



Published in final edited form as:

*Am J Ophthalmol.* 2016 December ; 172: 87–93. doi:10.1016/j.ajo.2016.09.013.

## Association of dry eye tests with extra-ocular signs among 3,514 participants in the Sjögren's Syndrome International Registry

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### Abstract

**Purpose**—To identify a screening strategy for dry eye patients with a high likelihood of having Sjogren's syndrome (SS) through the evaluation of the association of ocular surface tests with the extraocular signs used for the diagnosis of SS.

**Design**—Multi-center cross-sectional study.

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**Financial Disclosures:** No financial disclosures.

**Other Acknowledgments:** None.

**Methods**—The Sjogren's International Clinical Collaborative Alliance (SICCA) registry enrolled 3,514 participants with SS or possible SS from 9 international academic sites. Ocular surface evaluation included Schirmer I testing, tear break-up time (TBUT), and staining of the cornea (0 to 6 points) and conjunctiva (0 to 6 points). Multivariate logistic regression analysis was performed to identify predictive factors for: 1) histopathologic changes on labial salivary gland (LSG) biopsies (positive = focus score of  $\geq 1$  focus/4mm<sup>2</sup>) and 2) positive anti-SSA/B serology.

**Results**—The adjusted odds of having a positive LSG biopsy was significantly higher among those with an abnormal Schirmer I test (adjusted OR = 1.26, 95% CI 1.05 to 1.51, P=0.014), positive conjunctival staining (for each additional unit of staining 1.46; 95% CI 1.39 to 1.53, P < 0.001) or corneal staining (for each additional unit of staining 1.14; 95% CI 1.08 to 1.21, P < 0.001). The odds of having a positive serology was significantly higher among those with an abnormal Schirmer I test (adjusted OR=1.3; 95% CI 1.09 to 1.54 P=0.004), and conjunctival staining (adjusted OR=1.51; 95% CI 1.43 to 1.58, P < 0.001).

**Conclusions**—In addition to corneal staining which was associated with a higher likelihood of having a positive LSG biopsy, conjunctival staining and abnormal Schirmer I testing are of critical importance to include when screening dry eye patients for possible SS as they were associated with a higher likelihood of having a positive LSG biopsy and serology.

## Introduction

Sjögren's syndrome (SS) is the second most common autoimmune disease affecting nearly 4 million Americans, with an estimated prevalence of 0.5–5%.<sup>1</sup> Although common, diagnosis is often delayed by an average time of 6.5 years from symptom onset,<sup>2–4</sup> and the majority of SS patients are undiagnosed.<sup>5</sup> Diagnostic delays are of great clinical significance, as studies have consistently identified SS as an independent risk factor for non-Hodgkin's lymphoma.<sup>4,6,7</sup> Early detection of SS is important as patients who are started on biological agent treatment within the first 5 years of disease onset may be more likely to respond to treatment than those with delayed initiation of therapy.<sup>8–10</sup>

Clinically, SS is characterized by hypofunction of the salivary and lacrimal glands, which typically leads to dry mouth and dry eye<sup>11</sup>, although it may affect any organ system in the body. Because SS affects many organ systems, collaboration among multiple medical specialties is required and often contributes to delays in diagnosis. Currently, there are two sets of criteria used for the diagnosis of SS: the American-European Consensus Group (AECG) criteria<sup>12</sup>, and the more recent set of classification criteria developed by the SICCA group and provisionally endorsed by the American College of Rheumatology (ACR)<sup>13</sup>. The ACR criteria defines SS as requiring two out of three of the following signs: 1) positive serology (anti-SSA/SSB positivity or positive RF *and* ANA  $\geq 1:320$ ); 2) presence of focal lymphocytic sialadenitis (FLS) with a focus score (FS)  $\geq 1/4\text{mm}^2$  on a labial salivary gland (LSG) biopsy ("positive LSG biopsy"); or 3) an ocular staining score (OSS)  $\geq 3$ .<sup>13</sup> Recently, a revised set of classification criteria (ACR/European League Against Rheumatism (EULAR)) has been proposed in an attempt to reconcile differences between the AECG and ACR/SICCA criteria (Shiboski CH, American College of Rheumatology 2015).

Because dry eye is one of the most common symptoms of SS, patients often first seek care from eye care providers who can potentially play a key role in reducing time from symptom onset to diagnosis. Previous studies have shown that up to 10% of dry eye patients have SS.<sup>14</sup> However, because of the high prevalence of dry eye disease,<sup>15,16</sup> it is not practical or economically feasible for ophthalmologists to refer all dry eye patients for a SS work-up. In addition, screening is challenging as there is currently no universal standard regarding which dry eye patients should undergo a comprehensive work-up for SS (that includes a rheumatologic work-up with specific blood work, and a LSG biopsy).

Historically, assessment of dry eye symptoms alone has not been helpful in screening patients for SS, as multiple autoimmune diseases may present with dry eye symptoms without any known symptoms specific for SS-related dry eye.<sup>17–19</sup> Similarly, severity of symptoms is not a helpful distinguishing factor as SS-related dry eye patients experience a wide range of symptoms ranging from asymptomatic dry eye to severe dysfunction and decreased quality of life. Furthermore, there is limited evidence regarding specific ocular signs that in isolation can reliably distinguish SS-related from non-SS related dry eye for the purpose of identifying SS patients.<sup>20</sup> Thus historically, ocular symptoms and signs in isolation have been poorly predictive of extra-ocular objective signs required for the diagnosis of SS patients, in particular positive serology and a positive LSG biopsy.<sup>12,21,22</sup> However, while ocular signs in isolation may not be useful for diagnosing SS (in the absence of a systemic work-up), ocular signs may be useful for *screening* dry eye patients and deciding who should undergo a comprehensive work-up for SS.

Therefore, the goal of the present study is to explore the association of individual ocular surface diagnostic tests (Schirmer test I, tear break-up time, ocular surface staining of the cornea and conjunctiva) with extra-ocular objective diagnostic tests for SS, thus gaining insight about their potential role in the clinical work-up algorithm that may be used by ophthalmologists in screening dry eye patients for possible SS. The comprehensive data collected as part of the SICCA study offered a unique opportunity to explore this objective.

## Methods

### Study design and population

Enrollment in the SICCA cohort study occurred between 2004–2012 in nine international academic sites in Argentina, China, Denmark, Japan, India, United Kingdom, and the United States.<sup>22</sup> Institutional Review Board approval of the study protocol was obtained from all centers prior to the start of the study, and informed consent was obtained from all subjects. The objectives of the SICCA registry, funded primarily by the National Institute of Dental and Craniofacial Research, were to 1) develop new classification criteria for SS, and 2) establish a data and biospecimen repository that would be accessible by investigators worldwide for future studies on the pathogenesis, phenotypic, and genotypic features of the disease. The data-driven consensus methodology used in the development of classification criteria, and the role of a panel of expert clinicians representing the three specialties involved in the diagnosis and management of SS, have been previously described.<sup>13</sup> Expert panel members in the SICCA group agreed that the classification criteria should pertain to a target population of patients who may have signs and symptoms suggestive of SS, and be referred

to specialists involved in the diagnosis and management of SS, namely rheumatologists, ophthalmologists, or oral medicine specialists.<sup>11</sup> It was agreed that no diagnostic criteria or labels would be used for enrollment and that all participants in the cohort would undergo the same set of standardized tests and evaluations including eye examination, labial salivary gland biopsy, and serologic testing (anti-SS A or anti-SS B antibodies or RF positivity in combination with elevated ANA). Thus, patients reporting dry eye symptoms or those who lacked dry eye symptoms but either had extra-ocular symptoms or signs that may be suggestive of SS were included in the study.

Specifically, to be eligible for the SICCA registry, participants had to be 21 years of age, and were required to have one or more of the following: a) symptoms of dry eyes or dry mouth; b) bilateral parotid enlargement; c) recent increase in dental caries; d) a previous suspicion or diagnosis of SS; e) elevated serology of antinuclear antibodies (ANA), positive rheumatoid factor (RF), anti-SS A or anti-SS B antibodies; f) or have diagnoses of rheumatoid arthritis or systemic lupus erythematosus. Eligibility criteria were intended to target individuals with signs or symptoms of SS, not the general population *and* not patients exclusively reporting dry eye symptoms. These represent patients who may have been referred to an ophthalmologist by a rheumatologist or oral medicine specialist in the absence of dry eye symptoms. Exclusion criteria included known diagnoses of the following: hepatitis C, HIV infection, sarcoidosis, amyloidosis, active tuberculosis, graft-versus-host disease, autoimmune connective tissue diseases other than rheumatoid arthritis or systemic lupus erythematosus, or past head and neck radiation treatment.

Further exclusion criteria specific to the eye included current treatment with daily eye drops for glaucoma, corneal surgery in the last 5 years to correct vision, cosmetic eyelid surgery in the last 5 years, or physical or mental condition interfering with successful participation in the study. Contact lens wearers were asked to discontinue use 7 days prior to SICCA examination. We did not exclude participants taking prescription drugs that may affect salivary or lacrimal secretion, but recorded their use and asked that they discontinue use one day prior to the SICCA exam.

## Variables and Measures

**SICCA Registry Ocular Examination**—The sequence and details of the SICCA eye examination protocol have previously been described by the SICCA group,<sup>23</sup> and are only briefly described here. Because ocular surface staining with the vital dyes fluorescein and lissamine green may disrupt tear film stability, Schirmer test I (without anesthesia) was performed first. Next, tear break-up time (TBUT), grading of corneal staining with fluorescein (0.5% drops), and grading of conjunctival staining with lissamine green (1% drops) were performed in that order. Ocular surface staining assessments were performed within a specified time frame before the dye had sufficient time to diffuse and the intensity of the staining could be compromised.

**Outcome Variables**—The outcome variables, positive serology and positive LSG biopsy, were defined as follows: (1) positive serology as determined by the presence of SSA or SSB antibodies or RF positivity *and* ANA titer 1:320 (2) LSG biopsy with a diagnosis of FLS

and a focus score of  $\geq 1$  focus/4mm<sup>2</sup>. These extra-ocular outcomes are the other objective tests typically used for the diagnosis of SS, in addition to the ocular surface staining. Thus, they are studied here since they represent the basis of SS classification criteria that was recently endorsed by the ACR.<sup>13</sup>

**Statistical Analyses**—Summary statistics (proportions for categorical variables; means with 95% confidence intervals for continuous variables) were used to describe the SICCA participant characteristics with respect to the various objective tests measured (ocular, oral, serological).

We used logistic regression models to quantify the marginal association between ocular surface diagnostic test results and each of our two outcomes (positive LSG biopsy and positive serology). Variables for the ocular test results were defined as follows: (1) binary indicator of an unanesthetized Schirmer I test score  $\geq 5$  mm; (2) binary indicator of a TBUT score  $< 10$  seconds; (3) conjunctival component of the OSS (graded 0–6 for the conjunctival portion of the grading system) (4); corneal component of the OSS (graded 0–6 for the corneal portion of the grading system); and (5) binary indicator of an OSS score  $\geq 3$ . P-values of less than 0.05 were deemed statistically significant for regression results. To investigate the independent contribution of the ocular measures in predicting the two outcomes, we fitted two additional logistic models including the first four ocular variables defined above, as well as participant age and race.

All statistical analyses were performed using Stata 10.0 (StataCorp. 2007. Stata Statistical Software: Release 10. College Station, TX: StataCorp LP) and R (R Foundation for Statistical Computing, Vienna, Austria, v. 3.0 for MacIntosh). Participants with missing values were excluded from the analysis. Missing data occurred as follows: Schirmer score 5.4%, abnormal LSG focus scores 4.8%, and all other variables had smaller fractions of missing data.

## Results

### Sample characteristics

Data from a total of 3514 participants were available from the SICCA registry (Table 1). The proportion of participants with an abnormal Schirmer score (defined as  $\leq 5$ mm/5min) was 32%. The majority of participants (85%) had an abnormal TBUT (defined as  $< 10$  seconds). The mean conjunctival OSS score was 3 points (95% CI = 2.92 to 3.06) and the mean corneal OSS score was 2.2 (95% CI = 2.10 to 2.22). The mean total OSS score was 5.2 (95% CI= 5.03 to 5.27). The cohort also had the following features: 39.1% had a focus score greater than or equal to 1, 38.3% had a positive SSA or SSB, and 40.9% had positive RF *and* ANA titer  $\geq 1:320$ .

### Bivariate analyses exploring the association between eye-related phenotypic features and positive serology and biopsy

**Positive serology**—In the bivariate analysis of the independent predictors (Table 2), an increased odds of positive serology was associated with abnormal Schirmer's test (OR= 2.37, 95% CI= 2.04 to 2.75,  $P < 0.0001$ ) and abnormal TBUT (OR= 2.48, 95% CI= 2.0 to 3.07,  $P$

< 0.0001). For ocular staining scores, increased odds of positive serology was associated with conjunctival OSS scores (OR= 1.55, 95% CI= 1.49 to 1.6,  $P < 0.0001$ ), corneal OSS scores (OR= 1.43, 95% CI= 1.37 to 1.49,  $P < 0.0001$ ), and an abnormal total OSS score (OR= 1.28, 95% CI= 1.26 to 1.31,  $P < 0.0001$ ).

**Positive LSG biopsy**—Similarly, increased odds for having a positive LSG biopsy was associated with abnormal Schirmer's score (OR= 2.44, 95% CI= 2.1 to 2.85,  $P < 0.0001$ ) and abnormal TBUT (OR= 2.17, 95% CI= 1.75 to 2.68,  $P < 0.0001$ ). Increased odds of positive LSG biopsy was further associated with conjunctival OSS scores (OR= 1.57, 95% CI: 1.51 to 1.63,  $P < 0.0001$ ), corneal OSS scores (OR= 1.52, 95% CI: 1.45 to 1.58,  $P < 0.0001$ ), and an abnormal OSS score (OR=1.31, 95% CI=1.28 to 1.34,  $P < 0.0001$ ).

### Multivariate analysis

We fit separate models to explore dry-eye test results as potential explanatory variables of 1) a positive LSG biopsy, or 2) positive anti-SSA/B serology. We included four independent variables in our models as follows: abnormal TBUT, abnormal Schirmer's test, corneal staining score, and conjunctival staining score. Unadjusted multivariate model results are presented in the Supplemental Table.

We then fit separate models, adjusting for age and race (Table 3). The odds of a positive focus score on LSG biopsy were significantly higher among those with an abnormal Schirmer test (adjusted OR=1.26; 95% CI 1.05 to 1.51,  $P = 0.014$ ). In addition, the odds of a positive focus score on LSG biopsy were also significantly higher among those with positive conjunctival staining or corneal staining. Specifically, the adjusted odds ratio for having a positive focus score on LSG biopsy for each additional point of the conjunctival staining score was 1.46 (95% CI 1.39 to 1.53,  $P < 0.001$ ) and for one unit of corneal staining score was 1.11 (1.05 to 1.18,  $P < 0.001$ ). In contrast, the odds of a positive focus score on LSG biopsy were significantly lower for those with an abnormal TBUT (adjusted OR 0.76; 95% CI 0.58 to 0.99;  $P = 0.043$ ).

The odds of a positive serology were significantly higher among those with an abnormal Schirmer test (adjusted OR=1.3; 95% CI 1.12 to 1.61,  $P = 0.002$ ), and conjunctival staining (adjusted OR=1.51; 95% CI 1.43 to 1.59,  $P < 0.001$ ), but not for those with corneal staining (adjusted OR=0.983; 95% CI 0.93 to 1.05  $P = 0.586$ ), or abnormal TBUT (adjusted OR=1.1; 95% CI 0.83 to 1.42,  $P = 0.572$ ).

### Discussion

We examined the associations between individual ocular tests for dry eye in relation to objective tests assessing extra-ocular signs for SS in the SICCA registry. When each dry eye diagnostic test was assessed individually, we found that a positive LSG biopsy and positive anti-SSA/B serology were each significantly associated with all dry eye tests including Schirmer's test, TBUT, corneal staining, and conjunctival staining.

However, when all four dry eye diagnostic tests were included in a multivariate model adjusted for age and race, we demonstrated that the adjusted OR for a positive LSG biopsy



for one unit of conjunctival staining score was 1.46 and for one unit of corneal staining score was 1.16. In other words, the odds of having a positive LSG biopsy increased by approximately 50% for each unit increase in conjunctival staining and approximately 16% for each unit increase in corneal staining. The odds of having a positive LSG biopsy were also significantly higher among those with an abnormal Schirmer test. Surprisingly, we found the odds of having a positive LSG biopsy was lower among those with an abnormal TBUT, however this finding was of borderline significance. In addition, there is no known biologic basis for this association and further studies are needed to explore this finding.

In addition, we found that the odds of having positive serology was significantly higher in those with an abnormal Schirmer test or conjunctival staining, but not for those with corneal staining or an abnormal TBUT. Although we found independent associations for TBUT with extra-ocular tests, this variable did not significantly contribute to providing information necessary for predicting positive extra-ocular findings for SS in either of our final models.

Dry eye symptoms are one of the most common reasons patients seek care from an ophthalmologist, with an *estimated 11 percent of dry eye patients having underlying SS*.<sup>14</sup> The majority of SS patients first seek medical care for dry eye symptoms, but many are misdiagnosed as having non-autoimmune related dry eye. Because dry eye disease is highly prevalent in the general population and SS work-ups are costly, complex, and time-consuming, it is not practical or economically feasible to refer all dry eye patients for SS work-ups<sup>15,16</sup>. Ophthalmologists are severely hampered by the absence of evidence-based screening tools that reliably distinguish SS-related from non-SS related dry eye patients, resulting in under-referrals and increased delays in the diagnosis of SS.

The results of our study indicate that both Schirmer I testing and conjunctival staining with lissamine green are critical tests to include when screening dry eye patients for possible SS, as both of these dry eye tests were associated with predicting both a positive serology and positive LSG biopsy. In addition, corneal staining with fluorescein was significantly associated with having a positive LSG biopsy. While many ophthalmologists commonly use fluorescein staining of the cornea in their evaluation of dry eye patients,<sup>24,25</sup> few routinely assess ocular surface staining of the conjunctiva. For example, it has been reported that only 4.9–10% of eye care professionals routinely assess staining of the conjunctiva.<sup>24,25</sup> This underutilization of conjunctival staining may contribute to the under-referral of dry eye patients for SS work-ups.

Our results highlight the importance of including conjunctival staining when screening dry eye patients, as significant positive staining is associated with two of the non-ocular diagnostic criteria for SS (positive LSG biopsy and serology), and therefore is highly suggestive of SS. This is consistent with the findings of others who have noted the importance of conjunctival staining for the evaluation of both SS-related and non-SS dry eye. For example, Caffrey and colleagues found that rose bengal staining of the temporal conjunctiva was the most important ocular sign in distinguishing primary SS from non-SS dry eye.<sup>20</sup> In contrast, others have noted more nasal than temporal staining of the conjunctiva in SS patients.<sup>26</sup> Future studies comparing SS to non-SS dry eye patients are

needed to further elucidate specific patterns of conjunctival staining that may distinguish these two groups.

Other studies have also supported the important role of the conjunctiva in the pathogenesis of dry eye disease. Pro-inflammatory markers such as lymphatic endothelial markers, increased cytokine transcripts, chemokines, adhesion molecules, and major histocompatibility complex (MHC) class II-positive dendritic cells are abundantly positive in conjunctiva of dry eye patients.<sup>27-30</sup> In addition, Solomon and colleagues found that the conjunctival epithelium may be the source of increased interleukin-1 expression, likely leading to a cascade of pro-inflammatory events.<sup>29</sup> Inflammation in the conjunctiva may in turn trigger pathological inflammatory changes in the cornea, such as through the induction of MHC class II expression in corneal dendritic cells which are thought to play an important role in autoimmune responses.<sup>31</sup> Further studies focused on the conjunctiva of SS patients are needed to further elucidate these relationships and the role they play in SS-related ocular surface disease.

Our findings should be interpreted in light of the strengths and limitations of our study. The large sample size available for this analysis was a major strength for this study. With a large number of participants, systematic biases away from the null can be prevented and thus our results were less likely to overestimate associations between dependent and independent variables.<sup>32</sup> Given that the registry is comprised of individuals from 9 international sites, the generalizability of these results may be significant across different patient populations. However, these results may only be generalizable to patients suspected of SS, rather than to all dry eye patients given the inclusion criteria used for recruitment into the SICCA cohort.<sup>13</sup> Our study also has additional limitations. One limitation is potential inter-grader variability, which is multiplied by the large number of evaluators participating in the ocular exams. However, it was recently reported that there was high inter-grader agreement among trained ophthalmologists in the SICCA study.<sup>33</sup> Therefore, inter-grader variability was unlikely to have had a large effect on our results. Another limitation is that there was some overlap in the cohorts used to develop the OSS criteria and the SICCA/ACR classification criteria--thus resulting in some circularity in the analysis of the usefulness of tests. In addition, this study may have limited generalizability in clinical practice in that the ocular surface exam must be done in a specific order, utilizing the timelines provided for each test. Finally, our study did not examine the utility of combining ocular signs with symptoms (ocular and systemic) for screening for SS. Future studies would be helpful in determining if a combination of specific ocular signs and symptoms has an increased utility in screening dry eye patients for SS rather than the assessment of ocular signs alone.

In summary, we examined the associations of individual dry eye test results with extra-ocular findings for SS. Our findings suggest that in addition to corneal staining, both Schirmer I testing and conjunctival staining are critical tests that should always be included when screening dry eye patients to determine whether a further workup for SS is warranted. Given the strong association between SS and lymphoproliferative disease, ophthalmologists serve an integral role in screening for this debilitating and potentially life-threatening syndrome.



## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

**Funding/Support:** The SICCA Study Group is supported by the National Institute of Health (International Research Registry Network for Sjögren's syndrome contract N01-DE-32636 from the National Institute of Dental and Craniofacial Research, National Eye Institute, and Office of Research on Women's Health, 2003–2013). Vatinee Y. Bunya is supported by the National Eye Institute (K12-EY-015398) and Research to Prevent Blindness. Mina Massaro-Giordano receives support from Research to Prevent Blindness.

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**Table 1**

SS-related characteristics in the Sjogren's International Collaborative Clinical Alliance (SICCA) registry (N = 3514)<sup>a</sup>

Diagnostic Tests	N (%)
<b>Ocular eye tests</b>	
<b>Schirmer I test</b>	
Schirmer I test ≤ 5 mm	1026 (31.7)
Schirmer I test > 5 mm	2213 (67.7)
<b>Tear break-up time</b>	
TBUT < 10 seconds	2868 (84.5)
TBUT ≥ 10 seconds	528 (15.5)
<b>Ocular Staining Score (mean) <sup>b</sup></b>	
Conjunctival Score	2.99 (2.92 to 3.06)
Corneal Score	2.16 (2.10 to 2.22)
Total OSS score	5.15 (5.03 to 5.27)
<b>Salivary Gland Biopsy</b>	
Focus Score ≥ 1	1305 (39.1)
Focus Score < 1	2032 (60.9)
<b>Positive Serology</b>	
SSA or SSB antibodies	
Present	1296 (38.3)
Not present	2086 (61.7)
RF and ANA titer 1:320	
Present	1382 (40.9)
Not present	2000 (59.1)

<sup>a</sup>Due to missing data, some of the denominators used to compute the proportions above may differ from 3514.

<sup>b</sup>Confidence intervals are provided here; this was included as a continuous variable in the regression.

**Table 2**

Unadjusted association of ocular surface tests in relation to positive serology or positive LSG biopsy in the Sjogren's International Collaborative Clinical Alliance (SICCA) Registry (N = 3514)<sup>a</sup>

Diagnostic Tests	Unadjusted Odds Ratio: Positive serology (95% CI)	P-value	Unadjusted Odds Ratio: Positive LSG biopsy (95% CI)	P-value
<i>Ocular eye tests</i>				
Schirmer test I 5 mm/min <sup>b</sup>	2.37 (2.04 to 2.75)	<0.001	2.44 (2.1 to 2.85)	<0.001
TBUT < 10 seconds <sup>b</sup>	2.48 (2 to 3.07)	<0.001	2.17 (1.75 to 2.68)	<0.001
<b>Ocular Staining Score</b>				
Conjunctival OSS score <sup>b</sup>	1.55 (1.49 to 1.6)	<0.001	1.57 (1.51 to 1.63)	<0.001
Corneal OSS Score <sup>b</sup>	1.43 (1.27 to 1.49)	<0.001	1.52 (1.45 to 1.58)	<0.001
Abnormal OSS Score <sup>b</sup>	1.28 (1.26 to 1.31)	<0.001	1.31 (1.28 to 1.34)	<0.001

<sup>a</sup>Due to missing data, some of the denominators used to compute the calculations above may differ from 3514.

<sup>b</sup>Statistically significant result

**Table 3**

Logistic regression models fit to explore dry-eye test results as potential explanatory variables of positive labial salivary gland (LSG) biopsy and positive serology among participants in the Sjogren's International Collaborative Clinical Alliance (SICCA) registry

	Adjusted Odds Ratio (95% CI) <sup>a</sup>	P-value
<b>LSG BIOPSY (N=3153)</b>		
TBUT < 10 seconds	0.76 (0.58 to 0.99)	0.043
Schirmer I test 5 mm/5min	1.26 (1.05 to 1.51)	0.014 <sup>b</sup>
Conjunctival component of OSS	1.46(1.39 to 1.53)	<0.001 <sup>b</sup>
Corneal component of OSS	1.11 (1.05 to 1.18)	<0.001 <sup>b</sup>
<b>SEROLOGY (N=3232)</b>		
TBUT < 10 seconds	1.1 (0.83 to 1.42)	0.572
Schirmer I test 5 mm/5min	1.3 (1.12 to 1.61)	0.002 <sup>b</sup>
Conjunctival component of OSS	1.51 (1.43 to 1.59)	<0.001 <sup>b</sup>
Corneal component of OSS	0.98 (0.93 to 1.05)	0.586

<sup>a</sup> Adjusted for age and race.

<sup>b</sup> Statistically significant.