surface Disease Index and two used the 5-item Dry Eye Questionnaire. Only one study evaluated DED using the 2017 TFOS DEWS II criteria [345], using both symptoms and signs.

4.6.6.3.2. Risk of bias. Fig. 5 summarizes the risk of bias

A

	Research question and inclusion criteria	Methods established a priori	Selection of study design	Comprehensive literature search	Study selection	Data extraction	List of excluded studies	Included studies	ROB assessments	Sources of funding	Meta-analysis methods	ROB considered in meta-analysis	ROB in interpretation of results	Assessment of heterogeneity	Publication bias	Conflict of interest
Chen 2021	−	−	+	?	−	+	−	?	−	−	+	−	−	+	+	+

B

	Study	SELECTION				COMPARABILITY	OUTCOME			Total score (out of 9)
		Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cohorts	Ascertainment of outcome	Same method of ascertainment for cases and controls	Non-Response rate	
Multiple pain conditions	Chang 2018		★	★	★	★	★	★	★	7
	Lee 2017		★			★★	★		★	5
	Vehof 2014			★	★	★		★	★	5
	Vehof 2021			★	★	★	★	★	★	6
Migraine	Celikbilek 2015	★			★		★	★	★	5
	Ismail 2019		★			★★	★		★	5
	Koktekir 2012				★		★	★	★	4
	Kostev 2020		★			★★	★		★	5
	Paulsen 2014		★	★		★★		★	★	6
	Sarac 2017		★		★	★	★	★	★	6
	Shetty 2017				★	★	★	★	★	5
	Wang 2012		★		★	★★	★		★	6
	Wang 2020			★	★	★★	★	★	★	7
	Yang 2017		★	★	★	★★		★	★	7
Fibromyalgia	Chen 2016		★	★	★	★★	★		★	7
	Erkan Turan 2018				★	★	★	★	★	5
	Gallar 2009					★	★	★	★	4
	Klitsch 2019	★			★	★	★	★	★	6
	Turkyilmaz 2013	★		★	★	★	★	★	★	7
IBS	Asproudis 2016	★	★		★	★	★	★	★	7
	Barton 1999	★	★	★	★		★	★	★	7
	Uçar 2021	★		★		★	★	★	★	6

Fig. 5. Summary of risk of bias assessment using AMSTAR 2 tool (A) and the Newcastle-Ottawa scale (B).

assessments.

The systematic review by Chen et al. [328] was identified to have a high risk of bias in eight of the 16 AMSTAR - domains and judged to be of critically low quality, indicating that the study may not provide an accurate summary of the available evidence.

Of the 22 observational studies, seven were judged as having a total of seven out of nine stars [71,300,303,331,345,347,348], using the Newcastle-Ottawa tool. The lowest score was four out of nine stars [306, 329]. The domain with highest risk of bias was participant selection, where 16 studies had less than two stars out of four (Fig. 5). Sixteen studies did not have independent validation of pain cases and 11 studies did not provide information on participant recruitment strategy.

4.6.6.3.3. Effects summary

4.6.6.3.3.1. Migraine

Fifteen articles, including one systematic review and 14 observational studies, evaluated DED in individuals with migraine (Table 4). Migraine diagnosis was self-reported (n = 6), from International Classification of Diseases coding (n = 4), clinician diagnosed (n = 2), or not clear (n = 2). Pooled data analysis from 11 studies found that the odds of DED were 1.61 (95% CI 1.39–1.87) times higher in people with migraine compared to people without migraine (Fig. 6) [31,67,71,176,297,299, 303,341–343,345]. The statistical heterogeneity was substantial, with an I^2 value of 88%. The prediction interval, which provides a summary of the spread of underlying effects in the studies included in the meta-analysis, ranged from 0.98 to 2.65, indicating that findings of no association are possible in future studies. The GRADE certainty of the evidence for the association between DED and migraine was judged as very low (Table S1).

Three studies that did not report a dichotomous assessment of DED were not included in the meta-analysis. Of these, both Sarac et al. and Koktekir et al. independently reported that Ocular Surface Disease Index scores, Schirmer test values, tear breakup times with fluorescein, and either corneal fluorescein [304] or conjunctival lissamine green [306] staining were worse in the migraine group (total n = 79) than in controls (total n = 88). In contrast, Shetty et al. found that the Lipiview interferometric measure of lipid thickness was greater in migraine, but there was no difference in tear breakup time between migraine (n = 30) and control (n = 30) groups [344].

The systematic review by Chen et al. [328] found, from pooling seven studies (all of which are included in the present report) that people with migraine had significantly higher morbidity of DED compared with controls (OR 1.55; 95% CI 1.32–1.82; $p < 0.001$). However, this study was identified to have methodological concerns that potentially affect the validity of their findings (Fig. 5).

4.6.6.3.3.2. Fibromyalgia

Nine studies that evaluated DED in people with fibromyalgia compared to people without were included (Table 4). Fibromyalgia

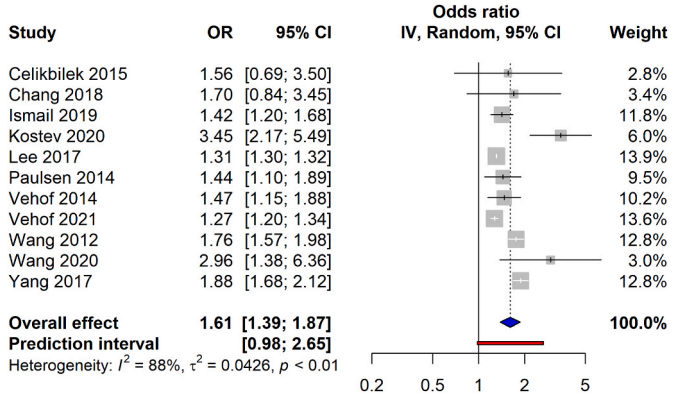

Fig. 6. Forest plot of comparison for odds of dry eye disease in migraine compared to people without migraine. Abbreviations: CI, confidence interval; IV, inverse variance.

diagnosis was self-reported (n = 3), diagnosed using the American College of Rheumatology 1990 criteria (n = 3), using International Classification of Diseases coding on database (n = 2), or not clear (n = 1).

Meta-analysis of six studies found that the odds of DED were 1.91 (95% CI 1.63–2.24) times higher in people with fibromyalgia compared to people without the condition (Fig. 7). The statistical heterogeneity was substantial ($I^2 = 84\%$). The GRADE certainty of the evidence for the association between DED and fibromyalgia was judged as very low (Table S1).

The study by Gallar et al. was not included in the meta-analysis as none of the 18 controls reported having DED symptoms, and an OR could not be estimated [329]. In this study, 18 of the 20 people in the fibromyalgia group reported having DED symptoms. Two studies did not report a dichotomous assessment of DED. Erkan Turan et al. found that Ocular Surface Disease Index scores, tear breakup time, and lissamine green grading were worse in people with fibromyalgia (n = 34) compared with controls (n = 42) but reported no intergroup differences in Schirmer test scores [301]. Türkyilmaz et al. found that the fibromyalgia group (n = 53) had worse Ocular Surface Disease Index scores and tear breakup time, as well as Schirmer scores and tear osmolarity compared to controls (n = 53) [347].

4.6.6.3.3.3. Irritable bowel syndrome

Six studies that evaluated DED in people with irritable bowel syndrome, compared to people without, were included (Table 4). Irritable bowel syndrome diagnosis was self-reported (n = 1), using International Classification of Diseases coding on database (n = 1), or diagnosed based on ROME III or IV criteria (n = 4).

Meta-analysis of five studies found that the odds of DED were 2.16 (95% CI 1.65–2.82) times higher in people with irritable bowel syndrome compared to those without (Fig. 8). The statistical heterogeneity was substantial ($I^2 = 85\%$); however, effect estimates from individual studies were all in the same direction. The GRADE certainty of the evidence for the association between DED and irritable bowel syndrome was judged as low (Table S1).

Uçar et al. did not report dichotomous assessment of DED and was not included in the meta-analysis [349]. This study reported that Ocular Surface Disease Index scores were significantly higher ($p = 0.008$), and tear breakup time was significantly lower, in individuals with irritable bowel syndrome (n = 29) compared to controls (n = 37).

4.6.6.3.3.4. Back pain

Three studies reported data on DED in people with back pain, which was either diagnosed using the International Classification of Diseases database coding (n = 1) or self-reported (n = 2). Pooled data analysis from the three studies found that the odds of DED were 1.60 (95% CI 1.39–1.83) times higher in people with back pain compared to people without back pain (Fig. 9). The statistical heterogeneity was substantial ($I^2 = 63\%$), but effects from individual studies were in the same direction. The GRADE certainty of the evidence for the association between DED and back pain was judged as very low (Table S1).

4.6.6.3.3.5. Other pain conditions

Three studies additionally reported an association between DED and other primary pain conditions.

Chang et al. [71] found that the odds of having mild or greater DED symptoms (5-item Dry Eye Questionnaire score >5) were 4.63 (95% CI 2.10–10.22) in muscle pain, 2.14 (1.16–3.95) in headaches, and 1.06 (0.33–3.44) in tendonitis, compared to people not reporting these pain conditions.

Using records from a US veteran population [297], Lee et al. found that the odds of having tear film dysfunction (via International Classification of Diseases-9 coding) were 1.61 (1.58–1.63) in tension headache, 1.82 (1.81–1.83) in temporomandibular joint dysfunction, 1.75 (1.74–1.76) in abdominal pain, 1.57 (1.54–1.60) in pelvic pain, 1.95 (1.77–2.15) in central pain syndrome, and 1.57 (1.56–1.58) chronic pain or chronic pain syndrome (as defined in medical records).

From the Twins UK study [299], it was also reported that the

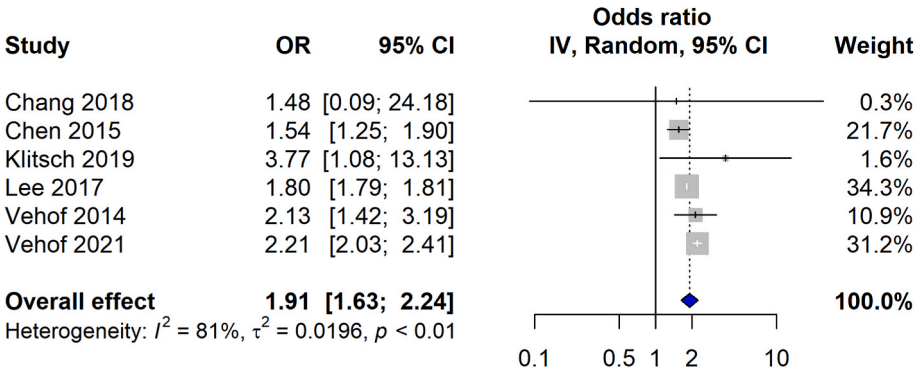

Fig. 7. Forest plot of comparison for odds of dry eye disease in fibromyalgia compared to those without fibromyalgia. Abbreviations: CI, confidence interval; IV, inverse variance.

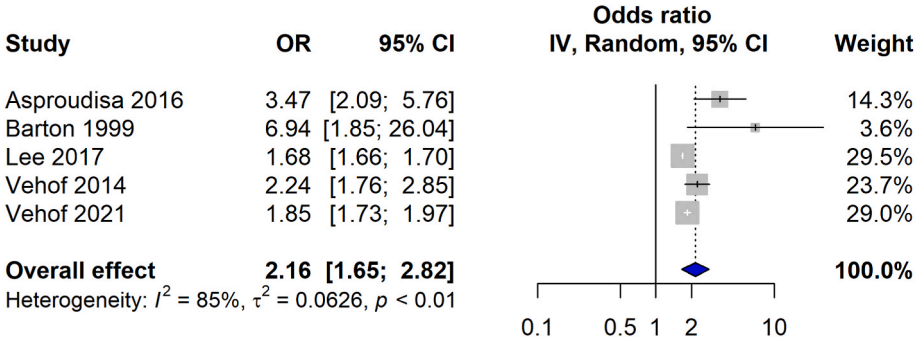

Fig. 8. Forest plot of comparison for odds of dry eye disease in irritable bowel syndrome compared to people without irritable bowel syndrome. Abbreviations: CI, confidence interval; IV, inverse variance.

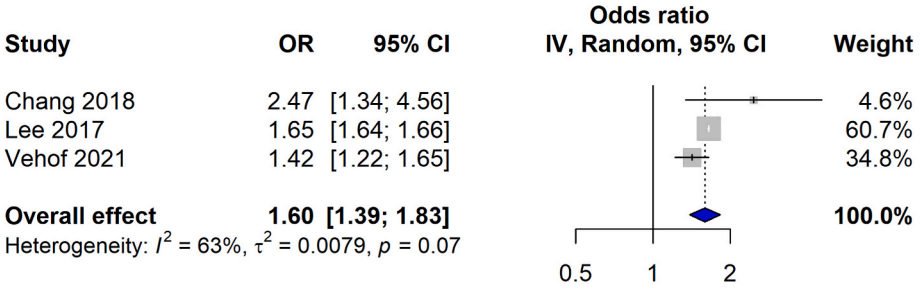

Fig. 9. Forest plot of comparison for odds of dry eye disease in back pain compared to people without back pain. Abbreviations: CI, confidence interval; IV, inverse variance.

association between self-reported diagnoses of DED and pelvic pain to be 1.86 (1.41–2.46).

4.6.6.3.4. Publication bias. Fig. 10 shows a funnel plot assessing potential publication bias for studies evaluating the association between DED and migraine. The funnel plot revealed a relative paucity of only small studies that report weaker associations between DED and migraine, indicating potential publication bias [350].

4.6.6.3.5. Sensitivity analysis. Table 5 shows findings of a sensitivity analysis excluding studies that did not evaluate DED using clinical assessments of symptoms or signs (i.e. where DED was self-reported or determined retrospectively from disease coding), as described in the study.

In the sensitivity analysis for migraine, overall heterogeneity reduced from 88% to 36%, and for fibromyalgia, overall heterogeneity reduced from 81% to 0%. These findings suggest that the method used to diagnose DED may be a factor contributing towards the between-study variability for these conditions. For irritable bowel syndrome, sensitivity analysis did not significantly reduce the statistical heterogeneity (I^2 = 79%).

Owing to an insufficient number of studies, sensitivity analysis could not be performed in the synthesis for back pain, to assess the effect of excluding studies based on DED diagnostic criteria.

4.6.6.4. Discussion. This systematic review included 23 studies evaluating the association between DED and chronic primary pain disorders. Meta-analyses were performed for four pain conditions, and a positive association was found between DED and each of migraine, fibromyalgia, irritable bowel syndrome, and back pain.

Observational studies were of several different designs: 18 were prospective cross-sectional studies and five were retrospective chart review of existing health records. Most studies, except for three, comprised a mixed-gender population; studies included data on between 38 and 3,265,894 people. The differences in study design and populations likely contributed to the heterogeneity of the effect estimates.

The GRADE certainty of the evidence for the association between DED and each of migraine, fibromyalgia, and back pain was judged as

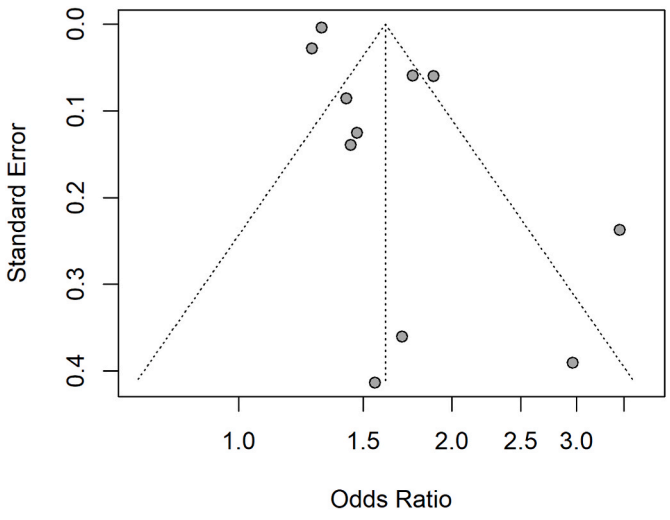

Fig. 10. Funnel plot of studies evaluating the association between dry eye disease and migraine.

very low, and between DED and irritable bowel syndrome was judged as low (Table S1). Low certainty indicates that confidence in the effect estimate is limited and that the true effect may be substantially different from the estimate of the effect. All four estimates were downgraded for risk of bias, as most studies scored five or six stars out of nine, indicating a moderate to high level of overall bias in these studies.

No studies scored more than seven out of nine in the Newcastle-Ottawa tool. Key methodological weaknesses were in the selection of participants, in particular inadequate information provided on case definition and participant sampling methods. Potential selection bias challenges the generalizability and applicability of findings in these studies. To minimize the risk of bias in future study designs, studies should clearly define the criteria and methods used to diagnose pain condition(s) and DED to enable greater certainty to be achieved in understanding the association between these conditions.

The differences in the criteria used to define pain condition(s) and to assess DED is also a potential factor contributing to the observed heterogeneity between studies. Only nine included studies diagnosed pain conditions using clinical diagnostic criteria, with the remaining diagnosed on the basis of self-reporting, from database disease coding, or were unclear with respect to how disease status had been classified.

Eleven studies included assessments of both DED signs and symptoms. However, only three of the 15 studies that classified DED dichotomously used criteria that considered both DED symptoms and signs [341,345,346]. One of the three studies [345] used the TFOS DEWS II criteria, which was published in 2017 and provided a recommended battery of tests for diagnosing DED, including assessments of symptoms and signs [345]. Prior research has shown that there is considerable discordance between DED signs and symptoms, particularly among people with chronic pain syndrome [13,351]. As an insufficient number of studies used composite DED diagnostic criteria, it was not possible to produce a summary effect that included only studies that adopted this definition.

4.6.6.4.1. Implications for clinical practice and future research. Across observational studies that evaluated DED in primary pain conditions, associations were identified between DED and each of migraine, fibromyalgia, irritable bowel syndrome, and back pain. However, the certainty of the evidence for the association between DED and each pain condition was judged as low or very low, indicating that the true effect may be substantially different from the estimate. Substantial heterogeneity observed between studies also challenges the ability to confidently ascertain the strength of this association with precision. Nonetheless, the positive association shown between DED and migraine, fibromyalgia, irritable bowel syndrome, and back pain indicate that patients with these conditions should be carefully screened for DED.

This review demonstrates the need for more consistency in study design and diagnostic definitions among observational studies evaluating DED in pain disorders, to enhance methodological rigor and reduce biases. Adoption of a core classification system (such as the International Association for the Study of Pain classification of chronic pain [334]) and clearly defining the clinical criteria used to diagnose pain conditions can reduce selection bias and enhance generalizability of study findings.

Key areas for future research include investigating the effects of the medication used for pain conditions as a potential contributory factor for DED symptoms and signs. Only six of the 23 included studies in the present review reported data on concomitant medications. It is also currently unclear whether the severity of pain disorders has an impact on the likelihood of having DED, or on DED severity.

To improve consistency, DED diagnosis should be made using best practice diagnostic criteria, comprising both assessments of DED symptoms and signs, such as those recommended in the TFOS DEWS II report [10]. Study cohorts should also be differentiated for DED subtypes (i.e., aqueous deficient versus evaporative DED). These practices can reduce potential clinical heterogeneity between studies and enable greater confidence in estimating the association between DED and chronic pain conditions.

Table 5
Sensitivity analysis excluding studies that did not evaluate dry eye disease (DED) using clinical assessments of symptoms or signs.

Analysis	Treatment effect (95% confidence interval)	I^2	Number of studies included in synthesis	Studies excluded
Migraine				
Main analysis	1.61 (1.39–1.87)	88%	11	–
Sensitivity analysis by dry eye disease diagnostic criteria	1.42 (1.17–1.72)	36%	5	Ismail et al., 2019 [176]; Kostev et al., 020 [342]; Lee et al., 2017 [297]; Vehof et al., 2014 [299]; Wang et al., 2012 [67]; Yang et al., 2017 [303].
Fibromyalgia				
Main analysis	1.91 (1.63–2.24)	81%	6	–
Sensitivity analysis by dry eye disease diagnostic criteria	2.21 (2.03–2.41)	0%	3	Chen et al., 2016 [300]; Lee et al., 2017 [297]; Vehof et al., 2014 [299].
Irritable bowel syndrome				
Main analysis	2.16 (1.65–2.82)	85%	5	–
Sensitivity analysis by dry eye disease diagnostic criteria	2.89 (1.50–5.54)	79%	3	Lee et al., 2017 [297]; Vehof et al., 2014 [15,299].

5. Psychosocial factors

5.1. Tobacco use

The number of people in the world using tobacco is reported to be declining, according to the World Health Organization's global report on trends in prevalence of tobacco use 2000–2025, third edition (Fig. 11) [352]. In 2000, half the men 15 years and older were tobacco users, projected to be 35.1% in 2025. In 2000, 16.7% of women 15 years and older were tobacco users, dropping to a projected value of 6.7% in 2025.

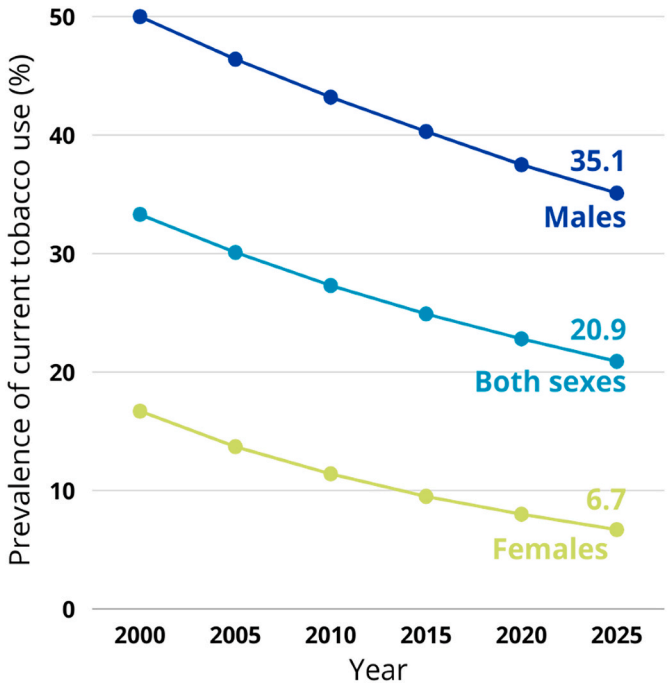

Fig. 11. Global trends in prevalence of tobacco use by sex, adapted from the World Health Organization global report on trends in prevalence of tobacco use 2000–2025, third edition. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.

5.1.1. What is tobacco use?

Tobacco use describes exclusive use of smoked tobacco products, exclusive use of smokeless tobacco products, or the use of both. Tobacco use is often referred to as a global epidemic, and while tobacco use is declining in developed countries, the prevalence of tobacco use continues to grow in low and middle-income countries. Currently, there are over 1.3 billion tobacco users across the globe aged 15 years or older [353].

5.1.1.1. Impact of tobacco use. Health risks due to tobacco use and economic costs to families and communities continue to rise. Household spending on tobacco can result in diversion from basic needs such as food and shelter, and individual and societal health care costs impact the overall economy, including losses in human capital from morbidity and mortality [354]. Global prevalence might be declining, but the morbidity and mortality are expected to rise as diseases related to tobacco use can take years before detection [355]. A significant health threat, tobacco use results in over 8 million deaths annually, 7 million due to primary use, and 1.2 million due to second-hand smoke exposure [356].

To combat tobacco use globally, the World Health Organization (WHO) tracks the implementation of the six MPOWER strategies to reduce tobacco use: 1) Monitor tobacco consumption and the effectiveness of preventive measures; 2) Protect people from tobacco smoke; 3) Offer help to quit tobacco use; 4) Warn about the dangers of tobacco; 5) Enforce bans on tobacco advertising, promotion and sponsorship; and 6) Raise taxes on tobacco [357,358]. The MPOWER measures have helped countries make progress. Today, 5.3 billion people in 115 countries are protected from the effects of tobacco use by at least one MPOWER strategy, and the number of countries with best-practice cessation policies has more than doubled [359].

5.1.1.2. Ingredients in tobacco. According to the American Lung Association, there are over 600 ingredients in cigarettes or cigarette smoke, including nicotine, acetone, benzene, formaldehyde, cadmium, acetic acid, carbon monoxide, tar, and ammonia. In 2012, the Food and Drug Administration established a list of 93 potentially harmful constituents in tobacco products and tobacco smoke (the HPHC list) as required by the Federal Food, Drug, and Cosmetic Act (the FD&C Act) [360,361]. The list classified constituents as carcinogen (CA), respiratory toxicant (RT), cardiovascular toxicant (CT), reproductive or developmental toxicant (RDT), addictive (AD) or a combination. Of the 93, only 20 have well-documented and established methods of measurement [360]. Many countries do not have any guidance relating to the composition of cigarettes, and through the WHO MPOWER strategy, this is improving [357,358]. It has long been understood that ingredients in cigarettes are toxic and present a high carcinogenic risk to humans, including through passive smoke exposure [362–364].

5.1.2. Tobacco and ocular surface diseases

5.1.2.1. Tobacco and DED. The link between tobacco, smoking exposure (passive and active) and DED has been contradictory, with some studies showing a positive association, some showing a negative association, and others showing no association. Several different study designs have been used to explore the impacts of smoking, some designed specifically to evaluate smoking, while others include smoking as a modifiable risk factor in a broader assessment of DED prevalence. A potential reason for differing findings could be the process by which data are collected and reported. Current smoking or smoking history data is often collected via survey or interview as part of a larger battery of systemic health questions in association with a clinical examination. Such studies are generally not designed to explore this association alone and, given their design, some studies may be underpowered to find an association. Studies exploring the association, as well as the potential impact on ocular surface parameters are discussed in this section.

A 2016 meta-analysis of DED prevalence and smoking identified 10 relevant studies (eight cross-sectional and two cohort studies; primarily from Asia), and found no significant association between smoking and DED when adjusted for age and sex [365]. However, this study has methodological limitations [16]. When outcomes from only three studies that used a general population study design were considered, a significant association was noted (OR 1.50, 95% CI 1.08–2.09). The authors cited several reasons for this inconsistency, including the larger sample size in the cohort and population-based nature of the studies. The authors also speculated that variations in DED definition (some symptom-based without clinical ocular surface testing) could have influenced the results. From the 10 studies included in this meta-analysis, as well as others discussed below, current smoking, previous smoking, any history of smoking (ever) and severity of smoking based on cigarettes per day are used to describe smoking status. Self-reported smoking data can additionally lead to the inability to find associations, due to inaccurate reporting, but also due to smaller numbers of smokers in these cohorts, thereby reducing power to find an association even though the studies are relatively large. Thus, this meta-analysis provided inconclusive results on the link between the two entities.

Relationships between DED symptom and sign severity have previously been examined in relation to systemic factors [366]. In this randomized controlled clinical trial that investigated the use of oral omega-3 supplements as a treatment for DED, current daily smoking was not associated with DED symptoms and sign severity, possibly due to low power due to the small number of current smokers (n = 26) compared to the total number of subjects (n = 535). However, a history of “ever” smoking was associated with more severe signs, discussed further below.

The present review identified eight papers showing a positive association between smoking and DED [365,367–373], and two reporting no association [365,374], including three that were included in the 2016 meta-analysis [365]. In addition to the cross-sectional prevalence

studies of DED reported above, an additional six studies in various countries also found either no significant associations between DED and smoking [368,375–378], or possibly a mild association in chronic or severe smokers [379,380]. Finally, a cross-sectional population-based cohort study in the Netherlands (n = 79,866) found that individuals defined as having DED (by the presence of both dryness and irritation either 'constantly' or 'often', and/or a report of a previous diagnosis of dry eye) had fewer current smokers (12.6%) compared to individuals defined as not having DED (16.1%), p < 0.001) [31]. Interestingly, smoking was associated with a clearly decreased risk of dry eye compared to never smoking (adjusted OR 0.87, 95% CI 0.80–0.94), but ever smoking (but stopped) was associated with a clearly increased risk (adjusted OR 1.09, 95% CI 1.03–1.15). To summarize, smoking history, including current smoking, may have a weak association with DED, but currently existing high-quality data is inconclusive.

5.1.2.1.1. Tobacco and ocular surface signs. Some studies examined smoking in relation to DED signs. In some of these studies smoking status was used to recruit and categorize participants, and DED testing was performed on each group, assessing differences in clinical findings between groups to understand the impact of smoking on the ocular surface [373,381–388]. In others, participants with a history of smoking and other associated factors underwent DED testing and sub-category analysis was performed to see if there were differences between smoking groups [389–394]. In a cross-sectional study of 88 office workers in Japan, smokers had decreased tear production, goblet cell density and tear mucin 5AC concentration compared to non-smokers. This study was one of the first to show differences in ocular surface markers in smokers [389]. In a 2009 study of 250 randomly selected eye clinic patients in Saudi Arabia, 44 smokers all had DED based on a symptom and clinical sign diagnosis. Of the clinical tests, a decreased tear breakup time most closely associated with smoking [390].

Four studies examined the association between DED and smoking in university students, two that specifically recruited students that smoked, and two that assessed DED prevalence in the sample. In a study conducted at King Saud University, Saudi Arabia [381], 30 healthy male smokers and age matched non-smokers were clinically evaluated. Again, a lower tear breakup time was noted in smokers versus non-smokers, along with more abnormal tear ferning patterns, and higher symptom scores via McMonnies questionnaire.

Numerous studies discuss waterpipe smoking, which uses combustible hookah tobacco (also known as waterpipe tobacco, maassel, shisha, narghile, or argileh). Hookah (waterpipe) smoke exposes the smoker and those in close proximity to nicotine and many of the same toxic chemicals that are in cigarette smoke, which can impact the ocular surface [395,396]. In many countries, such as in the Eastern Mediterranean Region, waterpipe smoking is often a preferred method of smoking, as it is believed (incorrectly) by many to have reduced risk because the compounds in tobacco pass through the water. It is also a social activity, where sharing between family and friends is common. There are ongoing waterpipe cessation interventions in development [397]. A study of university students in Jordan assessed the effects of tobacco waterpipe smoking on DED (tobacco waterpipe smokers n = 33; non-smokers n = 31). In this study, smokers had higher osmolarity and corneal fluorescein staining scores and lower tear breakup time values than non-smokers. Interestingly, no differences in symptoms (Ocular Surface Disease Index) were noted between the groups, suggesting that DED in smokers more closely associates with signs than with symptoms [387].

The other two studies in university-aged populations used a prospective non-interventional study design. A study in Malaysia evaluated 59 participants, comprising 27 smokers and 32 non-smokers [391]. Comparing the groups, smokers had shorter tear breakup time, increased nasal and temporal fluorescein corneal staining, and decreased goblet cell density. Symptom scores were also higher (McMonnies and Ocular Surface Disease Index) in the smoking versus non-smoking group [391]. Finally, in a university-based study in Brazil, 485 undergraduate students and 491 medical student volunteers completed questionnaires in class, and another 1182 students completed questionnaires online, to give a total of 2158 participants. Participants with DED symptoms were invited to participate in an ocular examination and 54 completed DED testing. It was not reported how many of the 54 were smokers, and only 5.6% of the entire sample smoked. However, in multivariate analysis, increased Ocular Surface Disease Index scores were associated with smoking, among other factors. Tear breakup time was performed in the subjects seeking examination, but outcomes were not differentiated according to smoking status [394]. In summary, in university populations, DED signs overall have been found to be more pronounced in smokers, including waterpipe users, than in non-smokers. It is interesting that symptoms may or may not be increased in smokers, perhaps because of the younger age of participants, better general health, and more robust tear defense mechanisms, making this topic worthy of further evaluation in older smokers.

Additional studies that compared smokers to non-smokers demonstrated findings consistent with those of the university-based studies. In a clinic-based study in India of 50 smokers and 50 non-smokers, tear breakup time and corneal sensitivity were significantly lower in the smoking vs non-smoking group [373]. Interestingly, tear production (Schirmer test with anesthesia) was normal in both groups at ~20 mm wetting per 5 min. The authors speculate that lipid peroxidation secondary to toxic chemical components of smoke impacts tear film stability more so than production, and that nerve toxicity with reduced corneal sensitivity may also occur as a result. Similar findings were also reported in 50 heavy smokers compared to 50 non-smokers in Turkey. Significant differences were found in Ocular Surface Disease Index scores (increased), tear breakup time (reduced), and goblet cell density (reduced). No differences were found in fluorescein corneal staining or tear production (Schirmer) [382]. Similarly, again, in 25 healthy smokers and 20 non-smokers (20–45 years) in Japan, reduced tear breakup time, goblet cell density, and tear spreading were shown in smokers, but not all smokers (80%) had symptoms [383]. However, higher symptom scores in smokers have been found in some studies. In a Turkish study, higher symptom scores, decreased tear breakup time and tear lysozyme concentration, higher tear production, and similar goblet cell density and rose bengal conjunctival staining were noted in the smoking (n = 44) versus non-smoking (n = 37) groups [384].

In recent years, there has been concern about the age of initiation of any tobacco use, including e-cigarette use (vaping). In general, boys commence smoking earlier than girls, and non-Hispanic whites earlier than other youth [398]. Most youth that are susceptible to initiation do so before the age of 18 years, including the use of e-cigarettes [399]. In a comparison of 21 vapers and 21 healthy non-smokers, vapers experienced greater DED symptoms (measured using the Ocular Surface Disease Index), reduced tear breakup time, increased corneal staining, and decreased tear meniscus height compared to non-vapers. Consistent with other studies, tear production (Schirmer test score) was not lower in smokers [385]. Compared to the university student cohorts, symptom scores were higher in the vaping group, perhaps indicating that vaping has negative effects on both symptoms and signs of DED. Passive exposure to smoke in children and adults has also been studied. Growing evidence shows similar deleterious effects to the tear film even with one exposure. In a series of studies, non-smokers exposed to smoke in a chamber environment showed an increase in tear inflammatory cytokines, tear lipid peroxidation products and a decrease in mucin function [400]. Similarly, contact lens wearers in the smoke chamber demonstrated an increase in tear film instability and damage to the ocular surface epithelial layer [401]. In a prospective clinical study, 112 children presenting with symptoms of eye discomfort were examined for DED based on a modified severity scale including symptoms (discomfort and visual), tear breakup time, Schirmer I test, and corneal fluorescein staining. Of the 112 children, 80 (71%) were found to be positive for a DED diagnosis based on the severity grading, and 76 experienced passive smoking. The number of smoked cigarettes the children were

exposed to per day and the duration of exposure to passive smoking were both significantly higher in children diagnosed with DED (17.70 ± 14.19 and 10.00 ± 3.77 h, respectively) compared to those without DED (0.65 ± 2.55 and 0.70 ± 2.38 h, respectively), $p < 0.0001$ for both. Specific clinical data was not presented, although the discussion suggests a lower tear breakup time and increased staining was found in those exposed to passive smoke, consistent with other studies. Multivariate analyses showed one of the most important determinants of a positive DED diagnosis was the number of cigarettes/day exposure [392].

5.1.2.2. Tobacco and other ocular surface diseases. While most of the literature has focused on symptoms of ocular dryness and irritation and smoking status specifically related to DED, there are other ocular surface conditions often linked to chronic, current, or past smoking. A 2007 systematic review evaluating the link between thyroid eye disease and smoking [402]. The authors reported a positive association between smoking and thyroid eye disease from four case-control studies, in Graves' disease with and without ophthalmopathy, and in seven case-control studies where the control did not have thyroid disease. The OR ranged from 1.2 to 20.2. Other studies included in the review addressed patient outcomes in smokers versus non-smokers, with more positive outcomes in the non-smoking groups. The authors surmised that while the quality and size of the studies was variable, the association between smoking and thyroid eye disease was strong [402].

The association between smoking and pterygium development is unclear. A 2014 systematic review that included 24 studies (20 cross-sectional, two case control, and two population-based studies, with over 95,000 participants), found that cigarette smoking was associated with a reduced risk of pterygium, especially in current smokers [403]. Similarly, in the Singapore Epidemiology of Eye Diseases study, which is a population-based cohort study from the 3 major ethnic groups in Singapore: Malay, Indian, and Chinese, current smoking status was associated with a lower risk of developing pterygium (OR 0.41; 95% CI 0.16–0.87) [404]. Similar findings were reported in several large population-based studies [405–410].

Other studies found no relationship between pterygium and smoking. The Barbados Eye study [411] and Yunnan Minority Eye Study [412] did not observe significant associations between previous smokers and the incidence of pterygium. However, one study found a positive relationship between smoking and pterygium. In a prospective population-based study that examined 5057 people above 50 years of age chosen randomly in Southern Harbin, Heilongjiang Province, China, the prevalence of pterygium was significantly higher (OR 1.90, 95% CI 1.51–2.35) among smokers ($p = 0.001$) [413].

Smoke itself can be an allergen and impact the ocular surface. Below, studies that examined the link between ocular allergy and smoking are described.

Allergic rhino-conjunctivitis is defined as an IgE-mediated immune reaction after allergen exposure resulting in sneezing or a runny or a blocked nose without a cold or flu, accompanied by itchy, watery eyes [414]. Allergens commonly reported to trigger an ocular surface response include pollen, pet dander, and environmental pollutants [415]. Smoke itself is considered more as an irritant rather than an allergen, and individuals with allergy conditions often have increased sensitivity of airways and the ocular surface [416].

Clinical evidence supports an increase over recent years in the rates of allergic diseases [417]. It is less clear whether there is a comparable increase in allergic conjunctivitis and rhino-conjunctivitis, and there is minimal evidence reporting the association of smoking with ocular allergy. One study examined associations between smoking and allergic rhino-conjunctivitis through analysis of the International Study of Asthma and Allergies in Childhood data set. The authors concluded that while tobacco rates decreased by 2% between the Phase I and Phase III data timepoints, there was no correlation between the change in tobacco use and change in allergic rhino-conjunctivitis in either the 6–7 or 13-14-year group ($p = 0.23$ and 0.62, respectively) [418]. The same research team explored markers for allergic disease in a retrospective chart review of allergy-asthma patients ($n = 1037$) treated at the University Hospital of Brooklyn (2016–2019). While allergic rhino-conjunctivitis was the most common subgroup ($n = 580$), the authors did not find associations between smoking status, with IgE levels, skin-prick test results, or eosinophil counts [419].

Smoking has also been examined in relation to chalazion. In a 2010–2015 study that examined this question in a veteran population across the US ($n = 3{,}453{,}944$, 20,8720 of whom had chalazion), smoking, blepharitis, conjunctivitis and history of allergy were all associated with chalazion in both univariate and multivariate analyses [420]. A further examination of how these contributing factors impact chalazion are needed.

Allergenic and irritative environmental exposures, both indoor and outdoor, have also been examined in relationship to DED [285], with indoor tobacco exposure being a factor that has been studied [421,422]. In one study, individuals with DED (symptoms and/or signs) underwent IgE quantification from Schirmer strips ($n = 75$) [423]. Individuals who reported exposure to indoor smoke were more likely to have high IgE levels than those not exposed to smoke (OR 38.6, $p = 0.008$). Whether components of smoke trigger the IgE response directly or augment an already primed immune system is unclear and warrants further study to determine the allergenic or irritative impact of tobacco smoke on the ocular surface.

5.1.2.3. Smoking and the cornea. Studies have examined the impact of tobacco on central corneal thickness (CCT) and corneal endothelial characteristics (endothelial cell density, endothelial cell variability, average of endothelial cell size and endothelial cell hexagonality) [424]. In a meta-analysis of 17 eligible studies, a total of 2077 smokers and 6429 non-smokers were included in the analysis. When compared to non-smokers, smokers had a higher CCT (mean difference of 3.3 μm, 95% CI + 0.9 to+5.7 μm, $p = 0.007$) and a lower endothelial cell density (mean difference of 140 cells/mm^2, 95% CI 30 to 250 cells/mm^2, $p = 0.01$). Other corneal endothelial measures such as hexagonality or average endothelial cell size did not differ significantly by smoking status. The overall conclusion was that while smoking may have an impact on endothelial cell function, no clinical differences were noted such as a higher risk of surgery (e.g., endothelial keratoplasty) in smokers.

5.1.3. Mechanisms

The effects of cigarette smoke on the ocular surface were studied in rabbits *in vivo* and *in vitro* [425]. In one study, the eyes of 12 healthy rabbits and 12 rabbits with hypercholesterolemia were directly exposed to smoke (filtered and unfiltered cigarettes). Epithelial cells were then harvested at certain time points after exposure. Cells exposed to unfiltered cigarettes were observed to have more 'damage' than filtered cigarettes and cells from hypercholesterolic rabbits had more 'damage' than control rabbits. The time course after exposure affected findings. Early cultures after exposure did not show differences whereas differences were noted 18 and 24 h after exposure. Later studies in mice and human corneal epithelial cells confirmed these findings in uninjured corneal epithelial cells [426,427] as well as in corneas with prior injury [428,429].

This question has also been examined with respect to corneal endothelial cells [430]. In one study, four adult female dogs along with 32 pups (16 male) were exposed to cigarette smoke (on and off) for 105 days. A 10% decrease in endothelial cell density was noted compared to the control group. Additionally, 524 proteins were found to be up or downregulated. Many of the downregulated proteins were associated with Descemet's membrane, perhaps linking cigarette smoke to endothelial cell numbers.

In humans, an immediate effect was found from smoke on the tear film with reductions in tear breakup time and lipid layer thickness 5 min after smoking a cigarette [388]. Destabilization of the lipid layer and tear film, possibly related to oxidation of lipids and interaction with tear film proteins [370] can impact the ocular surface after chronic exposure, leading to increased staining, inflammation, increased osmolarity and possibly symptoms of dryness and irritation. Cigarette smoke toxins in heated tobacco products have been shown to damage corneal epithelial cells [431], thus the clinical signs bear similarity to DED. Further biochemical exploration of the impact of smoke (as well as other indoor and outdoor allergens and irritants) on the ocular surface and the tear film may lead to a better understanding of tear film instability and the downstream negative effects on the tear film and ocular surface.

5.1.4. Treatment implications

Based on the evidence presented, it is unclear whether smoking status is definitively associated with DED, whether the DED diagnosis is based only on symptoms or clinical signs as well. What is clearer is that smoking has an impact on the tear film and epithelial cells, and that these clinical findings mimic findings commonly observed in DED. As DED is a multifactorial condition [3], the addition of smoking, even passive smoke exposure, can contribute to the DED status. This is important as smoking is a modifiable factor. As clinicians, discussions regarding smoking and the potential impact on the tear film and ocular surface should be discussed with patients. While programs exist to encourage alcohol and smoking cessation, there is minimal to no data to support the impact of cessation efforts on improving ocular surface health. Given this, specific cessation programs or treatments could be evaluated for their impact on DED and might be worthy of future investigation. Smoke-free legislation and programs to reduce smoking worldwide improve health outcomes [358,432], and these positive effects may translate to improved ocular surface health.

5.2. Cannabis

5.2.1. What is cannabis?

Cannabis, or marijuana, is derived from the *Cannabis sativa, indica,* and *rederalis* plants. It is among the most commonly used illicit substances globally, and is consumed by more than 180 million people worldwide [433]. Cannabis contains more than 540 natural compounds, including 110 compounds classified as cannabinoids due to their common chemical structures. The primary psychotropic component of cannabis is Δ9-tetrahydrocannabinol, while the major non-psychoactive ingredient is cannabidiol [434]. Cannabis is commonly smoked, either by mixing with tobacco or on its own.

5.2.2. Cannabis and DED

The potential impacts of cannabinoids on the ocular surface have been highlighted by a range of early experimental studies. Preliminary evidence from murine models have highlighted that the activation of cannabinoid (CB1) receptors in the lacrimal gland by Δ9-tetrahydrocannabinol can reduce aqueous tear production [435]. Other studies in murine, bovine, and human corneal epithelial cells have also shown that the activation of cannabinoid receptors, including CB1, CB2, GPR18, occurs during corneal wound healing and might act to reduce corneal opacification and neovascularization [436–441]. Both naturally-occurring and synthetic cannabinoids, including CBD, have also exhibited anti-nociceptive and anti-inflammatory effects in murine models of corneal hyperalgesia [442,443], although their potential therapeutic utility in reducing pain and inflammation from ocular surface injury warrants further investigation.

Clinical research investigating the impacts of cannabis consumption on the ocular surface is currently very limited. A case-control study comparing 28 individuals with cannabinoid use disorder with 32 age and sex-matched healthy controls suggested that long-term cannabis use was potentially associated with reduced corneal endothelial density (2900 ± 211 versus 3097 ± 214 cells/mm^2, $p < 0.01$) [444]. Although cannabis was hypothesized to exert toxic effects on the corneal endothelium, the underlying pathophysiological mechanisms remain unclear. In a case-control study, differences noted between long-term cannabis users and controls included higher basal lacrimation, higher intraocular pressure, greater photosensitivity, and poorer dark adaptation, however values in both groups were within normal limits [445].

Overall, the effects of cannabinoids on the ocular surface remain highly unclear, particularly in the context of the lack of high-quality clinical studies. Future clinical research is required to substantiate or refute anecdotal reports of the association between cannabis consumption and aspects of DED [446], and experimental models may be useful to investigate the potential therapeutic effects of cannabinoids in ocular surface injury [443,447].

5.3. Other recreational drugs

5.3.1. Recreational drugs and the eye

It has been well established that many recreational drugs cause not only general metabolic and physiological changes to the body but also can specifically affect the visual apparatus and visual function. Some of these effects are the desired results of drug-taking, such as hallucinations, whereas other effects are not, such as premature aging of the crystalline lens or changes in intraocular pressure or pupil size [448–450]. This section focuses on the effects of recreational drugs on the ocular surface with effects on other parts of the eye or visual function noted in the literature [451], desirable or otherwise, being considered beyond the scope of this review. Since most recreational drugs are illegal or have toxic effects, much of the reported literature is from case studies rather than case-control studies. The list of recreational drugs is growing all the time as new variants of existing products are trialed by users or new designer drugs, designed to circumvent criminal law enforcement, are developed. Furthermore, there exist legal substances that are abused by certain individuals, such as solvents or prescription medicines [452]. Alcohol is the world's most widely used recreational drug, although, since it is legal in most parts of the world, its use (and abuse) is often not considered as illegal recreational drugs [453]. The widespread consumption of alcohol means that addiction is common but also difficult to identify. Certainly, an awareness of the potential for ocular effects relating to drug abuse is something to which eye care practitioners should be alert [454,455].

5.3.2. Recreational drugs and ocular surface disease

5.3.2.1. Methamphetamines. Amphetamine-derived drugs, such as 3,4-Methylenedioxymethamphetamine (MDMA), commonly known as ecstasy, E, or molly, are sometimes taken by individuals engaging in music festivals or raves for the euphoric feeling and lowered anxiety they bestow upon the user. The drug is occasionally snorted but more commonly taken in tablet form. As little as a single dose of an amphetamine-based drug can be fatal, especially as drug-sellers will often mix in impurities. Users of these drugs need to keep their overall hydration levels high to avoid the risk of dehydration. Such acute dehydration has the potential to affect the ocular surface, although this has not been documented, likely in the context of the overall systemic dehydration that would be the prime concern for a treating physician. In case reports, methamphetamine use has been reported to be linked to corneal ulceration, that became infected and perforated [456,457]. A further complication associated with this drug is its vasoconstrictive properties. Decreases in ocular perfusion pressure, decreases ocular blood flow which could lead to ischemic pathologies. Methamphetamine administered via intravenous injection has been linked with cases of conjunctivitis and episcleritis [457].

5.3.2.2. Cocaine. Cocaine has been available for thousands of years and

some ancient cultures would chew the leaves of the coca plant, from which cocaine is derived. Cocaine is an alkaloid that is produced by Erthroxylum coca, a shrub found in the Andean Highlands and northern parts of the Amazon in South America. Pure cocaine is a white powder and is usually snorted up the nose. Crack cocaine (a purified solid form of cocaine) is yellow and is usually smoked in a crack pipe.

Cocaine is a powerful anesthetic and appetite suppressant, but the property that appeals to recreational drug takers is its stimulant effect. Users report a feeling of euphoria, bravado, hypersensitivity to sight, sound and touch. Systemic physiological effects include constricted blood vessels, dilated pupils, increased body temperature, heart rate and blood pressure. Increased intake of the drug can lead to erratic and violent behavior with users reporting irritability and paranoia, and users may even experience tremors, vertigo or muscle twitches. Sustained abuse can lead to cardiovascular problems, seizures, strokes, and coma. Death has been reported on first use of cocaine, or soon after. There is some evidence to suggest impairment to smooth pursuit eye movements in crack cocaine users [458].

Cocaine has been shown to have a local anesthetic effect on the cornea, achieved by blocking the sodium channels and preventing acetylcholine from binding [459]. A study that investigated the impact of habitual cocaine-snorting (n = 48) on the ocular surface found lower corneal sensitivity in cocaine users compared to heroin addicts (n = 22) and drug-free individuals (n = 30). In this study, 26 of the cocaine users, but no heroin users, had reduced corneal sensitivity, with 6 cases of neurotrophic keratitis noted [460]. Corneal epithelial defects, as well as microbial keratitis, have been reported in individuals who smoke or snort cocaine [461,462]. Reduced tear production has also been reported. In one study, individuals were examined both while under and not under the effect of cocaine. Seventeen of 22 eyes exhibited a reduction in tear production (Schirmer test) when under versus not under the effects of cocaine, with an average decrease of 16.52 ± 10.13 mm (range 1–38 mm), p = 0.0024 [463].

Crack cocaine smoking, which is a cheaper alternative to pure cocaine, is not without ocular surface complications [464,465]. Smoking crack cocaine has been linked to corneal ulcers and other corneal epithelial defects [466–469]. A systematic review of 11 case reports found that the majority (63%) of cases of 'crack eye' had bilateral involvement and 83% of all cases reported corneal infections. Of concern is that 22% were left with significant visual impairment (hand movements only) in the affected eye [469]. It has been hypothesized that the paranoia felt by crack users led to erratic behavior including significant eye-rubbing which in turn led to corneal surface damage [461]. 'Floppy eyelid syndrome' has also been linked to smoking crack cocaine in case reports [461,470]. One report of a user applying topical cocaine directly to the ocular surface reported ulceration that led to a dense corneal scar in one eye and the other eye had to be enucleated following secondary angle-closure glaucoma [471].

5.3.2.3. Opioids. Natural opioids, such as morphine, or synthesized opioids, such as heroin, are known to be extremely addictive. They have a strong painkilling property and derivatives can be used medicinally for patients requiring high levels of analgesia such as late-stage cancer patients who are receiving palliative care. Abusers of opioids describe euphoria or exhilaration from use, but the methods of delivery can be an additional concern. Users will snort, smoke or inject the drug. The latter group may experience severe blood-borne infections from shared hypodermic needles. Long-term abusers will suffer from withdrawal symptoms upon cessation of use, and this may lead to criminal activity from users to ensure that they are able to continue to purchase the drug rather than enter the phase of withdrawal. Ocular surface effects are not common with opioids but new psychoactive substances that are synthesized to by-pass the legal aspects of the drug are known to have effects on the hair, skin and ocular surface. A case series of 3 individuals reported hair loss, hair depigmentation, dermatitis and DED (not otherwise defined) after using the synthetic opioid MT-45 [472]. Opioid-dependent mothers prescribed methadone during pregnancy were found to have an increased chance of abnormal visual development in their new-born children [473]. The infants displayed increased rates of strabismus (25%, 10-fold higher than in unaffected children), decreased visual acuity (22%) and nystagmus (11%) [474].

5.3.2.4. Hallucinogens. Lysergic Acid Diethylamide (LSD) is a very powerful hallucinogen. It is ingested and, like other hallucinogens, it can cause distortions in visual perception and reality. This distortion of reality may be the prime reason for users to take these types of drugs but often the effects result in despair or anxiety, with some users even reporting long-term effects known as 'flashbacks'. There is no clear evidence on whether ocular surface parameters are affected by this type of recreational drug, although with modern manufacturing methods, a drug delivery system that applied LSD directly to the ocular surface may have adverse effects [475], and since one of the lesser-known side--effects of LSD is dry mouth, dryness in the eye is a possibility.

5.3.2.5. Other recreational drugs. Solvent abuse can arise from inhaling fumes from items that are commonly available in households. Products such as aerosols, petrol, nail varnish and glue are inhaled, usually from a bag or other container holding the product. Since this type of drug abuse is linked to vapors emitted from the product being directly inhaled it would suggest there is a high likelihood of ocular surface damage and symptoms. However, this question has not been specifically studied.

5.4. Alcohol

Ocular surface effects of alcohol can be separated into those caused by direct contact between alcohol and the ocular surface [476], and those resulting from increased alcohol consumption via drinking [477,478]. Direct contact of the ocular surface with alcohol may be accidental or deliberate in certain ophthalmic procedures, such as laser refractive surgery, corneal cross-linking or recurrent erosion. Alcohol loosens the corneal epithelium, allowing it to be cleaved from the anterior limiting lamina (Bowman's membrane) [479].

Oral intake of alcohol has been noted in many studies as a contributory factor to DED, but this relationship can be influenced by confounding factors, such as hot climates or psychological aspects [34,50,367,378,379,476,480–485]. A Dutch study found a relationship between alcohol use and DED in females but not males, suggesting possible sex-specific effects [481]. Alcohol is categorized as a depressant that disrupts diverse neurological networks within the central nervous system. This endorses alterations in the regular biological mechanisms within the human body [486]. Alcohol consumption may be part of a wider issue that involves additional poor nutrition of the individual [179,487–489]. Heavy consumption of alcohol could lead to both temporary effects on the eye affecting the visual function or influence the commencement of further chronic eye conditions [179,453]. A correlation has been demonstrated between the intake of alcohol and deterioration of the tear film [490], as well as reduction in tear volume [491]. A further study supported this and discovered the presence of ethanol within the tears, associated with an increase in tear osmolarity and exacerbation of DED symptoms [492]. Chronic alcohol consumption can cause vitamin A deficiency [493], resulting in keratinization of the corneal and conjunctival epithelia, which could induce or exacerbate DED [485,492].

5.5. Caffeine

Caffeine (1,3,7-trimethylxanthine) is a natural psychostimulant found in tea, coffee, and cacao plants, and is consumed daily by more than 70% of the adult population in modern Western societies [494]. At physiological concentrations, caffeine acts as an adenosine receptor

antagonist, and exerts widespread pharmacological effects across multiple organ systems of the human body [495].

The effects of caffeine on the ocular surface have been investigated in a number of cross-sectional and prospective studies. The potential protective effects of caffeine have been highlighted in two population-based cross-sectional studies which have reported that regular caffeine consumption is associated with a decreased odds of DED (by self-reported history and combination of symptoms and signs, OR 0.75 and 0.82, respectively, both $p < 0.05$) [367,496], although other population and hospital-based cross-sectional studies have shown non-significant trends following multivariate adjustment [374,497–501]. There is currently no dedicated study investigating the effects of synthetic caffeine in energy drinks on the ocular surface, although one cross-sectional study evaluated dietary caffeine from the intake of coffee, tea, cola, and energy drinks, and did not demonstrate a significant association with Women's Health Study-defined DED [501]. However, it is acknowledged that there is significant methodological heterogeneity between the cross-sectional studies, particularly surrounding DED definition, and most studies were dependent on self-reported levels of caffeine consumption which can introduce recall bias.

Two prospective, placebo-controlled, crossover studies have also demonstrated increased tear meniscus height (+0.08 mm; 95% CI + 0.05 to +0.10 mm; $p < 0.001$) and Schirmer test values within the first 2 h following a single dose of 5–7 mg/kg of caffeine (+2.96 mm; 95% CI + 1.21 to +4.71 mm; $p < 0.001$) [502,503]. Another prospective observational study investigating the ocular surface changes during the menstrual cycle showed that caffeine intake was positively correlated with tear breakup time and phenol red thread test values during the ovulatory phase ($r = 0.5$, $p = 0.02$; and $r = 0.5$, $p = 0.01$, respectively) [504]. To date, the mechanisms underlying the effects of caffeine on the ocular surface remain poorly understood but have been hypothesized to involve stimulation of aqueous tear production from the lacrimal glands through the inhibition of 3′,5′-cyclic nucleotide phosphodiesterase [502–504].

Overall, current evidence would suggest that caffeine may exert protective effects on the ocular surface, however, larger, high quality prospective and/or randomized studies are required to establish any potential utility of caffeine in the prevention and/or treatment of DED.

6. Conclusions and future directions

In conclusion, many factors in the domains of mental, physical, and social health have been associated with various aspects of DED, both symptoms and signs, and other ocular surface diseases. Most associations have been examined cross-sectionally and thus there is a need for future studies that examine these questions longitudinally, taking into account relevant confounders, and acknowledging the multifactorial nature of DED. Mechanistic and animal studies may also lend support in robustly studying relationships between various lifestyle challenges and the ocular surface.

Overall, the key messages that can be extracted from the lifestyle challenges section are:

- Different studies across multiple geographies and populations have noted relationships between mental health indices (e.g., depression, anxiety, stress) and DED. The link is stronger for DED symptoms rather than for signs. Mechanisms underlying these associations are not clear and guidance on optimal therapy for individuals with DED and a comorbid psychological diagnosis is lacking.
- Current evidence supports a strong association between sleep disorders (quality and quantity of sleep) and DED symptoms, for any cause or type of sleep disorder. Further research is required to evaluate whether this relationship remains significant after adjusting for underlying psychosocial disorders (e.g., depression, anxiety) that is present to some degree in almost all sleep disorder cases.
- Obesity has been linked to abnormalities in meibomian gland function and eyelid architecture. Comorbid conditions such as sleep apnea may contribute to the noted association.
- Face mask wear has emerged as a new risk factor for DED, particularly evaporative DED and meibomian gland dysfunction.
- Sexual and reproductive issues are common in adulthood, and, as a whole, have been linked to various aspects of DED. The mechanisms underlying many of these associations are not clear and require further study. Furthermore, there is a need to identify and study therapeutic and preventive strategies.
- Solid evidence supports comorbidity between chronic pain conditions –specifically migraine, chronic pain syndrome and fibromyalgia– and DED. While reports principally focus on symptoms of DED, heterogeneity of the literature calls for additional data on the impact of chronic pain on DED signs and subtype (evaporative versus aqueous deficient). Moreover, further efforts should be devoted to standardizing pain measures to facilitate comparison across studies.
- The effect of recreational drugs on the eye is dependent on the actions of that drugs and its method of delivery into the body. Since recreational drugs are typically illegal, the literature lacks case-control studies and relies heavily on publications that are either case reports or case series.

Declaration of competing interest

Anat Galor: Novartis (C), Novaliq (C), Oyster Point Pharma (C), Palatin Technologies (C), Oculis (C), Dompé (C), Allergan (C), Shire (C)

Alexis Ceecee Britten-Jones: Plano (R)

Yun Feng: None.

Giulio Ferrari: Bausch + Lomb (F)

David Goldblum: Roche (F), Novartis (P), Haag-Streit (C), Johnson & Johnson Vision (C)

Preeya K. Gupta: Alcon (C), Allergan (C), Aldeyra (C), Azura (C), Expert Opinion (C), HanAll Biopharma (C), Johnson & Johnson Vision (C), Kala (C), New World Medical (C), Novartis (C), Ocular Science (C), Ocular Therapeutix (C), Orasis (C), Oyster Point Pharma (C), Santen (C), Spyglass (C), , Sight Sciences (C), Surface Ophthalmics (C), Sun Pharmaceuticals (C), Tarsus (C), Tear Lab (C), Tear Clear (C), Tissue Tech (C), Visionology (C), Zeiss (C)

Jesus Merayo-Lloves: BTI + d(C), Brill(C), Faes Pharma, Sophia(C), Théa (C)

Kyung-Sun Na: None.

Shehzad A. Naroo: None.

Kelly K. Nichols: Azura (F), Tear Science (F), Oyster Point Pharma (I, C), Bausch + Lomb (C), Bruder (C), Dompé (C), HanAll Bio (C), Kala (F, C), Novartis/Shire/Takeda (C), Osmotica (F), Sight Sciences (F), Tear Film Innovations/Alcon/Acquiom (C), Thea (C), Tarsus (C), TopiVert (C), Trukera (C), Versea (C), Xequel (C), Nicox (C), Novaliq (C)

Eduardo M. Rocha: Christalia Lab (

Louis Tong: Azura (C), Allergan (C), Santen (C), Alcon/Novartis (F, R), Bausch + Lomb (R), Vivavision Biotech (C)

Michael T. M. Wang: None.

Jennifer P. Craig: Adelphi Values Ltd (R), Alcon (F,R,C), Asta Supreme (R), Azura Ophthalmics (F,R), E-Swin (F,R), Johnson & Johnson Vision (R), Manuka Health (F), Medmont International (R), Novoxel (R), Oculeve (F), Photon Therapeutics (R), Resono Ophthalmic (F,R), TFOS (S), Th'ea Laboratories (F,R), Topcon (F,R), TRG Natural Pharmaceuticals (F,R).

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Appendix A. Supplementary data

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