# Comorbidities and Prescribed Medications in Patients With or Without Dry Eye Disease: A Population-Based Study

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• PURPOSE: To assess the proportion of comorbidities in patients with dry eye disease (DED) compared with matched patients without DED in a comprehensive US population.

• DESIGN: Retrospective case-control study.

• METHODS: Healthcare records for insurance claims data, detailing medical services incurred by military personnel and their families and dependents in military and civilian facilities across the United States from January 1, 2003, to March 31, 2015, were obtained from the Department of Defense (DOD) Military Health System (MHS). Diagnostic and procedural codes related to DED from selected International Classification of Diseases, Ninth Revision (ICD-9) Current Procedural Terminology codes and prescriptions for cyclosporine A ophthalmic emulsion were used to identify patients with newly diagnosed and prevalent DED in the MHS database. Age, sex, and geographically matched patients without DED were also identified from healthcare claims records. Medication use and comorbidities in these patient populations were assessed and compared.

• RESULTS: In both the newly diagnosed and prevalent DED samples, the most common comorbidities were hypertension, cataracts, thyroid disease, type 2 diabetes, and glaucoma. All comorbidities were significantly higher in the DED vs non-DED groups ($P < .001$). Medication use (including, but not limited to, ophthalmic agents and drugs to treat comorbidities) was also significantly higher in the DED than in the non-DED groups ($P < .001$).

• CONCLUSIONS: The high proportions of patients with DED with a range of comorbidities and prescribed medications highlight the need for a multidisciplinary approach to the management of these patients. (Am J Ophthalmol 2019;198:181–192. © 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).)

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DRY EYE DISEASE (DED) IS A MULTIFACTORIAL ocular surface disease that may manifest as ocular sensations ranging from discomfort to pain, with or without loss of visual acuity, and has a potentially significant impact on overall quality of life.[1,2] While increasing age and female sex are universal risk factors for DED, certain comorbid conditions, including an array of systemic diseases and the medications used to treat them, are also demonstrated risk factors for DED.[1,3-7]

There are 2 main etiologic classifications of DED: tear-deficient dry eye, owing to insufficient lacrimal gland production; and evaporative dry eye, caused by a decrease in the lipid layer protection of the aqueous layer of the tear film. These conditions may overlap. While the etiologies of DED are not mutually exclusive, each may be more closely associated with certain comorbidities of DED.[8] Sjögren syndrome, an autoimmune disease affecting the body's moisture-producing glands, particularly the mouth and eyes, is associated with tear-deficient dry eye. Patients with DED with Sjögren syndrome are more likely to be comorbid with a number of other autoimmune diseases; these include diabetes, thyroid disease, fibromyalgia, myasthenia gravis, gastroesophageal reflux disease, and, more specifically, rheumatic autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, scleroderma, and polymyositis/dermatomyositis.[9-12]

Meibomian gland dysfunction (MGD), which describes abnormalities of the glands that produce oils present in the lipid layer of the tear film, is associated with evaporative dry eye. Patients with DED with MGD are more likely to be comorbid with androgen deficiency/androgen therapy, discoid lupus erythematosus, rosacea, and hypertension.[13-17]

Recent reviews of DED classification and epidemiology indicate that a patient with dry eye may have multiple etiologies that contribute to his or her disease history.[1,18,19] Across DED etiologies, studies have found that patients with DED are more likely to have cardiovascular diseases, such as ischemic heart disease and cardiac arrhythmias, hypertension, peripheral vascular disorders or pulmonary

circulation disorders, hyperlipidemia, and stroke.[3,7] Conditions causing systemic stress, such as chronic obstructive pulmonary disease, nonallergic asthma, anemia, and liver or kidney disease, have also been associated with higher rates of occurrence in patients with DED.[3,7,9,20]

Statistically significant associations between DED and allergic conditions have been found in a range of studies across Ghana, Japan, Korea, the United Kingdom, and the United States.[20-23] This includes ocular conditions, such as allergic conjunctivitis, as well as nonocular allergic conditions, such as asthma, allergic rhinitis, and house dust mite (*Dermatophagoides farinae*) sensitivity.[21,23,24]

Psychiatric stress, mood disorders, and sleeping disorders are all found to occur at a higher frequency in patients with DED than in those without.[5,25-29] In several studies that focused on women, those with DED were more likely than those without DED to describe severe psychological stress, depressive moods, anxiety/depression problems, or a history of psychological counseling.[25,30,31] Further studies found significant associations between DED and anxiety and depression in other populations.[26,27,32] DED in US veteran populations was found to be highly comorbid with posttraumatic stress disorder, depression, and neuropathic ocular pain.[5,33,34]

Iatrogenic DED can be caused by prescribed systemic and ophthalmic medications and ophthalmic procedures.[35] Drugs commonly used to treat many of the DED comorbidities already discussed have off-target anticholinergic activity. This activity affects how acetylcholine interacts with neural receptors in a way that may disrupt ocular homeostasis.[36] Anticholinergic effects have been found in systemic drugs prescribed for type 2 diabetes, cardiovascular diseases, hypertension, depression, and anxiety, as well as in ophthalmic treatments for allergy.[37,38] Research has shown that the ophthalmic preservative benzalkonium chloride (BAK), found in some formulations of prescribed glaucoma drugs, has a toxic effect that may cause or exacerbate DED.[39] Finally, ophthalmic procedures, such as cataract surgery and laser-assisted in situ keratomileusis (LASIK) surgery, have been associated with an increased risk for DED.[40-42]

Evidence of association between DED and an array of common comorbidities has been established for a variety of select populations, both with and without control groups. However, this study uniquely reports medication use and ophthalmic procedures of patients in the context of their DED-associated and common age-related comorbidities. In the present analysis, the proportion of US Department of Defense (DOD) Military Health System (MHS) beneficiaries with DED, and common age-related and non–age-related comorbidities, prescribed medications, and ocular procedures, is compared with a rigorously matched control group without DED from the DOD MHS.

## METHODS

• **STUDY POPULATION:** The MHS database is a large population sample (>9.7 million beneficiaries) that covers active duty, retired, and reserve military personnel and their families or dependents. It includes individuals of nearly all ages and has representation across the major population density centers of the continental United States, Alaska, and Hawaii (N sufficient for >95% confidence level for prediction when comparing with US census data).[43] The MHS claims records contain comprehensive health-related data, including inpatient and outpatient healthcare service records, prescription records, and demographic information. Beneficiary data from the MHS between January 1, 2003, and March 31, 2015, were used in this analysis. The research data were developed in cooperation with the Naval Medical Center in Portsmouth, Virginia, USA, and the study was approved by the Naval Medical Research Unit – Dayton, Institutional Review Board (IRB protocol NAMRUD.2015.0005).

• **STUDY DESIGN:** Two DED patient populations, newly diagnosed DED and prevalent DED, as well as matched control groups for each, were identified from MHS beneficiary claims records. The newly diagnosed population permitted characterization of patient and treatment profiles during the early-diagnosed stages of DED (eg, at disease onset), and the prevalent population permitted characterization of patient and treatment profiles in recent years of patients diagnosed with DED. For all groups, selected beneficiaries were required to have had a continuous healthcare plan enrollment, had to be ≥18 years of age, and had to reside in the United States. For each DED group (newly diagnosed DED and prevalent DED), an index date, defined as the date of DED diagnosis, was used to demarcate a baseline and a study period. The baseline period was defined as the 2-year period preceding the index date. The study period was defined as the 1-year period following the index date. For the newly diagnosed DED group, the index date was the date of the first DED indicator claim occurring between January 1, 2013, and March 31, 2014. Newly diagnosed DED beneficiaries had to have continuous healthcare plan enrollment for 5 years prior to the index date with no DED indicator claims during that time. For the prevalent group, who had DED indicator claims during the baseline period (between January 1, 2012, and December 31, 2013), the index date was January 1, 2014. Prevalent DED beneficiaries had to have continuous healthcare plan enrollment from January 1, 2012, to December 31, 2014.

• **DEFINITION OF DRY EYE DISEASE AND CONTROL GROUPS:** Beneficiaries with DED were identified using diagnostic and procedural codes related to dry eye from

**TABLE 1.** Driving and Nondriving Indicators for Dry Eye Disease

| Indicator | Description | Definition of Confirmed DED |
|---|---|---|
| Driving Indicators[a] | | |
| 370.33 | Keratoconjunctivitis sicca | Either 2 independent records for this diagnosis or a combination of this ICD-9 code with any of the other indicators |
| 370.34 | Exposure keratoconjunctivitis | Either 2 independent records for this diagnosis or a combination of this ICD-9 code with any of the other indicators |
| 372.53 | Conjunctival xerosis | Either 2 independent records for this diagnosis or a combination of this ICD-9 code with any of the other indicators |
| 375.15 | Tear film insufficiency unspecified | Either 2 independent records for this diagnosis or a combination of this ICD-9 code with any of the other indicators |
| 710.2 | Sicca syndrome, Sjögren | Either 2 independent records for this diagnosis or a combination of this ICD-9 code with any of the other indicators |
| 68760 | Closure of the lacrimal punctum; by thermocauterization, ligation, or laser surgery | ≥1 record for this procedure or a combination of this CPT code with any of the other indicators |
| 68761 | Punctal plugs | ≥1 record for this procedure or a combination of this CPT code with any of the other indicators |
| 09.91 | Obliteration of lacrimal punctum | ≥1 record for this procedure or a combination of this CPT code with any of the other indicators |
| Restasis | Prescription fill for cyclosporine A ophthalmic solution (Restasis) | Either 2 prescription fills or a combination of this prescription fill with any of the other indicators |
| Nondriving Indicators[b] | | |
| 370.2 | Superficial keratoconjunctivitis | A combination of this ICD-9 code with any of the following indicators: a diagnosis for either 370.33, 370.34, 372.53, 375.15, or 710.20; a procedure for punctal plugs; or a prescription fill for Restasis |
| 370.21 | Punctate keratitis | A combination of this ICD-9 code with any of the following indicators: a diagnosis for either 370.33, 370.34, 372.53, 375.15, or 710.20; a procedure for punctal plugs; or a prescription fill for Restasis |
| 714.0 | Rheumatoid arthritis | A combination of this ICD-9 code with any of the following indicators: a diagnosis for either 370.33, 370.34, 372.53, 375.15, or 710.20; a procedure for punctal plugs; or a prescription fill for Restasis |
| | Lupus<br>695.4: Discoid lupus erythematosus<br>710.0: Systemic lupus erythematosus<br>373.34: Discoid lupus erythematosus of eyelid | A combination of this ICD-9 code with any of the following indicators: a diagnosis for either 370.33, 370.34, 372.53, 375.15, or 710.20; a procedure for punctal plugs; or a prescription fill for Restasis |

CPT = Current Procedural Terminology; DED = dry eye disease; ICD-9 = International Classification of Diseases, Ninth Revision.

[a]DED driving indicators were defined as those where 2 independent records of the same diagnosis, procedure, or prescription fill were sufficient to confirm the diagnosis of DED.

[b]DED nondriving indicators were defined as those that had to be combined with a driving indicator to confirm DED diagnosis.

selected International Classification of Diseases, Ninth Revision (ICD-9) and Current Procedural Terminology (CPT) codes for driving or nondriving indicators of DED, and prescriptions for cyclosporine A ophthalmic emulsion (Restasis; Allergan, Irvine, California, USA; Table 1). DED driving indicators were defined as those for which 2 independent records of the same diagnosis, procedure, or prescription fill were sufficient to confirm the diagnosis of DED. DED nondriving indicators were defined as those that had to be combined with a driving indicator to confirm DED diagnosis. Driving and nondriving DED indicators were identified. Beneficiaries who had no diagnostic and procedural codes or prescriptions related to dry eye during the baseline and study periods were identified for construction of non-DED control groups. Non-DED beneficiaries were matched to newly diagnosed or prevalent DED beneficiaries by year, age, sex, and geographic region.

• **IDENTIFICATION OF COMORBIDITIES:** Targeted lists of conditions, procedures, and medications were used to search medical health records claims. Construction of these lists was based on clinical knowledge of ocular conditions and comorbidities that are associated with DED and common to the age groups studied. They are categorized into DED-associated physical comorbidities (12 conditions/types), non–DED-associated physical comorbidities (26 conditions),

**TABLE 2.** Sex- and Age-Related Patient Demographics in the Newly Diagnosed Dry Eye Disease and Non–Dry Eye Disease Groups and the Prevalent Dry Eye Disease and Non–Dry Eye Disease Groups (Matched for Age and Geographic Region)

| | Newly Diagnosed DED N = 41 052 | Newly Diagnosed Non-DED N = 41 052 | Prevalent DED N = 285 666 | Prevalent Non-DED N = 285 666 |
|---|---|---|---|---|
| Female, n (%) | 25 481 (62.1) | 25 481 (62.1) | 194 707 (68.2) | 194 707 (68.2) |
| Age at index date (years, mean ± SD [median]) | 65.0 ± 15.0 [68] | 65.0 ± 15.0 [68] | 67.0 ± 15.0 [70] | 67.0 ± 15.0 [70] |
| Age group, n (%) | | | | |
| 18-29 | 1301 (3.2) | 1301 (3.2) | 8831 (2.9) | 8831 (2.9) |
| 30-39 | 2000 (4.9) | 2000 (4.9) | 11 640 (4.1) | 11 640 (4.1) |
| 40-49 | 3212 (7.8) | 3212 (7.8) | 18 857 (6.6) | 18 857 (6.6) |
| 50-54 | 2264 (5.5) | 2264 (5.5) | 13 983 (4.9) | 13 983 (4.9) |
| 55-59 | 2817 (6.9) | 2817 (6.9) | 17 745 (6.2) | 17 745 (6.2) |
| 60-64 | 3998 (9.7) | 3998 (9.7) | 26 223 (9.2) | 26 223 (9.2) |
| 65-69 | 6985 (17.0) | 6985 (17.0) | 39 490 (13.8) | 39 490 (13.8) |
| 70-74 | 6481 (15.8) | 6481 (15.8) | 43 525 (15.2) | 43 525 (15.2) |
| 75-79 | 5510 (13.4) | 5510 (13.4) | 44 186 (15.5) | 44 186 (15.5) |
| 80+ | 6484 (15.8) | 6484 (15.8) | 61 636 (21.6) | 61 636 (21.6) |
| Region, n (%)[a] | | | | |
| Central | 6687 (16.3) | 6687 (16.3) | 47 075 (16.5) | 47 075 (16.5) |
| Southeast | 6610 (16.1) | 6610 (16.1) | 46 804 (16.4) | 46 804 (16.4) |
| Southwest | 5616 (13.7) | 5616 (13.7) | 41 816 (14.6) | 41 816 (14.6) |
| Northeast | 4998 (12.2) | 4998 (12.2) | 33 220 (11.6) | 33 220 (11.6) |
| Mid-Atlantic | 4140 (10.1) | 4140 (10.1) | 27 775 (9.7) | 27 775 (9.7) |
| Gulf South | 3706 (9.0) | 3706 (9.0) | 27 073 (9.5) | 27 073 (9.5) |
| Heartland | 3383 (8.2) | 3383 (8.2) | 22 651 (7.9) | 22 651 (7.9) |
| Southern California | 2398 (5.8) | 2398 (5.8) | 16 125 (5.6) | 16 125 (5.6) |
| Northwest | 1700 (4.1) | 1700 (4.1) | 11 197 (3.9) | 11 197 (3.9) |
| Golden Gate | 1061 (2.6) | 1061 (2.6) | 7396 (2.6) | 7396 (2.6) |
| Hawaii | 572 (1.4) | 572 (1.4) | 3416 (1.2) | 3416 (1.2) |
| Alaska | 181 (0.4) | 181 (0.4) | 1118 (0.4) | 1118 (0.4) |

DED = dry eye disease.

[a]Obtained as of the index date. For the Newly Diagnosed Sample, the index date was defined as the date of the first Dry Eye Disease (DED) driving indicator; for the Prevalent Sample, the index date was defined as January 1, 2014.

psychological comorbidities (22 conditions), ocular conditions (18 types), ocular comorbidities (5 categories), ocular medications (16 categories), nonocular medications (11 categories), and ocular procedures (6 types). Comorbidities were assessed during the baseline and study periods for all groups. Ocular and nonocular medications and ocular procedures were assessed only during the baseline period. In the manner of a study by Elixhauser, a list of comorbidities, with their corresponding ICD-9 diagnoses, was used to identify relevant records.[44,45]

• **STATISTICAL ANALYSIS:** During the baseline period, beneficiary demographics (continuous variables summarized by mean, standard deviation, median; categorical variables summarized by n and %) were compared between the DED and non-DED groups using Wilcoxon signed rank tests for continuous variables and McNemar test for categorical variables. During the baseline period, ocular and nonocular medications and ocular procedures were compared between the DED and non-DED groups using Wilcoxon signed rank tests for continuous variables and McNemar test for categorical variables. Additionally, fold increases (n DED/n non-DED) were reported for all comparisons where $P < .001$. During the study period, comorbidities (summarized by n and proportion) were compared between the DED and non-DED groups using the McNemar test for categorical variables. Additionally, fold increases (n DED/n non-DED) were reported for all comparisons where $P < .001$. Where newly diagnosed and prevalent DED samples are compared, only data from years 2012-2015 were used.

## RESULTS

• **DEMOGRAPHICS:** The newly diagnosed DED and matching non-DED groups each had 41 052 beneficiaries, with a mean age of 65.0 years (median 68 years). Those ≥50 years of age constituted 84.1% of the group, and 62.1% were female. The largest age group was 65-69 years, comprising

17.0% of the total. The prevalent DED and matching non-DED group each had 285 666 beneficiaries, with a mean age of 67.0 years (median, 70 years). Those ≥50 years of age constituted 86.4% of the group, and 68.2% were female. The largest age group was ≥80 years, comprising 21.6% of the total. For all groups, the largest segment by geographic region was the central region (16.3% for the newly diagnosed DED and non-DED matched groups, and 16.5% for the prevalent DED and non-DED matched groups; Table 2).

There were only minor differences between all groups in the distribution of beneficiaries in race and socioeconomic status (Table 3).

• **COMORBIDITIES:** The proportions of patients with comorbidities within each sample (newly diagnosed or prevalent) and group (DED or non-DED) are reported for the study period (post determination of DED status). In Tables 4-7, comorbid conditions with proportion >10% are highlighted in gray.

*Dry Eye Disease–Associated Physical Comorbidities*. Data for 12 types of common DED-associated physical comorbidities were analyzed among the DED and non-DED groups in the newly diagnosed and prevalent samples (Table 4). All 12 conditions occurred at significantly higher proportions in the DED than in the non-DED groups ($P < .001$). The top DED-associated physical comorbidities, with proportions >10% in both the newly diagnosed and prevalent DED samples, were hypertension, thyroid disease, type 2 diabetes, sleep apnea, depression, and cardiovascular diseases. Occurrences were 1.4- to 2.3-fold higher in the DED than in the non-DED groups.

*Non–Dry Eye Disease–Associated Physical Comorbidities*. Data for 27 types of common physical non–DED-associated comorbidities were analyzed among the DED and non-DED groups in the newly diagnosed and prevalent samples (Table 5). All conditions occurred at proportions significantly higher in the DED than in the non-DED groups ($P < .001$). The top comorbidities, which occurred at proportions >10% in both the newly diagnosed and prevalent DED samples, were type 2 diabetes, chronic pulmonary disease, hypothyroidism, deficiency anemia, peripheral vascular disease, and valvular disease. These occurred 1.5- to 1.6-fold more often in beneficiaries with both newly diagnosed and prevalent DED than in those without DED. Notably, the category of rheumatoid arthritis and collagen vascular diseases was observed at occurrences <4% in all groups; however, they were found 2.6-fold more often in the newly diagnosed DED group, and occurrence was 3.8-fold higher in the prevalent DED group, when compared with their respective non-DED groups.

*Psychological Comorbidities*. Of 22 psychological comorbidities evaluated (Table 6), across both the newly diagnosed and prevalent samples, all occurred at proportions significantly higher in the DED than in the non-DED groups ($P < .001$). Sleep disorders, depressive disorders, anxiety disorders, and substance- (alcohol and drug) related disorders were the top psychological comorbidities found. Each occurred at a proportion of ~5%. Psychological comorbidities were 1.6- to 1.9-fold higher in both the newly diagnosed and prevalent DED groups compared with the matched non-DED groups, except substance (alcohol- and drug-related) disorders and neurocognitive disorders, which were ≤1.4-fold higher.

*Ocular Comorbidities*. Of 6 ocular conditions evaluated (Table 7), across both the newly diagnosed and prevalent samples, all occurred at proportions significantly higher in the DED than in the non-DED groups ($P < .001$). Cataract, glaucoma, eyelid disorders, and macular degeneration were found significantly more often in the newly diagnosed and prevalent DED groups than in the matching non-DED groups. Overall, ocular conditions were observed 2.6- to 8.5-fold more often in the newly diagnosed DED group than in its matched non-DED group, and occurrence was 2.1- to 5.3-fold higher in the prevalent DED group than in its matched non-DED group.

• **OCULAR PROCEDURES:** The proportions of 6 ocular procedures were assessed during the baseline period (Table 7). Five procedures were performed on beneficiaries at proportions significantly higher in the DED than in the non-DED groups in both newly diagnosed and prevalent samples ($P < .001$). Cataract surgery and retinal procedures occurred in >10% of DED groups, LASIK/refractive and glaucoma surgery occurred in ~2%-3% of the DED groups, and the strabismus procedure occurred in 0.1% of the DED groups. The remaining procedure, eyelid surgery, was reported for only 1 patient, who was in the prevalent DED group. Ocular procedures were undertaken 1.6- to 6.8-fold more often in the newly diagnosed DED group and 1.8- to 4.5-fold more often in the prevalent DED group when compared with their matched non-DED groups.

• **MEDICATIONS:** The proportions of patients with prescribed medications within each sample (newly diagnosed or prevalent) and group (DED or non-DED) are reported for the baseline period.

*Nonocular Medications*. Across 11 categories of nonocular medications evaluated during the baseline period (Table 8), all were prescribed to beneficiaries at proportions significantly higher in the DED than in the non-DED groups for both newly diagnosed and prevalent samples ($P < .001$). The most commonly prescribed medications, with prescription proportions ≥20% for beneficiaries with DED, were narcotic analgesics/strong pain killers, decongestants/vasoconstrictors, β-blockers, antidepressants, diuretics, and anxiolytics. All medication

**TABLE 3.** Patient Demographics in the Newly Diagnosed Dry Eye Disease and Non–Dry Eye Disease Groups and the Prevalent Dry Eye Disease and Non–Dry Eye Disease Groups (Unmatched for Race and Socioeconomic Status)

| | Newly Diagnosed DED N = 41 052 | Newly Diagnosed Non-DED N = 41 052 | *P* Value | Prevalent DED N = 285 666 | Prevalent Non-DED N = 285 666 | *P* Value |
|---|---|---|---|---|---|---|
| Race, n (%) | | | | | | |
| White | 6956 (16.9) | 7143 (17.4) | .040[b] | 38 891 (13.6) | 41 489 (14.5) | <.001[b] |
| Black | 2146 (5.2) | 1767 (4.3) | <.001[b] | 13 035 (4.6) | 10 613 (3.7) | <.001[b] |
| Asian or Pacific Islander | 841 (2.0) | 588 (1.4) | <.001[b] | 5576 (2.0) | 3627 (1.3) | <.001[b] |
| Hispanic | 634 (1.5) | 475 (1.2) | <.001[b] | 3823 (1.3) | 2540 (0.9) | <.001[b] |
| American Indian or Alaskan Native | 117 (0.3) | 107 (0.3) | .498 | 715 (0.3) | 689 (0.2) | .486 |
| Other | 214 (0.5) | 172 (0.4) | .031[b] | 1441 (0.5) | 1085 (0.4) | <.001[b] |
| Unknown or missing | 30 144 (73.4) | 30 800 (75.0) | <.001[b] | 222 185 (77.8) | 225 623 (79.0) | <.001[b] |
| Socioeconomic status, n (%)[a] | | | | | | |
| Enlisted, senior | 26 534 (64.6) | 27 539 (67.1) | <.001[b] | 181 926 (63.7) | 191 940 (67.2) | <.001[b] |
| Officer, senior | 10 357 (25.2) | 9388 (22.9) | <.001[b] | 74 890 (26.2) | 65 138 (22.8) | <.001[b] |
| Enlisted, junior | 1116 (2.7) | 1302 (3.2) | <.001[b] | 8812 (3.1) | 9354 (3.3) | <.001[b] |
| Officer, junior | 1510 (3.7) | 1357 (3.3) | .003[b] | 9802 (3.4) | 9028 (3.2) | <.001[b] |
| Warrant officer | 1531 (3.7) | 1438 (3.5) | .082 | 10 210 (3.6) | 10 080 (3.5) | .352 |
| Other | 1 (0.0) | 5 (0.0) | .102 | 8 (0.0) | 1 (0.0) | .020[b] |
| Unknown | 3 (0.0) | 23 (0.1) | <.001[b] | 18 (0.0) | 125 (0.0) | <.001[b] |

DED = dry eye disease.
[a]Based on the sponsor's aggregated rank group at the index date.
[b]Patient characteristics were compared using Wilcoxon signed-rank tests for continuous variables and McNemar tests for categorical variables.

categories assessed were prescribed more often for DED beneficiaries than for beneficiaries in the matched non-DED groups (1.3- to 1.5-fold and 1.3- to 1.7-fold in the newly diagnosed and prevalent samples, respectively). Estrogen therapy, primarily a treatment for menopausal women, is reported to be associated with DED.[46,47] It was prescribed for 6.6% and 7.1% of the newly diagnosed and prevalent DED groups vs 4.4% and 4.6% in the matched non-DED groups.[46,47]

*Ocular Medications*. Across 16 categories of ocular medications evaluated during the baseline period (Table 8), all were prescribed to patients at proportions significantly higher in the DED than in the non-DED groups for both the newly diagnosed and prevalent samples ($P < .001$). The most commonly prescribed ocular medications were ophthalmic anti-infectives, ophthalmic steroids, ophthalmic nonsteroidal anti-inflammatory drugs, ophthalmic antiallergics (antihistamines), ophthalmic prostaglandins, and artificial tears and lubricants. All of these medications were prescribed to more DED beneficiaries, by 2.2- to 4.9-fold and 2.2- to 15.8-fold, respectively, in the newly diagnosed and prevalent samples.

## DISCUSSION

IN THE CURRENT ANALYSIS OF THE MHS CLAIMS DATABASE, data from newly diagnosed DED (~40 000 beneficiaries) and prevalent DED (>285 000 beneficiaries) samples are compared with demographically matched non-DED patient groups to assess the relative proportion of DED-associated and common age-related comorbidities, ocular procedures, and prescribed medications. The results are in agreement with previously reported DED-associated comorbidities and further expand the list of conditions that may be considered to be associated with DED.[3-7,9,29,34] Additionally, the new study reports on the therapeutic treatments undertaken by beneficiaries having various comorbidities, both with and without DED, and thus may provide additional context to the risk/benefit consideration of common treatments for the DED and at-risk-of-DED populations. For example, evidence was found of conditions in which DED associations may be attributable to ocular manifestations of a primary disease (eg, thyroid imbalance, rosacea). Analysis for common age-related conditions, in the context of prescribed medications or treatments that may cause iatrogenic DED, adds significantly to this important field of research.

Across all comorbidities evaluated, hypertension was the most commonly observed comorbidity in both the DED and non-DED groups of both the newly diagnosed and prevalent samples. However, significantly higher proportions of beneficiaries (>60%) were found in both the newly diagnosed and prevalent DED groups compared with the matched non-DED groups (44.1%-45.7%). This translates into a 1.4-fold higher rate of occurrence in DED beneficiaries. The primary ranking of hypertension is not unexpected, given that the mean age of the population sample

**TABLE 4.** Dry Eye Disease–Associated Physical Comorbidities

| DED-Associated Physical Comorbidities | Newly Diagnosed DED, N (%) | Newly Diagnosed Non-DED, N (%) | Fold[a] | Prevalent DED, N (%) | Prevalent Non-DED, N (%) | Fold[a] |
|---|---|---|---|---|---|---|
| Hypertension | 24 927 (60.7) | 18 123 (44.1) | 1.4 | 178 489 (62.5) | 130 441 (45.7) | 1.4 |
| Type 2 diabetes | 9995 (24.3) | 7109 (17.3) | 1.4 | 68 782 (24.1) | 50 704 (17.7) | 1.4 |
| Thyroid disease | 8953 (21.8) | 5796 (14.1) | 1.5 | 70 444 (24.7) | 44 259 (15.5) | 1.6 |
| Sleep apnea | 7628 (18.6) | 4277 (10.4) | 1.8 | 54 034 (18.9) | 29 354 (10.3) | 1.8 |
| Depression | 5466 (13.3) | 3460 (8.4) | 1.6 | 41 735 (14.6) | 26 359 (9.2) | 1.6 |
| Cardiovascular diseases | 4598 (11.2) | 2978 (7.3) | 1.5 | 36 250 (12.7) | 23 246 (8.1) | 1.6 |
| Obesity | 4216 (10.3) | 2867 (7.0) | 1.5 | 28 369 (9.9) | 19 687 (6.9) | 1.4 |
| Insomnia | 3425 (8.3) | 1871 (4.6) | 1.8 | 24 995 (8.7) | 13 927 (4.9) | 1.8 |
| Kidney disease | 3945 (9.6) | 2696 (6.6) | 1.5 | 32 037 (11.2) | 21 607 (7.6) | 1.5 |
| Autoimmune diseases (excluding DED indicators)[b] | 1997 (4.9) | 1145 (2.8) | 1.7 | 16 380 (5.7) | 7911 (2.8) | 2.0* |
| Rosacea | 1018 (2.5) | 434 (1.1) | 2.3* | 6587 (2.3) | 2963 (1.0) | 2.3* |
| Parkinson disease | 509 (1.2) | 285 (0.7) | 1.7 | 4285 (1.5) | 2162 (0.8) | 1.9 |

DED = dry eye disease.

For proportions >10%, cells are shaded gray.

[a]Fold = (DED %/non-DED %), numbers indicated by asterisk (*) are ≥2-fold, all DED vs non-DED $P < .001$.

[b]DED indicators excluded were rheumatoid arthritis and Sjögren sicca syndrome; included autoimmune diseases were ankylosing spondylitis, psoriasis, ulcerative colitis, Crohn disease, sarcoidosis, idiopathic fibrosing alveolitis, psoriatic arthritis, scleroderma or systemic sclerosis, and reactive arthritis.

**TABLE 5.** Physical Comorbidities

| Physical Comorbidities | Newly Diagnosed DED, N (%) | Newly Diagnosed Non-DED, N (%) | Fold[a] | Prevalent DED, N (%) | Prevalent Non-DED, N (%) | Fold[a] |
|---|---|---|---|---|---|---|
| Diabetes mellitus | 10 043 (24.5) | 7157 (17.4) | 1.4 | 69 157 (24.2) | 51 092 (17.9) | 1.4 |
| Chronic pulmonary disease | 8061 (19.6) | 5516 (13.4) | 1.5 | 61 922 (21.7) | 40 798 (14.3) | 1.5 |
| Hypothyroidism | 7616 (18.6) | 5007 (12.2) | 1.5 | 60 834 (21.3) | 38 473 (13.5) | 1.6 |
| Deficiency anemia | 5288 (12.9) | 3534 (8.6) | 1.5 | 42 503 (14.9) | 27 499 (9.6) | 1.6 |
| Peripheral vascular disease | 4550 (11.1) | 3056 (7.4) | 1.5 | 36 484 (12.8) | 24 045 (8.4) | 1.5 |
| Solid tumor without metastasis | 4267 (10.4) | 2892 (7.0) | 1.5 | 30 624 (10.7) | 21 076 (7.4) | 1.6 |
| Valvular disease | 4229 (10.3) | 2728 (6.6) | 1.6 | 34 030 (11.9) | 21 196 (7.4) | 1.6 |
| Neurologic disorder | 3676 (9.0) | 2609 (6.4) | 1.4 | 32 026 (11.2) | 20 982 (7.3) | 1.5 |
| Fluid electrolyte disorders | 3662 (8.9) | 2501 (6.1) | 1.5 | 31 013 (10.9) | 20 640 (7.2) | 1.5 |
| Renal failure | 3599 (8.8) | 2498 (6.1) | 1.4 | 29 441 (10.3) | 19 971 (7.0) | 1.5 |
| Rheumatoid arthritis and collagen vascular diseases | 3338 (8.1) | 1283 (3.1) | 2.6* | 35 740 (12.5) | 9314 (3.3) | 3.8* |
| Congestive heart failure | 2611 (6.4) | 1819 (4.4) | 1.4 | 22 388 (7.8) | 15 657 (5.5) | 1.4 |
| Psychoses | 2439 (5.9) | 1572 (3.8) | 1.6 | 19 187 (6.7) | 11 723 (4.1) | 1.6 |

DED = dry eye disease.

For proportions >10%, cells are shaded gray.

[a]Fold = (DED %/non-DED %), numbers indicated by asterisk (*) are ≥2-fold, all DED vs non-DED $P < .001$.

was 65.0 years for the newly diagnosed DED groups and 67.0 years for the prevalent DED groups, and more than 80% of beneficiaries overall were ≥50 years of age. There was a 1.6-fold higher rate of cardiovascular disease in both DED groups than in the matched non-DED groups. Patients with hypertension and cardiovascular disease are likely to be taking classes of medications that have known anticholinergic effects. Drugs with anticholinergic effects can disrupt ocular homeostasis and have been found to increase the occurrence or severity of symptoms of DED.[36-38] In this study, >25% of beneficiaries with DED, as well as >20% of those without DED, had prescriptions for β-blockers and diuretics, which have known anticholinergic activity. The proportion of beneficiaries

**TABLE 6.** Psychological Comorbidities

| Psychological Comorbidities | Newly Diagnosed DED, N (%) | Newly Diagnosed Non-DED, N (%) | Fold[a] | Prevalent DED, N (%) | Prevalent Non-DED, N (%) | Fold[a] |
|---|---|---|---|---|---|---|
| Sleep disorders | 8087 (19.7) | 4560 (11.1) | 1.8 | 58 000 (20.3) | 31 591 (11.1) | 1.8 |
| Other conditions that may be a focus of clinical attention[b] | 7163 (17.4) | 4389 (10.7) | 1.6 | 48 133 (16.8) | 29 859 (10.5) | 1.6 |
| Depressive disorders | 5511 (13.4) | 3485 (8.5) | 1.6 | 41 972 (14.7) | 26 538 (9.3) | 1.6 |
| Anxiety disorders | 4682 (11.4) | 2804 (6.8) | 1.7 | 35 472 (12.4) | 21 448 (7.5) | 1.7 |
| Substance- (alcohol and drug) related disorders | 2724 (6.6) | 2269 (5.5) | 1.2 | 17 162 (6.0) | 15 729 (5.5) | 1.1 |
| Trauma- and stressor-related disorders | 1959 (4.8) | 1022 (2.5) | 1.9 | 12 399 (4.3) | 7016 (2.5) | 1.7 |
| Neurocognitive disorder | 1608 (3.9) | 1240 (3.0) | 1.3 | 15 269 (5.3) | 10 768 (3.8) | 1.4 |

DED = dry eye disease.
For proportions >10%, cells are shaded gray.
[a]Fold = (DED %/non-DED %), all DED vs non-DED $P < .001$.
[b]Includes relational problems, abuse and neglect, educational and occupational problems, housing and economic problems, and other problems and circumstances of personal history.

**TABLE 7.** Ocular Comorbidities and Ocular Procedures

| Ocular Comorbidities and Ocular Procedures[a] | Newly Diagnosed DED, N (%) | Newly Diagnosed Non-DED, N (%) | Fold[b] | Prevalent DED, N (%) | Prevalent Non-DED, N (%) | Fold[b] |
|---|---|---|---|---|---|---|
| Cataract | 18 990 (46.3) | 6370 (15.5) | 3.0* | 100 241 (35.1) | 46 184 (16.2) | 2.2* |
| Glaucoma | 9395 (22.9) | 2833 (6.9) | 3.3* | 57 836 (20.2) | 21 693 (7.6) | 2.7* |
| Eyelid disorders | 8285 (20.2) | 1058 (2.6) | 7.8* | 40 355 (14.1) | 8183 (2.9) | 4.9* |
| Macular degeneration | 4383 (10.7) | 1678 (4.1) | 2.6* | 30 691 (10.7) | 14 290 (5.0) | 2.1* |
| Conjunctiva and sclera, chronic conjunctivitis | 2799 (6.8) | 331 (0.8) | 8.5* | 13 810 (4.8) | 2570 (0.9) | 5.3* |
| General eye symptoms | 2461 (6.0) | 498 (1.2) | 4.9* | 12 529 (4.4) | 3691 (1.3) | 3.4* |
| Cataract surgery | 6092 (14.8) | 2064 (5.0) | 3.0* | 38 538 (13.5) | 16 260 (5.7) | 2.4* |
| Retinal procedure | 4900 (11.9) | 3000 (7.3) | 1.6 | 39 279 (13.7) | 21 794 (7.6) | 1.8 |
| LASIK/refractive surgery | 1259 (3.1) | 250 (0.6) | 5.0* | 8312 (2.9) | 1859 (0.7) | 4.5* |
| Glaucoma surgery | 689 (1.7) | 203 (0.5) | 3.4* | 5023 (1.8) | 1575 (0.6) | 3.2* |
| Strabismus surgery | 27 (0.1) | 4 (0.0) | NA | 190 (0.1) | 54 (0.0) | NA |
| Eyelid surgery | 0 (0.0) | 0 (0.0) | NA | 1 (0.0) | 0 (0.0) | NA |

DED = dry eye disease; LASIK = laser-assisted in situ keratomileusis; NA = not applicable.
For proportions >10%, cells are shaded gray.
[a]Ocular comorbidities were assessed during the study period; ocular procedures were assessed during the baseline period.
[b]Fold = (DED %/non-DED %), numbers indicated by asterisk (*) are ≥2-fold, all DED vs non-DED $P < .001$.

with a history of renal failure was higher in beneficiaries with DED. Patients with renal insufficiencies are also often treated with diuretics. The association between DED and renal disease may arise from ocular manifestations of renal disease and anticholinergic effects of treatment with diuretics.

Type 2 diabetes is a common risk factor for ocular diseases, including retinopathy, cataracts, glaucoma, DED, and other ocular surface conditions.[48] When diabetes is not adequately controlled, it can cause a variety of corneal alterations, including prolonged healing times for epithelial damage, neuropathy, and decreased tear production. In the present study, diabetes was the second most common comorbidity in beneficiaries with DED. Diabetes was found in >24% of those with newly diagnosed and prevalent DED compared with 17.3%-17.7% in matched non-DED beneficiaries, a 1.4-fold increase for the DED groups. Anticholinergic effects have been found for metformin, which is first-line therapy for most patients with type 2 diabetes.[49]

The thyroid gland and the body's balance of thyroid hormones can be affected through a range of mechanisms (autoimmune, iodine-deficient, drug-induced, genetic mutation).[50]

**TABLE 8.** Nonocular and Ocular Medications Assessed During the Baseline Period

| Medications | Newly Diagnosed DED, N (%) | Newly Diagnosed Non-DED, N (%) | Fold[a] | Prevalent DED, N (%) | Prevalent Non-DED, N (%) | Fold[a] |
|---|---|---|---|---|---|---|
| Narcotic analgesics/strong pain killers | 21 629 (52.7) | 16 271 (39.6) | 1.3 | 159 101 (55.7) | 113 349 (39.7) | 1.4 |
| Decongestants/vasoconstrictors | 13 646 (33.2) | 8811 (21.5) | 1.5 | 99 550 (34.8) | 59 615 (20.9) | 1.7 |
| β-blockers | 12 052 (29.4) | 9504 (23.2) | 1.3 | 91 625 (32.1) | 70 511 (24.7) | 1.3 |
| Antidepressants | 11 623 (28.3) | 8535 (20.8) | 1.4 | 88 823 (31.1) | 61 976 (21.7) | 1.4 |
| Diuretics | 11 378 (27.7) | 8832 (21.5) | 1.3 | 86 019 (30.1) | 65 275 (22.9) | 1.3 |
| Anxiolytics | 8897 (21.7) | 6021 (14.7) | 1.5 | 67 642 (23.7) | 43 776 (15.3) | 1.5 |
| Diabetes medications | 7655 (18.6) | 6023 (14.7) | 1.3 | 52 744 (18.5) | 43 074 (15.1) | 1.2 |
| Sleep medications | 5786 (14.1) | 3768 (9.2) | 1.5 | 42 713 (15.0) | 26 208 (9.2) | 1.6 |
| Doxycycline | 4758 (11.6) | 3282 (8.0) | 1.4 | 36 365 (12.7) | 22 845 (8.0) | 1.6 |
| Estrogen therapy | 2713 (6.6) | 1812 (4.4) | 1.5 | 20 406 (7.1) | 13 074 (4.6) | 1.5 |
| Ophthalmic anti-infectives | 9010 (21.9) | 3430 (8.4) | 2.6* | 58 978 (20.6) | 25 135 (8.8) | 2.3* |
| Ophthalmic steroids | 8828 (21.5) | 3031 (7.4) | 2.9* | 63 750 (22.3) | 23 006 (8.1) | 2.8* |
| Ophthalmic NSAIDs | 4272 (10.4) | 1422 (3.5) | 3.0* | 25 400 (8.9) | 11 157 (3.9) | 2.3* |
| Ophthalmic antiallergics (antihistamines) | 3076 (7.5) | 1145 (2.8) | 2.7* | 26 897 (9.4) | 8033 (2.8) | 3.4* |
| Ophthalmic prostaglandins | 2834 (6.9) | 1314 (3.2) | 2.2* | 22 531 (7.9) | 10 176 (3.6) | 2.2* |
| Artificial tears and lubricants | 2530 (6.2) | 514 (1.3) | 4.9* | 49 565 (17.4) | 3232 (1.1) | 15.8* |

DED = dry eye disease; NSAID = nonsteroidal anti-inflammatory drug.
For proportions >10%, cells are shaded gray.
[a]Fold = (DED %/non-DED %), numbers indicated by asterisk (*) are ≥2-fold, all DED vs non-DED $P < .001$.

Research has found an association between DED and diseases that affect the thyroid gland.[22] An imbalance in thyroid hormones can cause negative effects on the lacrimal gland, tear film, and ocular surface.[3,6,7,26,32,51,52] Furthermore, thyroid enzyme antigens may attack ocular tissues and/or the thyroid stimulation hormone receptors in the lacrimal glands, which can cause aberrant signaling in tear production.[6,26,32,51,53,54] There was a 1.5- to 1.6-fold higher proportion of beneficiaries with thyroid disease in beneficiaries with DED vs those without DED. Hypothyroidism accounted for >85% of thyroid disease identified in both DED and non-DED beneficiaries in this study.

There are well-established associations between depression/antidepressants, anxiety/anxiolytics, and DED that are reinforced by the present results.[5,24,26,27,51] The 1.7-fold higher proportions of DED beneficiaries with anxiety, 1.4-fold higher proportion of DED patient prescriptions for anxiolytics, 1.6-fold higher proportion of DED beneficiaries with depressive disorders, and 1.4-fold higher proportion of DED patient prescriptions for antidepressants, compared with their non-DED groups, provides more context for DED risk from these common conditions. The Beaver Dam Eye Study assessed and found increased incidence of DED in patients using antianxiety medications and antidepressants. A study on a veterans population found increased DED risk for patients with depression (odds ratio [OR], 1.91; 95% confidence interval [CI], 1.73-2.10) and antidepressants (OR, 1.97; 95% CI, 1.79-2.17), as well as antianxiety medications (OR, 1.74; 95% CI, 1.58-1.91); however, anxiety was not found to increase DED risk.[33] In a retrospective study of University of North Carolina outpatient clinics identifying ICD-9 diagnosis codes for dry eye disease, anxiety, and depression, higher risk of DED was found for both conditions (anxiety OR, 2.8; 95% CI, 2.6-3.0; depression OR, 2.9; 95% CI, 2.7-3.1).[27] However, that study did not assess anxiolytic and antidepressant use.

Antidepressant drug prescriptions for beneficiaries in this study population were higher for the DED groups (28.3% newly diagnosed, 31.1% prevalent) compared with the non-DED groups (20.8% newly diagnosed, 21.7% prevalent). Interestingly, prescription rates were 2-fold higher in all groups than the proportion of beneficiaries with reported depressive disorders (DED: 13.4% newly diagnosed, 14.7% prevalent; non-DED: 8.5% newly diagnosed, 9.3% prevalent). This may be attributable to off-label prescriptions of antidepressants for conditions such as neuropathic pain.[2,4,34] Similarly, anxiolytic prescriptions for beneficiaries were 2-fold higher (DED: 21.7 newly diagnosed, 23.7% prevalent; non-DED: 14.7 newly diagnosed, 15.3% prevalent) than the proportion of beneficiaries with anxiety disorders (DED: 11.4 newly diagnosed, 12.4% prevalent; non-DED: 6.8 newly diagnosed, 7.5% prevalent). Because both antidepressant and anxiolytic medications are associated with a higher proportion of patients with DED,[5,17,22,29,36,54-56] their use by patients with DED, or at risk for DED, should be ascertained even in the absence of a clinical diagnosis of depression and/or anxiety.[5,17,22,29,36,53-55]

Closer alignment of conditions to associated prescribed medications was found for beneficiaries with sleeping disorders, including sleep apnea (the proportion of sleep medication prescriptions is ~70%-90% of the proportion of beneficiaries with sleep disorders across all groups). Sleep apnea has been associated with floppy eyelid syndrome, which, owing to incomplete blinking or an inability to close the eyes completely, is a risk factor for DED.[57] Insomnia, which occurs 1.8-fold more often in the DED groups than in the matched non-DED groups, has been linked to depression and may incur subsequent antidepressant use.[58] There was a 1.5- to 1.6-fold higher prescription rate for sleep medication in the DED groups compared with the non-DED groups.

Ocular manifestations of autoimmune disorders, such as Sjögren syndrome and rheumatoid arthritis, are known etiologies of DED.[1] Rheumatoid arthritis and collagen vascular diseases occurred more often in the newly diagnosed and prevalent DED groups compared with the matched non-DED groups (2.6- and 3.8-fold, respectively). The rate of autoimmune disease comorbidity across a wide range of conditions (ankylosing spondylitis, psoriasis, ulcerative colitis, Crohn disease, sarcoidosis, idiopathic fibrosing alveolitis, psoriatic arthritis, scleroderma or systemic sclerosis, and reactive arthritis) was also significantly higher in the DED groups than in the non-DED matched groups (1.7- to 2.0-fold). Some of these conditions are so strongly associated with DED that they are considered clinical indicators of DED. Medications used in the treatment of autoimmune diseases may also disrupt ocular immune homeostasis.[52,59]

Medication prescriptions across therapeutic classes were generally higher in the DED groups than in the non-DED groups. For ocular medications, all of which were prescribed ≥2-fold more often for the newly diagnosed and prevalent DED groups compared with the non-DED groups, artificial tears had the greatest DED/non-DED differential, with a 4.9-fold higher proportion for the newly diagnosed and a 15.8-fold higher proportion for the prevalent DED groups. The biggest difference between DED and non-DED group nonocular medication use was found in prescription of decongestants (1.5-fold higher for the newly diagnosed and 1.7-fold higher for the prevalent DED groups), which decrease tear production and can increase the risk of dry eye.[36]

Ocular comorbidities in beneficiaries occurred at higher proportions in the DED groups than in the non-DED groups, with cataract being the most common. Cataract surgery was undertaken in 14.8% and 13.5% of beneficiaries in the newly diagnosed and prevalent DED groups, compared with 5.0% and 5.7%, respectively, for the matched non-DED groups. While iatrogenic causes of DED from cataract treatment have been shown, the strong association between the 2 diseases may also arise from the increasing incidence and prevalence of both conditions with age.[40,60] Glaucoma proportions were also higher in the DED groups than in the non-DED groups. Ophthalmic treatments for glaucoma often include the preservative BAK, which can cause ocular surface inflammation and an increased risk of DED.[61] Ophthalmic prostaglandins, with or without BAK, were also shown to be prescribed at a higher proportion (2.2-fold) for beneficiaries with DED than for those without.

Although the present study did not analyze for concomitant comorbidities, most of these conditions are chronic and thus are likely to exist concomitantly. The findings support clinical perceptions that patients with DED experience more comorbidities than those without DED. While this result is expected for patients with DED with Sjögren syndrome or other autoimmune diseases, the findings demonstrate that a much wider category of physical and psychological conditions may be associated with DED.[53] These data also support the perception that the commonly prescribed medical treatments of many of these comorbidities may themselves be DED associated.[37,49,58] All of these findings indicate that full consideration of a patient's medical history may be needed to better treat patients with DED.

Because it was a retrospective analysis, the design aspects of the present study were limited to the data available. As such, assessments of specificity and selection bias of the DED and non-DED populations cannot be assessed. Limitations of these data and analyses may arise from inaccuracies or omissions in coded procedures, diagnoses, or medication claims in the MHS database (eg, prescribed medications not taken, over-the-counter artificial tears purchased without use of pharmacy benefit). The strengths of this study include its large sample size and demographic sampling coverage of the US population across regions and age ranges. Additionally, having demographically matched non-DED groups for both the newly diagnosed and prevalent DED samples allows for a direct comparison of patient comorbidity proportions between DED and non-DED beneficiaries.

In summary, the findings of the present study characterize the burden of a wide range of comorbidities among those with DED relative to those without DED across a wide range of ages and geographic regions in the United States. The results support many known associations of DED with diseases, conditions, and their medical treatments, and extend the number and types of conditions that may be considered associated with DED. Additionally, the results provide an important treatment context to many common age-related conditions experienced in this population. An enhanced understanding of how often DED occurs in association with other conditions, including common age-related and non–age-related diseases, as well as their treatments, may facilitate improved management strategies when caring for patients who have DED or risk factors for developing DED. The results of this study highlight the need for a multidisciplinary approach to assessment and treatment of patients with DED.

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