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How Are Ocular Signs and Symptoms of Dry Eye Associated With Depression in Women With and Without Sjögren Syndrome?

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Abstract

• **PURPOSE:** To determine whether ocular phenotypic features of keratoconjunctivitis sicca (KCS) and/or participant-reported symptoms of dry eye disease are associated with depression in women participants enrolled in the Sjögren's International Collaborative Clinical Alliance (SICCA).

• **DESIGN:** Cross-sectional study.

• **METHODS:** Women enrolled in the SICCA registry from 9 international research sites. Participants met at least 1 of 5 inclusion criteria for registry enrollment (including complaints of dry eyes or dry mouth, a previous diagnosis of Sjögren syndrome (SS), abnormal serology

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(positive anti-Sjögren syndrome antigen A and/or B [anti-SSA and/or anti-SSB]), or elevated antinuclear antibody and rheumatoid factor), bilateral parotid gland enlargement, or multiple dental caries). At baseline, participants had oral, ocular, and rheumatologic examination; blood and saliva collection; and a labial salivary gland biopsy (LSGB). They also completed an interview and questionnaires including assessment of depression with the Patient Health Questionnaire 9 (PHQ-9). Univariate logistic regression was used to assess the association between depression and demographic characteristics, participant-reported health, phenotypic features of Sjögren syndrome, and participant-reported symptoms. Mixed-effects modeling was performed to determine if phenotypic features of KCS and/or participant-reported symptoms of dry eye disease were associated with depression, controlling for health, age, country or residence, and sex and allowing for nonindependence within geographic site.

• **RESULTS:** Dry eye complaints produced a 1.82-fold (95% confidence interval [CI] 1.38–2.40) higher odds of having depression compared to being symptom-free ($P < .001$). Additionally, complaints of specific ocular sensations were associated with a higher odds of depression including burning sensation (odds ratio 2.25, 95% CI 1.87–2.72, $P < .001$) compared to those without complaints. In both women with and without SS, the presence of symptoms of dry eyes and/or dry mouth rather than SS itself resulted in higher odds of depression. One particular ocular phenotypic feature of SS, a positive ocular staining score, was inversely correlated with depression.

• **CONCLUSIONS:** Participant-reported eye symptoms, particularly specific ocular sensations such as burning, were found to be positively associated with individual American College of Rheumatology/EUropean League Against Rheumatism (ACR/EULAR) SS criteria items.

Sjögren syndrome (SS) is an autoimmune condition that is classically characterized by exocrine dysfunction owing to inflammatory infiltration and subsequent scarring, but also exhibits more protean manifestations including neuropathy, generalized fatigue, and lymphoproliferative disorders. Previous studies have shown that depression is more frequent in patients with less prominent SS-related dry eye signs compared to controls.[1,2] Thus, patient-reported complaints of ocular dryness do not correlate well with the ocular features of keratoconjunctivitis sicca (KCS). Indeed, it can be difficult to differentiate between symptoms owing to aqueous deficiency and ocular discomfort that may occur independent of aqueous deficiency.[3] The cornea, with its rich innervation of nociceptive afferent nerve fibers, is now known to produce allodynia, hyperalgesia, photoallodynia, and dysthesias—features of neuropathic pain that can be found in patients without demonstrable clinical parameters of aqueous deficiency.[4–6] Given that SS patients are known to have bodily neuropathic pain (including fibromyalgia and chronic pain syndromes),[7–9] it is important to determine whether ocular discomfort in any one SS patient is related to aqueous deficiency/ocular sicca or neuropathic pain, as the treatment approach is entirely different. The implementation of appropriate treatments for the physiologic dysfunction and symptoms of SS are critical to decreasing the higher levels of depression in SS compared to those without SS.[8,10–13] With respect to ocular sicca, a recent meta-analysis of studies evaluating patients with dry eye disease compared to controls found that the prevalence and severity of depression was highest in those with SS.[14] However, even in patients without SS, but with dry eye complaints, depression severity was higher than in controls.[14] The SICCA registry

represents a resource for understanding the impact of ocular signs and symptoms on depression.

Previous studies have noted that while the signs of dry eye are not associated with depression, patient-reported symptoms are correlated with depression.[15,16] In this study we investigate the relationship between depression and SS ocular phenotypic features/objective tests that are individual criteria items of the 2016 American College of Rheumatology/ EUropean League Against Rheumatism (ACR/EULAR) Classification criteria for SS, as well as between depression and ocular symptoms in women participants enrolled in the SICCA cohort.[17–19]

METHODS

• STUDY DESIGN AND POPULATION:

The SICCA cohort represents a cross-sectional study of participants with signs and symptoms suggestive of SS enrolled from 9 international research sites. Participants (≥21 years of age) met at least 1 of the following inclusion criteria: (1) complaint of dry eyes or dry mouth, (2) previous diagnosis of primary or secondary SS, (3) abnormal serology (positive anti-Sjögren syndrome antigen A and/or B [anti-SSA and/or anti-SSB], or elevated antinuclear antibody and rheumatoid factor), (4) bilateral parotid gland enlargement, or (5) multiple cervical/incisal dental caries. At the baseline SICCA visit, participants completed an interview and questionnaires and underwent ocular examinations that included slit-lamp examination, Schirmer 1 testing, tear break-up time (TBUT), and determination of the Ocular Staining Score (OSS), a previously described quantitative grading system.[17–20] There are 2 ocular phenotypes consistent with KCS seen in SS. The first ocular phenotype is when the OSS ≥ 5 in at least 1 eye and yields a weight of 1 in the 2016 ACR/EULAR classification criteria for SS (out of a total score of 4 required to meet the criteria).[20] Alternatively, a van Bijsterveld score of ≥4 can be used in place of the OSS. The second KCS phenotype is a Schirmer 1 test of ≤5 mm in 5 minutes, also yielding a weight of 1 in the criteria.

For this study we included all female participants (regardless of SS status). In addition to the 2 ocular phenotypes noted above, the ACR/EULAR criteria include positive anti-SSA/Ro antibody and a labial salivary gland biopsy yielding a focal lymphocytic sialadenitis with ≥1 focus/4 mm^2 (each of these yields a score of 3); and an unstimulated salivary flow rate of ≥0.1 mL/min (with a score of 1).[17,18] The only exclusion criterion was male sex. We decided to focus on women because sexual dimorphisms have been previously described for reporting specific types of bodily pain in major depression[21] as well as in biomarkers and risk factors for some rheumatologic diseases.[22,23]

• VARIABLES AND MEASURES:

Depression was assessed using the Patient Health Questionnaire 9 (PHQ-9).[24,25] This survey of 9 questions queries patients regarding their frequency of being bothered by problems (including displeasure in doing things, feeling down, trouble concentrating, feeling badly about oneself, and suicidal ideation) over the past 2 weeks and assigns a cumulative score

from 0 to 27, with scores signifying depression severity (minimal depression to severe depression). For the purposes of this study, we conservatively dichotomized depression scores into those with the lowest total scores (scores 0–9, minimal depression and mild depression) as "not depressed" while those with higher total scores (scores 10–27, moderate depression to severe depression) were categorized as "depressed." A cutoff between scores of 0–9 and 10–27 has been suggested by others.[24,26] Independent variables that were analyzed included KCS (OSS ≥ 5 in at least 1 eye or Schirmer 1 ≥ 5 mm in 5 minutes in at least 1 eye), and participant-reported symptom of eyes feeling dry, burning, gritty, or experiencing light sensitivity. Participant-reported symptoms were dichotomized as "yes" and "no" responses depending on the presence or absence of such symptoms.

Participants were asked to respond affirmatively or negatively to questions including "are you able to make your own tears?", "do your eyes feel dry?", "does your mouth feel dry?", "do your eyes feel gritty?", "do you have light sensitivity?", and "do your eyes have a burning sensation?"

Participant-reported health was assessed using a general physical health-related question ("In general, would you say your health is:") with responses including "excellent," "very good," "good," and "fair." Responses were dichotomized as healthy (which included "excellent," "very good," and "good") and not healthy ("fair"). Chronic health conditions were recorded from a medical history questionnaire and responses were dichotomized as "no health condition present" and "any health condition present."

- **STATISTICAL ANALYSIS:**

Univariable logistic regression models were used to identify associations between depression and KCS criteria items and participant-reported ocular symptoms in the female cohort. Mixed-effects modeling was performed to determine if ocular phenotypic features (OSS and Schirmer 1) or participant-reported symptoms (gritty sensation, light sensitivity, burning sensation) were associated with depression controlling for health, age, country of residence, and sex and allowing for nonindependence within study site (STATA 11.0 software; StataCorp LP, College Station, Texas, USA). We also performed sensitivity analyses in the multivariable analyses by adjusting for the presence of chronic health conditions and the presence of blepharitis.

RESULTS

A TOTAL OF 3514 PARTICIPANTS FROM 9 INTERNATIONAL sites were enrolled in SICCA (Table 1). Women made up the majority of participants (3185 [91%] women vs 309 [9%] men). Sex was missing for 20 participants. Most participants reported being systemically healthy (Table 2). SS was diagnosed in 1440 (45.2%) of the cohort women participants while 1653 (51.9%) women participants were negative for SS by ACR/EULAR criteria. There were 92 women (2.9%) who could not be classified (often because of too few labial salivary glands capable of yielding a result on biopsy). The majority of female participants (2075) had either no or minimal depression as assessed by the PHQ-9 (score 0–9), while 1110 female participants had moderate-to-severe depression (score of 10–27). Thus, the prevalence of depression in women participants for this cohort was 34.9%. Most

SS women (1309 or 90.9%), as well as non-SS women (1428 or 86.4%), considered themselves healthy compared to women who considered themselves in poor health ($P < .001$). Most SS women (1258 or 76.1%) as well non-SS women (1183 or 82.2%) did not have a chronic health condition compared to women who did ($P < .001$) (Table 2).

- **PHENOTYPIC FEATURES OF SJÖGREN SYNDROME AND DRYEYES:**

Univariate analyses demonstrating the relationship between depression and ACR/EULAR SS diagnostic criteria, other ocular signs, participant demographics, and participant-reported symptoms are shown in Table 3. Briefly, having an OSS ≥ 5 was associated with a reduced odds of depression and was statistically significant. When assessing participant-reported ocular complaints, specifically for certain ocular sensations (gritty sensation, light sensitivity, and burning), there was an increased odds of depression compared to absence of such sensations. All variables having a statistically significant association with depression in univariate analyses were included in multivariate analyses.

A multivariate mixed-effects logistic regression clustering by geographic site found that women with an OSS ≥ 5 also showed a lower odds of depression compared to women with an OSS < 5, but this was not statistically significant (95% confidence interval [CI] 0.70–1.03, $P = .105$) (Table 3). We examined other non-SS criterion signs of KCS to determine if these predicted depression. TBUT did not exhibit a statistically significant association with depression in univariate or multivariate analyses. While participants with corneal filaments on examination showed 2.94-fold greater odds of depression compared to those without filaments (95% CI 2.15–3.97, $P < .001$,) on univariate analysis, this association was no longer present in multivariate analysis.

- **SYMPTOMS:**

Women participants endorsing the question “do your eyes feel dry?” had a 1.82-fold greater odds of having depression compared to those without such complaints (95% CI 1.38–2.40, $P < .001$). Similarly, participant report of any specific ocular sensation (gritty sensation, burning, and/or light sensitivity) was associated with a 2.45-fold higher odds of depression (95% CI: 1.85–3.25, $P < .001$) compared to those without such complaints. We found that there were 2745 women (86.2% of female participants) who complained of dry eyes. Further, participants complaining of an ocular burning sensation had a higher odds of depression compared to those complaining of light sensitivity and gritty sensation (Table 3). Vision fluctuation was also associated with an increased odds of depression compared to those without fluctuations in vision, particularly as the fluctuation increased in frequency.

In women with no signs of aqueous deficiency as defined by OSS and Schirmer 1 testing, complaints of “eyes feel dry” were frequent (716 women [83.2%] with normal OSS and 2399 women [85.6%] with normal Schirmer 1 testing).

We performed a subgroup analysis of asymptomatic (no complaints of dry eyes and dry mouth) participants to evaluate whether SS status (positive or negative) predicted depression. We identified 315 asymptomatic women without SS and 290 asymptomatic women with SS. There were 1338 SS-negative women who complained of dry eyes and/or dry mouth and 1150 SS-positive women who complained of the same symptoms. Mixed-effects logistic

regression (clustering by site) revealed that being classified as SS was associated with a lower odds of depression compared to not meeting SS criteria. Being classified as SS was also associated with a lower odds of depression when we examined only symptomatic (complaints of dry eyes and/or dry mouth) women (odds ratio [OR] = 0.68, 95% CI: 0.57–0.83, $P < .001$) or, separately, asymptomatic SS women (OR = 0.59, 95% CI: 0.37–0.95, $P = .03$).

Long-lasting dry eye sensation (all day and two thirds of the day) was associated with depression when compared to those with intermittent symptoms of dryness (none of the day or one third of the day) (Table 3).

- **EFFECTS OF DRY EYE THERAPY:**

The use of artificial tears (1–3 times/day, 4–9 times/day, 10 times/day or more) was not associated with a statistically significant difference in odds of having depression compared to those not using artificial tears. Very few participants used topical corticosteroids or topical cyclosporine drops at baseline, so drawing conclusions about the association with depression was not possible. The presence of punctal plugs was associated with a slightly lower odds of depression compared to those without punctal plugs (OR = 0.75, 95% CI 0.56–1.00, $P = .05$).

As a sensitivity analysis, we repeated all multivariable analyses adjusting for the presence of chronic health conditions and the presence of blepharitis, but this did not significantly or qualitatively change the results.

- **PREVALENCE OF DEPRESSION:**

We found that the prevalence of depression in SS women without a systemic health condition (337 or 80.8%) was higher than that of SS women who had at least 1 systemic health condition (80 or 19.2%), but this was not statistically significant by Pearson χ^2 test ($P = .40$). We found that the prevalence of depression in non-SS women without a systemic health condition (489 or 75%) was higher than that of non-SS women with a systemic health condition (163 or 25%), though this was not statistically significant by Pearson χ^2 test ($P = .40$).

DISCUSSION

IN THIS STUDY WE INVESTIGATED THE ASSOCIATION between depression and SS signs of KCS and symptoms of dry eye in women participants in the SICCA cohort. We found that the prevalence of depression in our cohort was much higher than the 10% that is found in the general population.[27] The prevalence of depression in our cohort of participants was consistent with other chronic health conditions including rheumatoid arthritis,[28] cancer,[29] and other chronic ocular immune-mediated diseases, such as uveitis.[30]

We examined the association between depression and the signs and symptoms associated with KCS (using the ACR/EULAR criteria for SS[17,18]), and found that OSS ≥ 5 was associated with a lower odds of depression compared to having a negative OSS. This is interesting because recent revision to the KCS-compatible OSS updated the score of ≥3 to

that of ≥5.[17,18] Thus, even with more pronounced features of KCS, the odds of depression were still lower in those manifesting a dryer ocular surface. Additionally, recent studies using SICCA registry data have found that being classified with SS was also associated with a lower odds of depression compared to not being diagnosed with SS.[16] Such a "protective" effect is not readily intuitive. However, when we consider that participants for SICCA were recruited from doctors' offices because they had either complaints of ocular or oral dryness, a previous diagnosis of SS, or abnormal serologic or biopsy results, several explanations for the protective effect may be plausible. It is possible that SS is protective for depression, or that knowing one's diagnosis reduces anxiety that could lead to (or be interpreted as) depression. Alternatively, the association may be artefactual: participants were not selected in a population-based manner, but were recruited for the study because they had abnormal signs or test results or bothersome symptoms. Those without symptoms would be more likely to have signs and be categorized as SS. Even correcting for symptoms using an imperfect questionnaire likely leaves some residual bias, resulting in the nonintuitive association of SS with disturbing symptoms, which in turn might be associated with depression. We should also consider that participants with SS (in particular those with positive serology or focus score) are clearly biologically different from participants without SS. Thus, having a diagnosis of SS or having a positive serologic test or LSGB may not reflect a truly direct protective mechanism. For example, others have shown that higher serum amyloid A levels in patients with SS are negatively correlated with anti-SSA.[31] This is interesting because higher serum amyloid A levels are prionflammatory. Higher serum amyloid A levels (in addition to other proinflammatory mediators) in turn have been associated with depression in other women.[32] Thus, having an elevated (or positive) anti-SSA titer may mediate the reduced expression of other depression-inducing inflammatory substances (such as serum amyloid A), leading to a reduction in depression.

We found that participants with reported symptoms of dry eyes exhibited a higher odds of depression compared to symptom-free participants, which is consistent with the findings in other large cohorts.[15] The fact that symptoms predict depression better than signs (ACR/EULAR criteria or otherwise) should not be overlooked. For example, in women SICCA participants, there was a subset who did not manifest features of KCS (be it by OSS, TBUT, or Schirmer 1) but still complained of the sensation of ocular dryness. A possible explanation for this lack of correlation between signs and symptoms of dry eye is that TBUT and Schirmer 1 are known to exhibit poor repeatability and reproducibility.[33,34] The strength of the ACR/EULAR criteria with respect to assessing the signs of dryness is that it uses a combination of tests that assess KCS.

Interestingly, we also found that specific dry eye symptoms, such as a burning sensation, were associated with a higher odds of depression. It has been suggested that certain ocular symptoms of KCS, such as burning and stinging, may be better categorized as neuropathic ocular pain.[35,36] Neuropathic ocular pain is being increasingly identified in patients with dry eye symptoms.[37,38] SS KCS, then, represents a unique entity that may straddle the realms of both dry eye syndrome (owing to the aqueous deficiency that results from lacrimal gland inflammation) and neuropathic ocular pain. Understanding what component of an SS patient's ocular discomfort is related to sicca vs neuropathic pain is vital to appropriately identifying therapeutics that will adequately address each specific sensation and situation.[37]

Since Sjögren syndrome is known to be associated with bodily neuropathic pain, it is important to query patients with SS KCS and non-SS KCS about specific features of neuropathic ocular pain.[7–9]

In conclusion, our finding that participant-reported eye symptoms were positively associated with depression while KCS phenotypic features were not is consistent with previous reports.[15] Because depression and dry eye syndrome can both significantly decrease quality of life, it is important to better understand the relationship between these 2 diseases. Future studies that assess neuropathic ocular pain using specific questionnaires and the assessment of anatomic features of neuropathy using confocal microscopy would be helpful, as this may help guide treatment and improve quality of life.

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REFERENCES

1. Vehof J, Sillevis Smitt-Kamminga N, Nibourg SA, Hammond CJ. Predictors of discordance between symptoms and signs in dry eye disease Ophthalmology. 2017; 124(3):280–286. [PubMed: 28024826]
2. Bezzina OM, Gallagher P, Mitchell S. Subjective and objective measures of dryness symptoms in primary Sjögren's syndrome - capturing the discrepancy Arthritis Care Res (Hoboken). 2017; 69(11):1714–1723. [PubMed: 27992710]
3. Segal B, Bowman SJ, Fox PC. Primary Sjögren's syndrome: health experiences and predictors of health quality among patients in the United States Health Qual Life Outcomes. 2009; 7:46. [PubMed: 19473510]
4. Zhang X, Chen Q, Chen W, Cui L, Ma H, Lu F. Tear dynamics and corneal confocal microscopy of subjects with mild self-reported office dry eye Ophthalmology. 2011; 118(5):902–907. [PubMed: 21146227]
5. Rosenthal P, Baran I, Jacobs DS. Corneal pain without stain: is it real? Ocul Surf. 2009; 7(1):28–40. [PubMed: 19214350]
6. Rosenthal P, Borsook D. The corneal pain system. Part I: the missing piece of the dry eye puzzle Ocul Surf. 2012; 10(1):2–14. [PubMed: 22330055]
7. Choi BY, Oh HJ, Lee YJ, Song YW. Prevalence and clinical impact of fibromyalgia in patients with primary Sjögren's syndrome Clin Exp Rheumatol. 2016; 34(2 Suppl 96):S9–S13.
8. Koh JH, Kwok SK, Lee J. Pain, xerostomia, and younger age are major determinants of fatigue in Korean patients with primary Sjogren's syndrome: a cohort study Scand J Rheumatol. 2017; 46(1): 49–55. [PubMed: 27098775]
9. Segal BM, Pogatchnik B, Rhodus N, Sivils KM, McElvain G, Solid CA. Pain in primary Sjögren's syndrome: the role of catastrophizing and negative illness perceptions Scand J Rheumatol. 2014; 43(3):234–241. [PubMed: 24392761]
10. Eyigor S, Sezgin B, Karabulut G, Ozturk K, Gode S, Kirazli T. Evaluation of swallowing functions in patients with Sjögren's syndrome Dysphagia. 2017; 32(2):271–278. [PubMed: 27838793]

11. Dassouki T, Benatti FB, Pinto AJ. Objectively measured physical activity and its influence on physical capacity and clinical parameters in patients with primary Sjogren's syndrome Lupus. 2017; 26(7):690–697. [PubMed: 27798360]
12. Al-Ezzi MY, Pathak N, Tappuni AR, Khan KS. Primary Sjogren's syndrome impact on smell, taste, sexuality and quality of life in female patients: a systematic review and meta-analysis Mod Rheumatol. 2017; 27(4):623–629. [PubMed: 27760487]
13. Milin M, Cornec D, Chastaing M. Sicca symptoms are associated with similar fatigue, anxiety, depression, and quality-of-life impairments in patients with and without primary Sjogren's syndrome Joint Bone Spine. 2016; 83(6):681–685. [PubMed: 26774177]
14. Wan KH, Chen LJ, Young AL. Depression and anxiety in dry eye disease: a systematic review and meta-analysis Eye (Lond). 2016; 30(12):1558–1567. [PubMed: 27518547]
15. Labbe A, Wang YX, Jie Y, Baudouin C, Jonas JB, Xu L. Dry eye disease, dry eye symptoms and depression: the Beijing Eye Study Br J Ophthalmol. 2013; 97(11):1399–1403. [PubMed: 24013959]
16. Chou A, Gonzales JA, Daniels TE, Criswell LA, Shiboski SC, Shiboski CH. Health-related quality of life and depression among participants in the Sjögren's International Collaborative Clinical Alliance (SICCA) Registry Rheum Muscul Dis. 2017; 3(2):1–10. https://doi.org/10.1136/rmdopen-2017-000495.
17. Shiboski CH, Shiboski SC, Seror R. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjogren's syndrome: a consensus and data-driven methodology involving three international patient cohorts Arthritis Rheumatol. 2017; 69(1): 35–45. [PubMed: 27785888]
18. Shiboski CH, Shiboski SC, Seror R. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjogren's syndrome: a consensus and data-driven methodology involving three international patient cohorts Ann Rheum Dis. 2017; 76(1):9–16. [PubMed: 27789466]
19. Shiboski SC, Shiboski CH, Criswell L. American College of Rheumatology classification criteria for Sjogren's syndrome: a data-driven, expert consensus approach in the Sjogren's International Collaborative Clinical Alliance cohort Arthritis Care Res (Hoboken). 2012; 64(4):475–487. [PubMed: 22563590]
20. Whitcher JP, Shiboski CH, Shiboski SC. A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjögren's Syndrome International Registry Am J Ophthalmol. 2010; 149(3):405–415. [PubMed: 20035924]
21. Jeon HJ, Woo JM, Kim HJ. Gender differences in somatic symptoms and current suicidal risk in outpatients with major depressive disorder Psychiatry Investig. 2016; 13(6):609–615.
22. Alonso MD, Martinez-Vazquez F, Riancho-Zarrabeitia L. Sex differences in patients with systemic lupus erythematosus from Northwest Spain Rheumatol Int. 2014; 34(1):11–24. [PubMed: 23812032]
23. Masi AT, Rehman AA, Jorgenson LC, Smith JM, Aldag JC. Sexual dimorphisms of adrenal steroids, sex hormones, and immunological biomarkers and possible risk factors for developing rheumatoid arthritis Int J Endocrinol. 2015; 2015:929246. [PubMed: 26693225]
24. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure J Gen Intern Med. 2001; 16(9):606–613. [PubMed: 11556941]
25. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire JAMA. 1999; 282(18):1737–1744. [PubMed: 10568646]
26. Lambert SD, Clover K, Pallant JF. Making sense of variations in prevalence estimates of depression in cancer: a cocalibration of commonly used depression scales using Rasch analysis J Natl Compr Canc Netw. 2015; 13(10):1203–1211. [PubMed: 26483060]
27. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication Arch Gen Psychiatry. 2005; 62(6):617–627. [PubMed: 15939839]
28. Margaretten M, Yelin E, Imboden J. Predictors of depression in a multiethnic cohort of patients with rheumatoid arthritis Arthritis Rheum. 2009; 61(11):1586–1591. [PubMed: 19877099]

29. Massie MJ. Prevalence of depression in patients with cancer J Natl Cancer Inst Monogr. 2004; (32):57–71. [PubMed: 15263042]

30. Qian Y, Glaser T, Esterberg E, Acharya NR. Depression and visual functioning in patients with ocular inflammatory disease Am J Ophthalmol. 2012; 153(2):370–378. e372. [PubMed: 21924399]

31. Pertovaara M, Jylhava J, Uusitalo H, Pukander J, Helin H, Hurme M. Serum amyloid A and C-reactive protein concentrations are differently associated with markers of autoimmunity in patients with primary Sjögren's syndrome J Rheumatol. 2009; 36(11):2487–2490. [PubMed: 19833744]

32. Kling MA, Alesci S, Csako G. Sustained low-grade pro-inflammatory state in unmedicated, remitted women with major depressive disorder as evidenced by elevated serum levels of the acute phase proteins C-reactive protein and serum amyloid A Biol Psychiatry. 2007; 62(4):309–313. [PubMed: 17178112]

33. van Bijsterveld OP. Diagnostic tests in the Sicca syndrome Arch Ophthalmol. 1969; 82(1):10–14. [PubMed: 4183019]

34. Lemp MA. Report of the National Eye Institute/Industry workshop on Clinical Trials in Dry Eyes CLAO J. 1995; 21(4):221–232. [PubMed: 8565190]

35. Crane AM, Levitt RC, Felix ER, Sarantopoulos KD, McClellan AL, Galor A. Patients with more severe symptoms of neuropathic ocular pain report more frequent and severe chronic overlapping pain conditions and psychiatric disease Br J Ophthalmol. 2017; 101(2):227–231. [PubMed: 27130915]

36. Kalangara JP, Galor A, Levitt RC. Characteristics of ocular pain complaints in patients with idiopathic dry eye symptoms Eye Contact Lens. 2017; 43(3):192–198. [PubMed: 26925537]

37. Galor A, Batawi H, Felix ER. Incomplete response to artificial tears is associated with features of neuropathic ocular pain Br J Ophthalmol. 2016; 100(6):745–759. [PubMed: 26377416]

38. Galor A, Covington D, Levitt AE. Neuropathic ocular pain due to dry eye is associated with multiple comorbid chronic pain syndromes J Pain. 2016; 17(3):310–318. [PubMed: 26606863]

TABLE 1.

Sjögren's International Collaborative Clinical Alliance Sites and Enrollment Numbers

Site (Country)	Total Number (%) Enrolled	Number of Women in Cohort (% of Site Participants)
University of California, San Francisco (USA)	718 (20.4%)	638 (88.9%)
University of Buenos Aires, German Hospital (Argentina)	441 (12.6%)	413(93.7%)
Peking Union Medical College Hospital (China)	333 (9.5%)	323 (97%)
Copenhagen University Hospital (Denmark)	610 (17.4%)	546 (85.3%)
Kanazawa Medical University (Japan)	368 (10.5%)	338 (91.9%)
Aravind Eye Hospital (India)	161 (4.6%)	130 (80.8%)
King's College, London (UK)	312 (8.9%)	285 (91.3%)
University of Pennsylvania (USA)	266 (7.6%)	239 (89.9%)
Johns Hopkins University (USA)	304 (8.7%)	273 (89.8%)
TOTAL	3514(100%)	3185(90.6%)

TABLE 2.

Demographic Information for Female Participants in the Sjögren's International Collaborative Clinical Alliance Cohort

Variable	Number	Percent	*P* Value
Sjögren syndrome status			<.001[a]
Positive	1440	45.2%	
Negative	1653	51.9%	
Depression (assessed with PHQ-9)			<.001[a]
Depressed	1110	34.9%	
Not depressed	2075	65.2%	
Age			<0.001[a]
≤50 years of age	1219	38.3%	
≤50 years of age	1966	61.7%	
Health (patient-reported)			<.001[b]
Healthy			
Classified as SS	1309	90.1%	
Not meeting SS criteria	1428	86.4%	
Not healthy			
Classified as SS	131	9.1%	
Not meeting SS criteria	225	13.6%	
Chronic health condition			<.001[b]
None			
Classified as SS	1183	82.2%	
Not meeting SS criteria	1258	76.1%	
At least 1 chronic condition			
Classified as SS	257	17.9%	
Not meeting SS criteria	395	23.9%	

PHQ-9 = Patient Health Questionnaire 9; SS = Sjögren syndrome.

Percentages may not total 100%, as some participants did not respond to questions.

[a]Calculated via *t* test.

[b]Calculated via Pearson χ^2 test.

TABLE 3.

Univariable and Multivariable Analyses With Depression as Outcome Variable in Cohort Women

	Univariable Analysis		Multivariable Analysis[a]	
Predictor	**Odds Ratio (95% Confidence Interval)**	***P* Value**	**Odds Ratio (95% Confidence Interval)**	***P* Value**
OSS ≥ 5	1.00(0.86–1.16)	1.00	0.90 (0.76–1.06)	.21
Abnormal Schirmer 1 (<5 mm/5 min)	1.01 (0.81–1.27)	.89	1.01 (0.76–1.34)	.95
Abnormal TBUT (<10s)	1.11 (0.90–1.37)	.33	1.17(0.91–1.50)	.22
Tear production[b]	0.63 (0.54–0.75)	<.001	0.83 (0.67–1.03)	.08
Filaments	2.95(2.14–4.06)	<.001	0.89 (0.56–1.43)	.64
Age	0.99 (0.98–0.99)	<.001		
Race[c]				
Hispanic	1.49 (1.18–1.89)	.001	1.26 (0.88–1.79)	.21
Native American	1.91 (1.33–2.98)	.001	1.70 (1.07–2.69)	.02
Asian	0.85(0.71–1.01)	.069	0.75(0.49–1.14)	.18
African	1.67(1.12–2.49)	.011	1.52 (1.00–2.33)	.05
Eyes feel dry	2.70(2.10–3.49)	<.001	1.82 (1.38–2.40)	<.001
Mouth feels dry	2.21 (1.66–2.95)	<.001	2.13(1.51–2.98)	<.001
Gritty sensation	2.93 (2.42–3.53)	<.001	1.88 (1.51–2.33)	<.001
Light sensitivity	2.98(2.51–3.54)	<.001	2.12 (1.74–2.58)	<.001
Burning sensation	3.53(2.99–4.16)	<.001	2.25 (1.87–2.72)	<.001
Amount of day eyes dry[b]				
≤1/3 of day	1.53 (1.23–2.09)	.01	1.24 (0.88–1.74)	.22
>1/3 of day & ≤2/3 of day	2.68 (1.98–3.64)	<.001	1.78 (1.27–2.49)	.001
>2/3 of day	3.20(2.47–4.15)	<.001	2.07 (1.56–2.76)	<.001

OSS = ocular staining score; TBUT = tear break-up time.

[a]Multivariable analyses adjusted for country of residence, age, and health status, clustering by Sjögren's International Collaborative Clinical Alliance site.

[b]Participant-reported.

[c]Compared with white.