

Sjögren's Versus Non-Sjögren's Ocular Features: Similar Symptoms, But Significantly Worse Signs

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PURPOSE. To examine the ocular signs and symptoms in participants of the Sjögren's International Collaborative Clinical Alliance cohort, and to compare them across Sjögren's disease (SjD) status.

METHODS. Our study population comprised 3380 Sjögren's International Collaborative Clinical Alliance participants who had no missing data relevant to this study. Participants' SjD status was assessed using the updated 2016 American College of Rheumatism/European League Against Rheumatism SjD classification criteria. Participants completed baseline questionnaires of ocular symptoms and underwent ocular examinations. Differences in the ocular signs and symptoms between SjD and non-SjD groups were assessed. We used multivariable linear and linear mixed-effects models to investigate the impact of SjD on Ocular Surface Disease Index-6 and OSS.

RESULTS. Among 1532 participants classified as SjD, their Ocular Surface Disease Index-6 did not clinically differ from those classified as non-SjD (adjusted difference, -0.97 ; 95% confidence interval, -1.52 to -0.41). However, SjD participants exhibited an elevated ocular staining score (adjusted difference, 3.47 ; 95% confidence interval, 3.36 – 3.57 ; $P < 0.001$) compared with non-SjD participants. In addition, SjD was associated with increased odds of ocular signs, such as reduced tear break-up time, abnormal Schirmer I test, and corneal abnormalities, and was strongly related to more intense corneal and conjunctival staining, as well as additional corneal staining points.

CONCLUSIONS. SjD is associated with a higher risk of ocular signs and pathology compared with non-SjD, whereas ocular symptoms remain similar. In addition, corneal abnormalities and corneal staining patterns could serve as a potential biomarker in identifying SjD-related dry eye.

Keywords: sjögren's disease, dry eye disease, keratoconjunctivitis sicca, ocular staining, ocular signs and symptoms

Sjögren's disease (SjD, previously known as Sjögren's syndrome) is a multisystem autoimmune disorder associated with lymphocytic infiltration of exocrine glands, particularly salivary and lacrimal glands, which produces mild to severe dry (or sicca) signs and symptoms in the mouth and eyes.^{1–3} Similar to other autoimmune disorders, SjD overwhelmingly affects women, typically between the ages of 30 to 60 years. More than 95% of patients complain of oral and/or ocular dryness.⁴ The characteristic ocular finding in SjD is keratoconjunctivitis sicca, or aqueous deficient dry eye.⁵ In the updated American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for SjD, dry eye disease (DED) is assessed via the Schirmer I test (abnormal if ≤ 5 mm in 5 minutes in at ≥ 1 eye) and ocular staining score (abnormal if ≥ 5 in at least one eye).^{6–8} SjD-related DED can negatively impact quality of life by producing symptoms of ocular discomfort

and affecting vision owing to poor lubrication of the ocular surface.^{9–11} Moreover, SjD can be associated with potentially serious vision-threatening ocular complications, including corneal melt with subsequent perforation, corneal vascularization, uveitis, scleritis, retinal vasculitis, and optic neuritis.^{12–17} Despite such important and potentially devastating complications, SjD remains underdiagnosed in patients with dry eye.⁹

The Sjögren's International Collaborative Clinical Alliance (SICCA) was established to develop and validate universally accepted classification criteria for SjD, characterize the SjD phenotype and genotype, and to develop a data and biospecimen repository to support future research.⁸ By virtue of participants enrolled into the cohort, SICCA intrinsically contains one of the largest dry eye cohorts and offers an opportunity to study the full extent of the ocular manifestations of SjD, particularly the lids and anterior segment.¹⁸

The purpose of the present study was to interrogate the SICCA database to identify associations between SjD classification status and anterior segment pathology. We hypothesized that SICCA participants classified as SjD would feature more potentially vision-threatening clinical manifestations compared with those not meeting ACR/EULAR SjD classification criteria.

METHODS

Study Population

The SICCA cohort assemblage has been published previously.^{8,19} In brief, 3514 participants aged between 21 and 89 years at baseline were enrolled from nine research sites (6 international and 3 U.S. sites) between September 2004 and September 2012. Participants who had been diagnosed with SjD (using prior classification or diagnostic criteria); who had symptoms, signs, or abnormal test results suggestive of SjD; or who were suspected of having SjD by their referring ophthalmologist, rheumatologist, or oral medicine specialist were recruited into SICCA. Each participant provided informed consent, and the study protocol was approved by the institutional review boards of the University of California, San Francisco, and enrolling sites. For our analytical purpose, we excluded participants who were unable to be classified as SjD or non-SjD ($n = 114$) or who had more than 20% missing information ($n = 20$). The remaining 3380 participants comprised our study population.

Participants were classified as SjD or non-SjD using the 2016 ACR/EULAR classification criteria.⁸ Participants were queried about ocular symptoms including eye redness, itching, tearing, light sensitivity, grittiness or scratchiness, burning or stinging, blurred vision, fluctuating vision, pain, eye irritation and discomfort, and their corresponding frequencies (none of the time, some of the time, half of the time, most of the time, and all of the time). Participants were also asked if their eyes felt dry, when ocular dryness started, and the dry eye therapies they used. The six-item Ocular Surface Disease Index (OSDI-6) was calculated for each participant.²⁰

To ensure the test accuracy and reproducibility, participants had their eyes examined by trained ophthalmologists following the specific sequence: Schirmer I test (normal ≥ 5 mm, abnormal <5 mm at 5 minutes), slit-lamp examination of the lids, conjunctiva, and cornea for any abnormalities, tear break-up time (normal ≥ 10 seconds, abnormal <10 seconds), corneal fluorescein staining, and conjunctival lissamine green staining. The Ocular Staining Score (OSS; continuous, 0–12 points) was calculated by combining the results of corneal fluorescein staining and conjunctiva lissamine green staining.⁷

Statistical Analyses

For the distribution of patients' characteristics by SjD classification status, categorical variables were expressed as counts and percentages, which were compared by chi-squared tests. Continuous variables were summarized as mean with SD or medians with interquartile ranges (IQR), and the differences between SjD groups were evaluated by t tests or Kruskal Wallis H tests, depending on whether the data were normally distributed or not. Because diagnostic measurements were eye related (rather than participant related), we used tetrachoric correlation for clinical signs having binary features

(e.g., present or absent) and Pearson correlation for continuous variables to assess the correlation between paired organs (eyes) in each individual participant. To account for the correlation structure for the subunits (eyes) within a cluster (participants), univariable logistic and linear mixed-effects regression models were used for categorical and continuous outcomes, respectively, to assess the odds ratios (ORs) or differences in the clinical features between the SjD and non-SjD groups. We conducted additional analyses on ocular staining pattern to explore if there were any differences based on SjD status. The significance level was adjusted for the multiple comparisons using Bonferroni correction.

We further conducted multivariable linear regression and linear mixed-effects models, as appropriate, to assess SjD classification influence on OSDI-6 and OSS while adjusting for age, sex, region, smoking status, education, employment, and general health status. To explore whether age, sex, and health status might affect participants' perception of ocular symptoms or ocular health, we performed subgroup analyses defined by age (≤ 55 , >55 years, which approximated the median age of the cohort), sex (female, male), and health status (poor [self-reported poor and fair general health] or good [self-reported good and above general health]). The interaction between SjD status and subgroup factors was assessed by entering cross-product terms into the linear models. Statistical analyses were conducted using R statistical software, version 4.2.3.

RESULTS

Demographics

Details of participants' baseline characteristics by SjD status are shown in [Table 1](#). Of the 3380 study participants included, 1532 (45.3%) were classified as having SjD. The overall mean age was 53.0 ± 13.2 years. The majority (91.1%) of our study population was female. A large proportion of participants were from North and South America (49.9%), were Caucasian (58.3%), had an education degree of college or above (59.2%), were currently working (61.6%), and never smoked (59.1%). One-half of the participants rated their health as good or above, whereas the other one-half reported as fair or poor. Compared with participants classified as non-SjD, SjD participants were more likely to come from Asia, be of Asian ethnicity, be used, to have never smoked, and reported an inability to produce their own tears.

Symptoms

Ocular symptoms of participants are summarized in [Table 2](#). Light sensitivity, eye irritation, and discomfort during daily activities were common complaints among our study population, whereas tearing and fluctuating vision only presented in a small proportion of participants. In those classified as having SjD, ocular symptoms such as light sensitivity, gritty or scratchy sensation, burning or stinging, eye irritation, and discomfort were less prevalent compared with those classified as non-SjD ([Table 2](#)). Most participants complained of eye dryness (85.6%) and poor vision (63.2%), which did not differ significantly between SjD and non-SjD participants. The median OSDI-6 of study participants was 8.43 (IQR, 6.21). In those classified as having SjD, the OSDI-6 was 1.27 points (95% confidence interval [CI], 0.86–1.69) lower than

TABLE 1. Demographics of 3390 SICCA Participants by SjD Status

Characteristic	All (n = 3380)	Non-SjD (n = 1848)	SjD (n = 1532)	Difference (95% CI)	P Value
Age (years)	53.0 ± 13.2	53.6 ± 13.0	52.3 ± 13.4	-1.3 (-2.2 to -0.5)	0.003
Sex					<0.001
Female	3078 (91.1)	1646 (89.1)	1432 (93.5)	4.4% (2.5% to 6.3)	
Male	293 (8.7)	196 (10.6)	97 (6.3)	-4.3% (-6.2% to -2.4%)	
Region					<0.001
America	1687 (49.9)	1024 (55.4)	663 (43.3)	-12.1% (-15.6% to -8.7%)	
Asia	805 (23.8)	278 (15.0)	527 (34.4)	19.4% (16.4% to 22.3%)	
Europe	888 (26.3)	546 (29.5)	342 (22.3)	-7.2% (-10.2% to -4.2%)	
Race/ethnicity					<0.001
Caucasian	1969 (58.3)	1248 (67.5)	721 (47.1)	-20.5% (-23.8% to -17.1%)	
Asian or Pacific Islander	919 (27.2)	324 (17.5)	595 (38.8)	21.3% (18.3% to 24.4%)	
Hispanic/Latino	352 (10.4)	202 (10.9)	150 (9.8)	-1.1% (-3.3% to 1.0%)	
African	93 (2.8)	47 (2.5)	46 (3.0)	0.5% (-0.7% to 1.6%)	
Native American	35 (1.0)	19 (1.0)	16 (1.0)	0.0% (-0.7% to 0.7%)	
Education					0.003
High school and lower	1378 (40.8)	701 (37.9)	677 (44.2)	6.3% (2.9% to 9.6%)	
College and above	2002 (59.2)	1147 (62.1)	855 (55.8)	-6.3% (-9.6% to -2.9%)	
Employment					<0.001
Not Working	547 (16.2)	362 (19.6)	185 (12.1)	-7.5% (-10.0% to -5.0%)	
Working	2082 (61.6)	1063 (57.5)	1019 (66.5)	9.0% (5.7% to 12.3%)	
Retired	740 (21.9)	416 (22.5)	324 (21.1)	-1.4% (-4.2% to 1.5%)	
Others	481 (14.2)	248 (13.6)	233 (14.8)	1.2% (-1.2% to 3.6%)	
Smoking					<0.001
Never	1995 (59.0)	975 (52.8)	1020 (66.6)	13.8% (10.5% to 17.2%)	
Ever	1063 (31.4)	627 (33.9)	436 (28.5)	-5.5% (-8.7% to -2.3%)	
Current	322 (9.5)	246 (13.3)	76 (5.0)	-8.4% (-10.3% to -6.4%)	
General health					0.004
Poor	396 (11.7)	257 (13.9)	139 (9.1)	-4.8% (-7.0% to -2.6%)	
Fair	1270 (37.6)	687 (37.2)	583 (38.1)	0.9% (-2.5% to 4.2%)	
Good	1149 (34.0)	596 (32.3)	553 (36.1)	3.8% (0.6% to 7.1%)	
Very Good	491 (14.5)	267 (14.4)	224 (14.6)	0.2% (-2.3% to 2.6%)	
Excellent	63 (1.9)	33 (1.8)	30 (2.0)	0.2% (-0.8% to 1.2%)	
Ability to produce tears					<0.001
No	760 (22.5)	288 (15.6)	472 (30.8)	15.2% (12.3% to 18.1%)	
Yes	2603 (77.0)	1551 (83.9)	1052 (68.7)	-15.3% (-18.2% to -12.3%)	
Dry eye therapy					
Artificial tears	2140 (63.3)	1164 (63.0)	976 (63.7)	0.7% (-2.6% to 4.0%)	>0.999
Punctal occlusion	317 (9.4)	160 (8.7)	157 (10.2)	1.6% (-0.5% to 3.6%)	>0.999
Steroids	130 (3.8)	75 (4.1)	55 (3.6)	-0.5% (-1.8% to 0.9%)	>0.999
Antibiotics	192 (5.7)	86 (4.7)	106 (6.9)	2.3% (0.6% to 3.9%)	0.047
Cyclosporine	327 (9.7)	188 (10.2)	139 (9.1)	-1.1% (-3.2% to 1.0%)	>0.999
No. of dry eye therapies				1.000	
0	1134 (33.6)	641 (34.7)	493 (32.2)	-2.5% (-5.8% to 0.7%)	
1	1600 (47.3)	861 (46.6)	739 (48.2)	1.6% (-1.8% to 5.1%)	
≥2	646 (19.1)	346 (18.7)	300 (19.6)	0.9% (-1.9% to 3.6%)	
Length of feeling eye dry (years)	3.91 (7.65)	3.73 (7.46)	4.16 (7.80)	0.43 (-0.09 to 0.93)	0.210

Values are mean ± SD, number (%), or median (IQR) unless otherwise noted.

that of those classified as non-SjD. Participants under the age of 55 years, females, and those self-reported poor health exhibited overall higher OSDI-6 scores compared with their older, male, and healthier counterparts, respectively, particularly in the non-SjD group (Fig. 1 and Table 3). After adjusting for confounding factors, the difference in OSDI-6 between SjD and non-SjD participants remained statistically significant (-0.97; 95% CI, -1.52 to -0.41), although the clinical significance of the difference might be limited. Similar findings were observed in the younger age group, females and those self-identified as being in poor health, and there existed interactions between SjD status and age (P for interaction = 0.003), as well as health status (P for interaction = 0.042).

Clinical Examination Findings

Clinical features of participants' two eyes were strongly correlated (Table 3). Pinguecula was a common manifestation (23.5%; the larger percentage between the right eye and the left eye was reported, same below) among study participants, followed by meibomitis (20.5%). Entropion, ectropion, and corneal ulceration were found in relatively few participants. Compared with those classified as non-SjD, those classified as having SjD had a higher likelihood of exhibiting pathology including blepharitis (OR, 1.17; 95% CI, 1.00-1.36; $P = 0.044$), corneal pathology such as filaments (OR, 3.63; 95% CI, 2.76-4.78; $P < 0.001$), vascularization (OR, 3.02; 95% CI, 1.86-4.91; $P < 0.001$), scarring (OR, 1.70; 95% CI, 1.28-

TABLE 2. Ocular Symptoms of 3390 SICCA Participants by SjD Status

Symptom	All (n = 3380)	Non-SjD (n = 1848)	SjD (n = 1532)	Difference (95% CI)	P Value
Redness					0.021
None of the time	1008 (29.8)	531 (28.7)	477 (31.1)	2.4% (−0.8% to 5.6%)	
Some of the time	1457 (43.1)	788 (42.6)	669 (43.7)	1.0% (−2.4% to 4.4%)	
Half of the time	298 (8.8)	170 (9.2)	128 (8.4)	−0.8% (−2.8% to 1.1%)	
Most of the time	443 (13.1)	237 (12.8)	206 (13.4)	0.6% (−1.7% to 3.0%)	
All of the time	160 (4.7)	112 (6.1)	48 (3.1)	−2.9% (−4.4% to −1.5%)	
Itching					0.020
None of the time	662 (19.6)	323 (17.5)	339 (22.1)	4.6% (1.9% to 7.4%)	
Some of the time	1682 (49.8)	913 (49.4)	769 (50.2)	0.8% (−2.7% to 4.2%)	
Half of the time	443 (13.1)	264 (14.3)	179 (11.7)	−2.6% (−4.9% to −0.3%)	
Most of the time	465 (13.8)	268 (14.5)	197 (12.9)	−1.6% (−4.0% to 0.7%)	
All of the time	119 (3.5)	74 (4.0)	45 (2.9)	−1.1% (−2.4% to 0.2%)	
Tearing					<0.001
None of the time	2389 (70.7)	1165 (63.0)	1224 (79.9)	16.9% (13.8% to 19.9%)	
Some of the time	806 (23.8)	554 (30.0)	252 (16.4)	−13.5% (−16.4% to −10.7%)	
Half of the time	82 (2.4)	61 (3.3)	21 (1.4)	−1.9% (−3.0% to −0.9%)	
Most of the time	50 (1.5)	34 (1.8)	16 (1.0)	−0.8% (−1.7% to 0.1%)	
All of the time	41 (1.2)	27 (1.5)	14 (0.9)	−0.5% (−1.3% to 0.2%)	
Light sensitivity					<0.001
None of the time	1200 (35.5)	584 (31.6)	616 (40.2)	8.6% (5.3% to 11.9%)	
Some of the time	979 (29.0)	549 (29.7)	430 (28.1)	−1.6% (−4.8% to 1.5%)	
Half of the time	233 (6.9)	135 (7.3)	98 (6.4)	−0.9% (−2.7% to 0.9%)	
Most of the time	528 (15.6)	316 (17.1)	212 (13.8)	−3.3% (−5.8% to −0.8%)	
All of the time	430 (12.7)	258 (14.0)	172 (11.2)	−2.7% (−5.0% to −0.4%)	
Gritty					<0.001
None of the time	927 (27.4)	438 (23.7)	489 (31.9)	8.2% (5.1% to 11.3%)	
Some of the time	1308 (38.7)	712 (38.5)	596 (38.9)	0.4% (−3.0% to 3.7%)	
Half of the time	371 (11.0)	212 (11.5)	159 (10.4)	−1.1% (−3.3% to 1.1%)	
Most of the time	510 (15.1)	323 (17.5)	187 (12.2)	−5.3% (−7.7% to −2.8%)	
All of the time	255 (7.5)	157 (8.5)	98 (6.4)	−2.1% (−3.9% to −0.3%)	
Burning					<0.001
None of the time	1417 (41.9)	697 (37.7)	720 (47.0)	9.3% (5.9% to 12.7%)	
Some of the time	1095 (32.4)	601 (32.5)	494 (32.2)	−0.3% (−3.5% to 3.0%)	
Half of the time	316 (9.3)	212 (11.5)	104 (6.8)	−4.7% (−6.7% to −2.7%)	
Most of the time	387 (11.4)	229 (12.4)	158 (10.3)	−2.1% (−4.3% to 0.1%)	
All of the time	156 (4.6)	103 (5.6)	53 (3.5)	−2.1% (−3.6% to −0.7%)	
Blurred vision					0.058
None of the time	1256 (37.2)	663 (35.9)	593 (38.7)	2.8% (−0.5% to 6.2%)	
Some of the time	1422 (42.1)	766 (41.5)	656 (42.8)	1.4% (−2.0% to 4.8%)	
Half of the time	269 (8.0)	171 (9.3)	98 (6.4)	−2.9% (−4.7% to −1.0%)	
Most of the time	260 (7.7)	158 (8.5)	102 (6.7)	−1.9% (−3.7% to 0.0%)	
All of the time	161 (4.8)	82 (4.4)	79 (5.2)	0.7% (−0.8% to 2.2%)	
Fluctuating vision					0.001
None of the time	1594 (47.2)	807 (43.7)	787 (51.4)	7.7% (4.3% to 11.1%)	
Some of the time	1220 (36.1)	691 (37.4)	529 (34.5)	−2.9% (−6.2% to 0.4%)	
Half of the time	212 (6.3)	135 (7.3)	77 (5.0)	−2.3% (−4.0% to −0.6%)	
Most of the time	253 (7.5)	153 (8.3)	100 (6.5)	−1.8% (−3.6% to 0.1%)	
All of the time	89 (2.6)	55 (3.0)	34 (2.2)	−0.8% (−1.9% to 0.4%)	
Pain					0.003
None of the time	1960 (58.0)	1015 (54.9)	945 (61.7)	6.8% (3.4% to 10.1%)	
Some of the time	764 (22.6)	426 (23.1)	338 (22.1)	−1.0% (−3.9% to 1.9%)	
Half of the time	140 (4.1)	89 (4.8)	51 (3.3)	−1.5% (−2.9% to −0.1%)	
Most of the time	306 (9.1)	194 (10.5)	112 (7.3)	−3.2% (−5.2% to −1.2%)	
All of the time	200 (5.9)	118 (6.4)	82 (5.4)	−1.0% (−2.7% to 0.6%)	
Irritation while reading or driving					<0.001
None of the time	956 (28.3)	466 (25.2)	490 (32.0)	6.8% (3.6% to 9.9%)	
Some of the time	1166 (34.5)	632 (34.2)	534 (34.9)	0.7% (−2.6% to 3.9%)	
Half of the time	318 (9.4)	183 (9.9)	135 (8.8)	−1.1% (−3.1% to 0.9%)	
Most of the time	510 (15.1)	295 (16.0)	215 (14.0)	−1.9% (−4.4% to 0.5%)	
All of the time	346 (10.2)	220 (11.9)	126 (8.2)	−3.7% (−5.8% to −1.6%)	
Irritation while watching TV or computer					<0.001
None of the time	861 (25.5)	418 (22.6)	443 (28.9)	6.3% (3.3% to 9.3%)	
Some of the time	1141 (33.8)	592 (32.0)	549 (35.8)	3.8% (0.5% to 7.1%)	
Half of the time	352 (10.4)	199 (10.8)	153 (10.0)	−0.8% (−2.9% to 1.3%)	
Most of the time	579 (17.1)	350 (18.9)	229 (14.9)	−4.0% (−6.6% to −1.4%)	
All of the time	387 (11.4)	248 (13.4)	139 (9.1)	−4.3% (−6.5% to −2.2%)	

TABLE 2. Continued

Symptom	All (n = 3380)	Non-SjD (n = 1848)	SjD (n = 1532)	Difference (95% CI)	P Value
Uncomfortableness in wind					
None of the time	1032 (30.5)	500 (27.1)	532 (34.7)	7.7% (4.5% to 10.9%)	<0.001
Some of the time	984 (29.1)	537 (29.1)	447 (29.2)	0.1% (-3.0% to 3.3%)	
Half of the time	206 (6.1)	122 (6.6)	84 (5.5)	-1.1% (-2.8% to 0.5%)	
Most of the time	640 (18.9)	376 (20.3)	264 (17.2)	-3.1% (-5.8% to -0.4%)	
All of the time	504 (14.9)	302 (16.3)	202 (13.2)	-3.2% (-5.6% to -0.7%)	
Uncomfortableness in dry or heated environment					
None of the time	1070 (31.7)	525 (28.4)	545 (35.6)	7.2% (3.9% to 10.4%)	0.001
Some of the time	931 (27.5)	502 (27.2)	429 (28.0)	0.8% (-2.2% to 3.9%)	
Half of the time	276 (8.2)	166 (9.0)	110 (7.2)	-1.8% (-3.7% to 0.1%)	
Most of the time	628 (18.6)	368 (19.9)	260 (17.0)	-2.9% (-5.6% to -0.3%)	
All of the time	456 (13.5)	273 (14.8)	183 (11.9)	-2.8% (-5.2% to -0.5%)	
Eye dryness	2892 (85.6)	1601 (86.6)	1291 (84.3)	-2.4% (-4.8% to 0.1%)	0.719
Poor vision	2135 (63.2)	1160 (62.8)	975 (63.6)	0.9% (-2.5% to 4.2%)	1.000

Values are number (%) or median (IQR) unless otherwise noted.

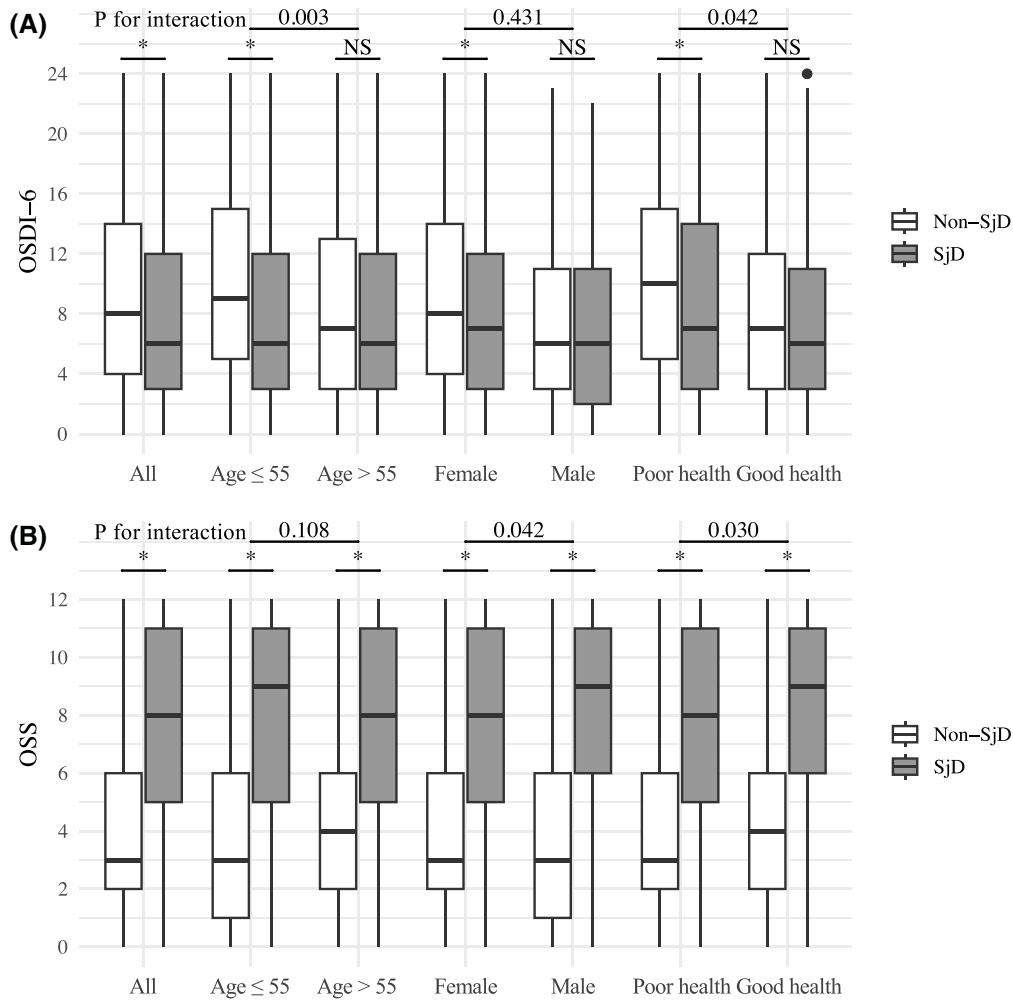


FIGURE 1. Box plot depicting difference in ocular symptoms and signs between the SjD and non-SjD participants across all participants and subgroups defined by age, sex, and health status. Horizontal line through each box represents the median. **P* < Bonferroni-corrected *P* value threshold. (A) OSDI-6. (B) OSS. NS, not significant.

TABLE 3. Differences in OSDI-6 Between Participants Classified as SjD and Non-SjD Across Subgroups Defined by Age, Gender, and Health Status

Subgroup	Non-SjD	SjD	Difference (95% CI)	Adjusted Difference (95% CI)*	P Value for Interaction
All	9.01 (6.24)	7.74 (6.09)	-1.27 (-1.69 to -0.86)	-0.97 (-1.52 to -0.41)	
Age (years)					0.003
≤55	9.83 (6.29)	7.71 (6.20)	-2.13 (-2.70 to -1.56)	-0.97 (-1.52 to -0.41)	
>55	8.12 (6.03)	7.81 (5.95)	-0.31 (-0.92 to -0.30)	0.06 (-0.53 to 0.64)	
Sex					0.431
Female	9.26 (6.28)	7.80 (6.10)	-1.46 (-1.90 to -1.02)	-0.50 (-0.92 to -0.08)	
Male	7.17 (5.43)	6.96 (5.87)	-0.21 (-1.61 to -1.19)	-0.32 (-1.69 to 1.05)	
Health status					0.042
Poor	10.20 (6.32)	8.46 (6.46)	-1.74 (-2.36 to -1.12)	-0.76 (-1.35 to -0.16)	
Good	7.82 (5.90)	7.12 (5.67)	-0.71 (-1.26 to -0.16)	-0.38 (-0.92 to 0.17)	

* Adjusted for age, sex, region, smoking status, education, employment, and general health status. Values are mean ± SD.

TABLE 4. Anterior Segment Pathology and Clinical Signs of 3390 SICCA Participants by SjD Status

Manifestation	All		Non-SjD		SjD		OR (95% CI)	P Value
	Right	Left	Right	Left	Right	Left		
Lagophthalmos	40 (1.2)	36 (1.1)	25 (1.4)	22 (1.2)	15 (1.0)	14 (0.9)	0.74 (0.46 to 1.18)	0.204
Entropion	7 (0.2)	8 (0.2)	3 (0.2)	4 (0.2)	4 (0.3)	4 (0.3)	1.38 (0.50 to 3.80)	0.538
Ectropion	9 (0.3)	11 (0.3)	6 (0.3)	7 (0.4)	3 (0.2)	4 (0.3)	0.65 (0.26 to 1.62)	0.353
Trichiasis	66 (2.0)	50 (1.5)	32 (1.7)	26 (1.4)	34 (2.2)	24 (1.6)	1.23 (0.85 to 1.78)	0.274
Pterygium	55 (1.6)	62 (1.8)	31 (1.7)	29 (1.6)	24 (1.6)	33 (2.2)	1.15 (0.79 to 1.65)	0.467
Pingueculum	791 (23.4)	795 (23.5)	436 (23.6)	441 (23.9)	355 (23.2)	354 (23.1)	0.96 (0.86 to 1.08)	0.529
Meibomitis	684 (20.2)	694 (20.5)	367 (19.9)	373 (20.2)	317 (20.7)	321 (21.0)	1.05 (0.93 to 1.18)	0.423
Blepharitis	378 (11.2)	373 (11.0)	194 (10.5)	189 (10.2)	184 (12.0)	184 (12.0)	1.17 (1.00 to 1.36)	0.044
Corneal abnormality								
Filaments	135 (4.0)	140 (4.1)	33 (1.8)	38 (2.1)	102 (6.7)	102 (6.7)	3.63 (2.76 to 4.78)	<0.001
Corneal vascularization	37 (1.1)	43 (1.3)	8 (0.4)	15 (0.8)	29 (1.9)	28 (1.8)	3.02 (1.86 to 4.91)	<0.001
Corneal scarring	100 (3.0)	104 (3.1)	40 (2.2)	46 (2.5)	60 (3.9)	58 (3.8)	1.70 (1.28 to 2.25)	<0.001
Corneal ulceration	3 (0.1)	8 (0.2)	1 (0.1)	1 (0.1)	2 (0.1)	7 (0.5)	5.43 (1.17 to 25.13)	0.031
Tear film								
Abnormal TBUT	2733 (80.9)	2726 (80.7)	1363 (73.8)	1372 (74.2)	1370 (89.4)	1354 (88.4)	2.83 (2.47 to 3.23)	<0.001
Debris	1329 (39.3)	1337 (39.6)	483 (26.1)	496 (26.8)	846 (55.2)	841 (54.9)	3.40 (3.07 to 3.76)	<0.001
Abnormal Schirmer I	1126 (33.3)	1104 (32.7)	405 (21.9)	384 (20.8)	721 (47.1)	720 (47.0)	3.28 (2.95 to 3.65)	<0.001

TBUT, tear break-up time. Values are number (%) or mean ± SD.

2.25; $P < 0.001$), and ulceration (OR, 5.43; 95% CI, 1.17–15.13; $P = 0.031$) (Table 4).

Dry Eye Tests

We found that 2733 participants (80.9%) had abnormal tear break-up time. The abnormal results of Schirmer I test were seen in 891 participants (26.4%). The mean OSS of the study population was greater than 5 (right: 5.04 [IQR, 3.70]; left: 5.15 [IQR, 3.69]) (Table 4). Compared with those classified as non-SjD, those classified as SjD had an increased odds of exhibiting an abnormal tear break-up time (OR, 2.83; 95% CI, 2.47–3.23; $P < 0.001$) and Schirmer I test (OR, 2.88; 95% CI, 2.56–3.23; $P < 0.001$). The OSS within the same SjD status group showed minimal variation, regardless of subgroups defined by age, sex, or health status (Table 5). Overall, SjD participants had a significantly higher OSS compared with non-SjD participants, with a mean difference of 3.70 points (95% CI, 3.49–3.91; $P < 0.001$). Specifically, participants classified as having SjD presented with

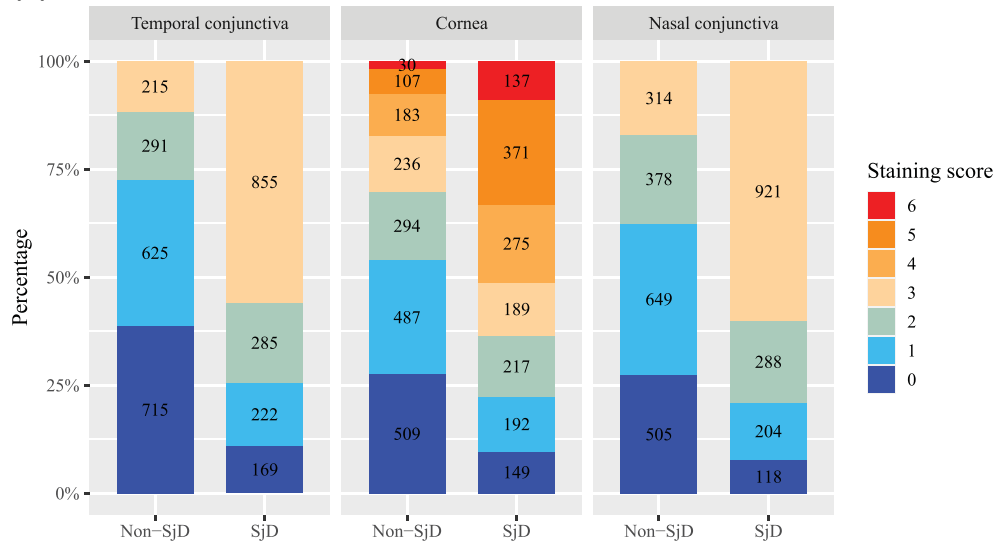
significantly more intense ocular staining patterns, with notably increased odds of temporal conjunctival staining (OR, 4.71; 95% CI, 4.16–5.34; $P < 0.001$), followed by nasal conjunctival staining (OR, 4.68; 95% CI, 4.13–5.30; $P < 0.001$) (Fig. 2 and Supplementary Table 1). Corneal staining was also pronounced in SjD participants, but showed a relatively smaller magnitude (OR, 3.51; 95% CI, 3.10–3.98; $P < 0.001$) compared with conjunctival staining. However, the three additional corneal staining points, including staining in the pupillary area (OR, 3.30; 95% CI, 2.92–3.72; $P < 0.001$), corneal filaments (OR, 5.01; 95% CI, 3.87–6.49; $P < 0.001$), and patches of confluent staining (OR, 5.17; 95% CI, 4.60–5.81; $P < 0.001$), were also much more frequently observed in SjD participants. After adjusting for confounding factors, the higher OSS among SjD participants remained statistically and clinically significant (adjusted difference, 3.47; 95% CI, 3.36–3.57). This pattern was observed consistently across subgroups defined by age, sex, and health status, and we observed interactions between SjD status with sex (P for interaction = 0.042) and health status (P for interaction = 0.030).

TABLE 5. Differences in OSS Between Participants Classified As SjD and Non-SjD Across Subgroups Defined by Age, Gender, and Health Status

Subgroup	Non-SjD		SjD		Difference (95% CI)	Adjusted Difference (95% CI)*	P Value for Interaction
	Right	Left	Right	Left			
All	3.36 (2.88)	3.47 (2.94)	7.07 (3.56)	7.18 (3.48)	3.70 (3.49 to 3.91)	3.47 (3.36 to 3.57)	
Age (years)							0.108
≤55	3.33 (2.95)	3.39 (3.00)	7.22 (3.58)	7.28 (3.50)	3.90 (3.61–4.19)	3.51 (3.22 to 3.81)	
>55	3.41 (2.80)	3.58 (2.87)	6.85 (3.52)	7.03 (3.45)	3.45 (3.14–3.76)	3.34 (3.03 to 3.65)	
Sex							0.042
Female	3.40 (2.87)	3.49 (2.91)	7.03 (3.57)	7.13 (3.49)	3.65 (3.43–3.87)	3.40 (3.18 to 3.63)	
Male	3.14 (2.96)	3.41 (3.18)	7.60 (3.34)	7.70 (3.28)	4.37 (3.63–5.12)	4.16 (3.42 to 4.90)	
Health status							0.030
Poor	3.27 (2.76)	3.30 (2.81)	6.76 (3.70)	6.84 (3.57)	3.52 (3.23–3.82)	3.33 (3.02 to 3.64)	
Good	3.47 (3.01)	3.67 (3.06)	7.34 (3.40)	7.46 (3.38)	3.84 (3.54–4.13)	3.59 (3.29 to 3.89)	

* Adjusted for age, sex, region, smoking status, education, employment, and general health status. Values are mean ± SD.

(A) Ocular staining pattern



(B) Cornea staining pattern

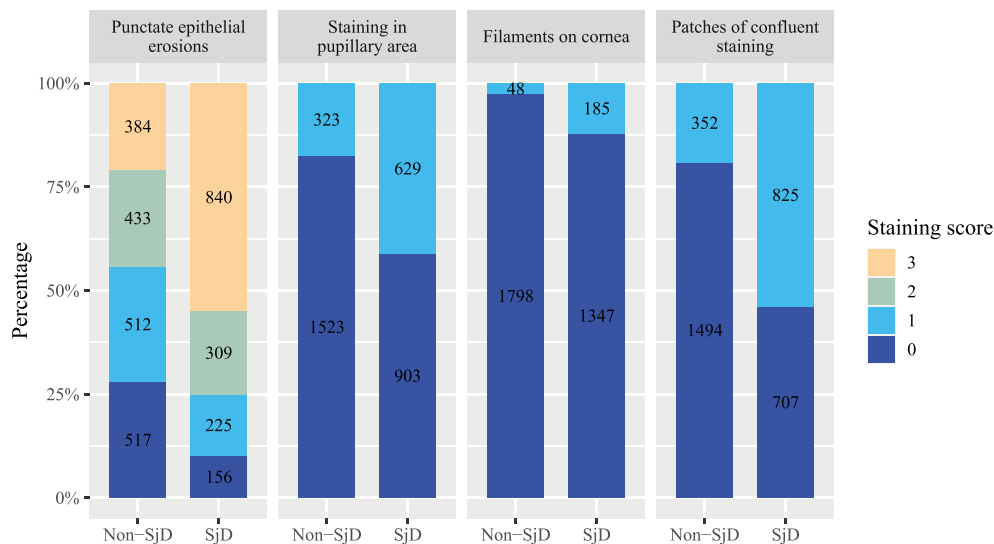


FIGURE 2. Ocular staining patterns based on constituent components of the OSS. **(A)** Ocular staining patterns by region. **(B)** Cornea staining patterns assessed with fluorescein.

DISCUSSION

Using data from the SICCA cohort, our study represents the largest cohort that comprehensively compares ocular signs and symptoms between participants with SjD and non-SjD. Our findings indicated that, although the ocular symptoms were similar between SjD and non-SjD participants, those with SjD demonstrated an increased risk of anterior segment abnormalities compared with those classified as non-SjD. It was noted that some of these ocular abnormalities such as corneal filaments can be potentially vision threatening. Therefore, more aggressive interventions to avert the most deleterious sequela of DED should be considered for individuals with SjD compared with those without SjD dry eye.^{21,22} Moreover, corneal and conjunctival staining was more severe as assessed by the OSS in those classified as SjD compared with those classified as non-SjD.

It has been observed consistently that SjD patients may experience significant visually compromising ocular complications.^{14,23,24} The mechanism by which SjD is associated with corneal pathology is not entirely clear, but may be related to ocular surface inflammation as well as ocular surface dysbiosis.²⁵ For example, the ocular surface in SjD has been demonstrated to feature less microbial diversity compared with those with non-SjD dry eye.²⁶ Decreased microbial diversity may allow for the development of atypical ocular infections in SjD.²⁷ It has been demonstrated that SjD-related aqueous-deficient dry eye can feature corneal filaments, and 95% of corneal filaments are secondary to keratoconjunctivitis sicca.^{28,29} Additionally, a previous study reported that corneal opacities, corneal ulcers, and corneal melts and perforations occur in up to 70% of patients when followed long term.³⁰ Although our results did not feature as high a prevalence of corneal pathology, it should be noted that the present study was a cross-sectional study with participants of relatively younger age. Another study showed that there was no difference in long-term outcomes, including the development of corneal ulcers and melts, between those classified as SjD and non-SjD.³¹ Of importance, however, was that most patients in this previous study had their dry eye therapy escalated, which may have decreased the incidence of vision-threatening complications in both the SjD and non-SjD groups. This finding would imply that aggressive management of DED in SjD is imperative for preserving vision. Indeed, some investigators have suggested that systemic immunomodulatory therapy may be beneficial in some SjD patients with severe DED.³² Although our results did not reveal an escalated DED therapy use among participants with SjD, it could be attributed partially to the fact that our participants had varying durations of experiencing ocular dryness and might have been in the early stages of dry eye treatment, where artificial tears were the mainstay of treatment.

Despite the notable anterior segment pathology exhibited by those classified as SjD, they actually had comparable dry eye-related symptoms as those classified as non-SjD. This finding is akin to what has been found by others in the sense that ocular signs and dry eye symptoms are frequently discordant.³³ The discordance in DES symptomatology could be attributed partially to the altered corneal nerve density and morphology in SjD patients.^{34,35} Additionally, some investigators have suggested that such discordance may be related to comorbid conditions such as anxiety

and depression and self-perceived health, where those with lower self-perceived health had an increased odds of complaining of DED symptoms.^{33,36} Mirroring these prior studies, we found that while the OSS of participants who reported poor health were generally lower compared with those who self-reported good health, their OSDI-6 scores were higher, especially in those without SjD. In addition to the rationales discussed elsewhere in this article, it is worth noting that the SICCA cohort included participants who had either diagnosed SjD or symptoms related to SjD. Participants without SjD or ocular signs must have abnormal ocular symptoms compared with the general population to meet the SICCA inclusion criteria, which led to Berkson's bias.³⁷ As a result, SICCA participants without SjD generally showed severe symptoms while their ocular signs were absent.

Our data have revealed a significant finding of interest, suggesting that ocular staining, especially conjunctival staining and additional corneal staining patterns, was more frequently intense in SjD participants compared with participants without SjD. These results align with previous findings that such intense ocular staining could be predictive of being classified as SjD.^{38,39} The underlying biological mechanisms driving the progression of ocular staining in DED have not been investigated thoroughly. However, it is hypothesized that conjunctival epithelial erosions in DED begins in the nasal area and spreads to the temporal area as the disease advances, given that tears flow from the lacrimal gland to the temporal side of the globe and then toward the nasal globe.⁴⁰ Consequently, temporal conjunctival staining may be more prominent in SjD because of the severity of DED in SjD. The present study adds to the existing evidence and highlights the importance of using the OSS, as well as lissamine green staining for conjunctiva, which is not used routinely in clinical practice, in the assessment of patients with DED to help discriminate those who are suspected of having SjD. Further, novel methods are warranted to differentiate SjD keratoconjunctivitis sicca from other forms of DED. Recent evidence suggests that patients with SjD may exhibit lower corneal nerve metrics and small fiber neuropathies under *in vivo* confocal microscopy as compared with healthy controls, making small fiber neuropathy a potential biomarker for classifying SjD.⁴¹

It is worth noting that enrolling participants who may have already had a prior diagnosis of SjD (using a prior Sjögren's classification system) or had symptoms or signs compatible with SjD, for example, dry eye, might have created the potential selection bias in our study, because SjD and dry eye both were related to participant enrollment. However, those classified as non-SjD in the SICCA cohort are not healthy controls. Therefore, it is possible that, if compared with healthy controls (which were not recruited into SICCA), the odds of the complications we identified may actually be even higher. Moreover, we are unable to explore the causal association given the cross-sectional study design. Finally, residual confounding variables and unknown causative factors such as comorbidities, systemic medications, and lifestyle and dietary approaches may further influence our results. Nevertheless, we were able to leverage the extensive data from the SICCA cohort to examine the pattern of ocular symptoms, signs, and pathology by SjD status across a diverse geographical area and age range, which provides evidence and insights for generating hypotheses and identifying areas for future research.

CONCLUSIONS

In our study, SjD participants demonstrate more vision-threatening features of the anterior segment compared with those without SjD while DED symptoms remain similar between SjD groups. This study highlights the importance of close ophthalmological follow-up for individuals who are suspected of having SjD and the need for aggressive interventions to avert the deleterious sequela of DED. Furthermore, ocular staining could serve as a potential biomarker for classifying SjD during ophthalmologic clinics.

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