Research Paper

Significance and Implications of Patient-reported Xerostomia in Sjögren's Syndrome: Findings From the National Institutes of Health Cohort

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ABSTRACT

Background: Xerostomia is a chief complaint of patients with Sjögren's syndrome (SS). However, newer proposals for SS classification remove xerostomia and hyposalivation from the criteria list. Given these developments and the importance of patient-centered research outcomes, we sought to evaluate the utility of patient-reported xerostomia with implications for classification criteria, and clinical trials targeting SS treatment modalities.

Methods: A nested case-control study was designed within The National Institute of Dental and Craniofacial Research/National Institutes of Health (NIDCR/NIH) SS Cohort - one of the largest SS cohorts in the US. Clinical characteristics of those with and without xerostomia in SS and other salivary gland dysfunctions were compared. Several analytical methods were employed, including multivariable logistic regression modeling.

Findings: The NIDCR/NIH Sjögren's Syndrome Clinic has an open cohort with ongoing enrollment since 1984. This open cohort comprised of 2046 participants by August 27, 2015. Baseline data of 701 SS, 355 Sicca, and 247 ISS participants within the source cohort were analyzed. Xerostomia was highest among SS participants (87.4%, 95% CI: 84.8%–89.8%) compared to Sicca (72.4%, 95% CI: 67.4%–77.0%, p < 0.001) and ISS groups (38.1%, 95% CI: 32.0%–44.4%, p < 0.001). Those with xerostomia were more likely to have SS than Sicca/ISS (OR = 4.98, 95% CI: 3.78–6.56). The ability of xerostomia to screen for SS among those with salivary gland dysfunction was higher than screening for Sicca/ISS. Screening diagnostics of xerostomia were of greater utility compared to hyposalivation. After adjusting for confounding in multivariable modeling, SS participants with xerostomia were more likely to be White (Black/African Americans (OR: 0.40, 95% CI: 0.23–0.68, p-value = 0.001) and Asians (OR: 0.49, 95% CI: 0.25–0.96, p-value = 0.038) were less likely to have xerostomia compared to Whites), have dry eye symptoms for >3 months (OR: 5.80, 95% CI: 3.62–9.28, p-value <0.001), a lower Van Bijsterveld score (OR: 0.55, 95%CI: 0.34–0.90, p-value = 0.017), a lower stimulated salivary flow rate (OR: 1.67, 95% CI: 1.06–2.65, p-value = 0.028), a focus score of >2 (OR: 1.92, 95% CI: 1.20–3.09, p-value = 0.007), and salivary gland swelling (OR: 49.39, 95% CI: 2.02–1206.30, p-value = 0.017). Age, gender, fatigue, pain, anxiety, and autoantibodies were not significantly associated with xerostomia.

Interpretation: Findings from this study indicate that patient-reported xerostomia is highly prevalent among SS patients and is associated with several clinical phenotypes of this complex syndrome, thereby making it an important indicator of SS. The evidence also suggests that xerostomia is not limited to low salivary flow but might be reflective of compositional changes of saliva. Consequently, these findings suggest the need to consider xerostomia in the development of SS classification criteria and in patient-centered outcomes research in SS intervention trials.

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1. Introduction

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In 1933, Henrik Sjögren, in his doctoral dissertation introduced the neologism, *keratoconjunctivitis Sicca* (Murube, 2010, Sjögren, 1933). His findings now known as Sjögren's syndrome (SS), has come to be

understood as a multi-faceted autoimmune disorder primarily affecting the salivary and lacrimal glands, presenting with oral and ocular dryness, and often accompanied by extraglandular manifestations. Lymphocytic infiltration of the salivary glands has been a hallmark finding. However, the dysregulated immune response and salivary gland dysfunction are not always correlated and salivary gland dysfunction could precede autoimmunity or even be a result of an independent process in the pathogenesis of this syndrome (Nikolov and Illei, 2009). Several models of pathogenesis have been proposed, involving genetics, the environment, the innate and adaptive immune system, the autonomic nervous system, hormonal factors, or an interplay of these factors (Nikolov and Illei, 2009, Lessard, 2013, Burbelo et al., 2014, Iwakiri et al., 2009, Deshmukh et al., 2009, Zheng et al., 2010, Alevizos et al., 2011, Nocturne and Mariette, 2013, Gabor Illei. and Alevizos, 2013 Hernandez-Molina et al., 2011, Valtysdottir et al., 2001, Laine et al., 2007, Porola et al., 2008, Forsblad-d'Elia et al., 2009, Cai et al., 2008, Barendregt et al., 1998, Mandl et al., 2007, Andonopoulos et al., 1998).

Since first described by Henrik Sjögren, the chief oral complaint of individuals with SS most commonly has been the symptom of dry mouth or xerostomia, associated with significant morbidity and affecting the oral-health-related quality of life of patients (Sjögren, 1933, Visvanathan and Nix, 2010, Fox et al., 2008, Napenas and Rouleau, 2014, Ying Joanna and Thomson, 2015). However, patient-reported xerostomia is not an exclusive characteristic of Sjögren's syndrome, but could be a result of other conditions (Manuel Ramos-Casals and Moutsopoulos, 2012, Porter and Scully, 2000, Sreebny and Schwartz, 1997, Rad et al., 2010). This subjective complaint of xerostomia does not necessarily correlate with objective measures of hyposalivation (Manuel Ramos-Casals and Moutsopoulos, 2012, Fox et al., 1985, Ying Joanna and Thomson, 2015). Rather, xerostomia has been found to be associated with compositional changes of saliva (Alliende et al., 2008). Studies have also shown differences in the composition of stimulated saliva from the major salivary glands in patients with SS compared to healthy controls, and there is no correlation between compositional changes of stimulated saliva and salivary flow rates (Atkinson et al., 1990, Kalk et al., 2002, Mathews et al., 2008, Helenius et al., 2005). Xerostomia is also dependent on individual patient thresholds for oral dryness, tolerance, and adaptation (Manuel Ramos-Casals and Moutsopoulos, 2012, Scully and Felix, 2005).

Recently, new classification criteria for SS have been proposed (Shiboski et al., 2012). While the current American-European consensus classification criteria for SS include xerostomia and hyposalivation in the assessment algorithm, the new classification set does not (Shiboski et al., 2012, Vitali et al., 2002). Consequently, salivary gland involvement in SS is assessed partially by the new criteria by the presence of focal lymphocytic sialadenitis (Daniels et al., 2011). Therefore, the new approach to classification has a potential for misclassification and for missing cases that are in an early stage of disease progression (Vitali et al., 2013).

Given that xerostomia is a chief oral complaint of patients with SS and the assessment of salivary gland dysfunction is essential for diagnosis, we sought to investigate whether patient-reported xerostomia is still a valuable classification criterion and an important end-point in clinical trials targeting treatment modalities for SS (Aim-1). Furthermore, evaluation of this objective would be important if xerostomia is a composite indicator of various factors functioning within this complex syndrome, capturing factors such as salivary gland dysfunction expressed as compositional changes of saliva, and underlying pathways of pathogenesis including, but not limited to lymphocytic infiltration. Next, we wanted to evaluate xerostomia-related factors that impact screening for SS (Aim-2). Consequently, we sought to determine test accuracy measurements of xerostomia as a screening aid for SS among those with salivary gland dysfunction. Test accuracy measurements of hyposalivation were also determined for comparison. Finally, we wanted to ascertain similarities and differences in the clinical characteristics of those with and without xerostomia among those diagnosed

with SS, and also among those with other salivary gland dysfunction for comparison (Aim-3).

2. Materials & Methods

2.1. Study Population

The NIDCR Sjögren's Syndrome and Salivary Gland Dysfunction Unit (SSGDU) has been evaluating and enrolling participants with clinical suspicion of SS or salivary gland dysfunction since 1984, making the NIDCR/NIH SS cohort one of the largest in the US. To investigate the proposed objectives we designed a nested case-control study within the overall cohort comprising all participants enrolled before August 27, 2015.

2.2. Main Outcome Variables

We compared three groups (SS, Sicca, ISS) at high-risk for salivary gland dysfunction. SS was defined according to the American-European consensus group classification criteria (AECG) (Vitali et al., 2002). Sicca was defined as the presence of oral dryness determined by a whole unstimulated salivary flow rate (WUS) of ≤1.5 ml/15 min or ocular dryness determined by a Schirmer's test of ≤5 mm/5 min without anesthesia or Van Bijsterveld score of ≥4 in at least one eye, with the absence of focal lymphocytic sialadenitis (focus score < 1 per 4 mm^2) and the absence of anti-SSA (Ro) and anti-SSB (La) autoantibodies. The oral dryness experienced in the Sicca group would be due to salivary gland dysfunction other than SS. This could include developmental causes (e.g. salivary gland aplasia), iatrogenic (e.g. postsurgical), inflammatory (e.g. IgG4-related disease), neoplastic, sialolithiasis, or systemic causes (e.g. diabetes mellitus). Incomplete Sjögren's syndrome (ISS) was defined as the presence of a focus score of ≥1 per 4 mm^2 or autoantibodies SSA or SSB but not meeting the AECG criteria for SS classification.

2.3. Main Exposure Variables

Xerostomia was defined as patient-reported daily feeling of dry mouth for more than three months. Hyposalivation was defined as WUS of 1.5 ml/15 min or lower (Vitali et al., 2002). Data were imputed with total unstimulated salivary flow rate (TUS), which is the sum of parotid and submandibular/sublingual unstimulated salivary flow, for missing WUS. This combination of WUS and imputed TUS was termed as imputed unstimulated salivary flow rate (IUS); for TUS and IUS a cut off threshold of ≤1.5 ml/15 min was set to indicate hyposalivation. Analyses were undertaken with WUS, TUS, and IUS separately. Stimulated salivary flow rates were modeled with a flow rate of ≤7.5 ml/15 min representing salivary dysfunction (Manuel Ramos-Casals and Moutsopoulos, 2012).

2.4. Covariates

Demographic data on age, gender, race, and ethnicity of participants were collected. Current use of medications was categorized into five mutually exclusive categories: i) medications that reduce salivary flow, ii) sialagogues, iii) medications for extraglandular manifestations, iv) combination of medications of the three categories, and v) other medications. Autonomic nervous system assessment was undertaken, in which, patient-reported fatigue and anxiety were defined as the presence of any number of episodes of fatigue or anxiety in a month or daily. Brief pain inventory was ascertained. Past medical history of thyroid disease and diabetes mellitus type I and II was also ascertained. Cigarette smoking, alcohol use, and caffeine use status was defined as any use of cigarettes, any alcoholic drinks per week, and one or more caffeinated beverages per day respectively.

2.5. Study Procedures

A comprehensive oral and medical history was recorded. Head and neck and oral examination, and physical examination were performed. Salivary gland function evaluation (unstimulated followed by stimulated salivary flow rates), labial minor salivary gland biopsy, assessment of lacrimal function and standard eye examinations were performed. The van Bijsterveld and Oxford scores based on lissamine green were the ocular scoring systems used in this study. Clinical laboratory studies were done to test the general health of the participant and to assess for autoimmune markers. Testing for hepatitis B and C, and HIV was also undertaken. All study participants provided Informed Consent prior to the initiation of any study procedures and clinical protocols were approved by the NIH Institutional Review Board, conforming to the standards indicated by the Declaration of Helsinki.

2.6. Bias Assessment

Selection of SS, Sicca, and ISS participants was based on standard criteria (AE classification criteria) and objective tests irrespective of xerostomia status rendering the study to be devoid of selection bias. Furthermore, selection bias is diminished when cases and controls are selected from a defined cohort compared to the traditional case-control study design. As the exposure of interest, xerostomia is of considerable duration (>3 months) the introduction of recall bias and subsequent misclassification is not possible. The study design is also not jeopardized by misclassification of outcomes of interest (SS, Sicca and ISS), as the detection of these high-risk groups was based on standard, accepted criteria and objective tests, and was ascertained prior to establishing study objectives. Therefore, observer/investigator bias was avoided. Screening tests were applied to only the three high-risk groups and not normal volunteers, as were all comparative analyses; therefore, the exaggeration of the magnitude of association of any risk factor was avoided. No postulation of causation was set and therefore temporal bias does not play a role in the interpretation of results. The validity of comparison between cases (SS) and controls (Sicca and ISS) regarding exposure status (xerostomia) in this nested case-control study is justified by the use of a defined source cohort from which cases and controls were selected during the same study period.

2.7. Statistical Methods

Baseline data of all variables of interest were analyzed. A statistical significance level of $\alpha = 0.05$ was chosen. Descriptive data analysis was performed using standard summary statistics. Exploratory data analyses were performed on all variables of interest, including checks for normality (Shapiro Wilk test) and equal variance (Levene's test). Non parametric tests (Mann-Whitney U) were employed when indicated. Sensitivity and specificity analyses were conducted. Two sample test of proportions were carried out. Correlations were assessed with Point-biserial correlation coefficient. Correlation coefficients were computed including and excluding outliers as outliers are known to influence the correlation coefficient by rendering it non-significant. An outlier was determined as any data point >1.5 times the interquartile range (IQR) below the first quartile or above the third quartile of the data. Total effects were studied by simple logistic regression models. Multivariate logistic regression models were constructed after checking for collinearity. Models by various methods (forward and backward stepwise, and likelihood ratio testing) were compared to check for consistency of results. Apart from model-selected variables, variables of interest were locked into the model. Forward stepwise selection with correction for dispersion determined the final model. Statistical significance was assessed on a set two-tailed p-value of 0.05. Non- statistically significant variables were verified by testparm. Checks for pertinent interactions/effect modification were undertaken. Goodness of fit of the final model was assessed using Hosmer-Lemeshow test. All statistical analyses were performed using STATA 14.0 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

3. Results

As of August 27, 2015, the SSGDU at NIDCR/NIH has evaluated 3349 and enrolled 2046 participants. In this study, we compared baseline data of three groups at high-risk for salivary gland dysfunction with 701 SS, 355 Sicca, and 247 ISS participants (Fig. 1). Demographic characteristics of these groups were assessed, stratified by the presence or absence of xerostomia (Table 1). In the SS group, age, race and ethnicity were significantly different between those with and without xerostomia. In the Sicca group, differences in gender and ethnicity were statistically significant and in the ISS group, no differences in demographics by xerostomia status were found. The three groups, SS, Sicca, and ISS differed in the prevalence of key characteristics, i.e., xerostomia, positive focus score, and positive serology (Supporting Information (SI)), with the SS group having the highest prevalence of these characteristics. The duration of dry mouth symptoms also differed across groups with the SS group having the longest median duration (SI).

Among the 1303 participants in our study, 74% (n = 964) reported xerostomia (Table 2). Xerostomia prevalence was highest among SS participants (87.4%, 95% CI: 84.8%–89.8%) followed by Sicca participants (72.4%, 95% CI: 67.4%–77.0%) and the ISS group (38.1%, 95% CI: 32.0%–44.4%). The absolute difference in xerostomia prevalence between SS and Sicca participants was significant (15.0%, 95% CI: 9.8%–20.3%, p < 0.001) as was the absolute difference in prevalence between SS and ISS participants (49.4%, 95% CI: 42.9%–55.9%, p < 0.001).

The sensitivity of xerostomia for detecting SS among high-risk participants was 87.4% (95% CI: 84.8%–89.8%) and specificity was 41.7% (95% CI: 37.7%–45.7%) (Table 2A). SS participants were 50% more likely to have xerostomia compared to other high risk participants, namely Sicca and ISS (LR + = 1.50, 95% CI: 1.39–1.61). Moreover, SS participants were 70% less likely to be without xerostomia compared to other high risk participants (LR − = 0.30, 95% CI: 0.24–0.37). Further, SS participants had a 5-fold higher risk of xerostomia compared to other high-risk participants (OR = 4.98, 95% CI: 3.78–6.56). Consequently, a participant with salivary gland dysfunction presenting with xerostomia is 5 times more likely to have SS than Sicca or ISS. The positive predictive value (PPV) and negative predictive value (NPV) of xerostomia indicate that a high-risk participant with xerostomia has a 64% chance of having SS, and if without xerostomia, has a 74% chance of not having SS.

In contrast, Sicca and ISS participants had a lower likelihood of having xerostomia and a higher likelihood of being without xerostomia compared to SS participants. The odds ratios of having xerostomia in Sicca and ISS compared to SS participants were significantly lower, indicating the utility of xerostomia for distinguishing between SS and other high-risk participants. The PPV and NPV of xerostomia in Sicca and ISS participants were also significantly lower than that seen in SS participants. Given these test statistics, among high-risk participants, patient-reported xerostomia was a better screening aid for SS than for Sicca or ISS, and therefore a better indicator of SS.

Unlike xerostomia which is subjective, hyposalivation is a quantifiable measure. Test diagnostics indicated the sensitivity of WUS for detecting SS was 63.8% (95% CI: 56.3%–70.9%) while the specificity was 51.3% (95% CI: 43.1%–59.4%). The OR, PPV, and NPV test statistics for WUS in detecting SS were lower compared to those of xerostomia. Although SS participants were 50% more likely to have xerostomia compared to other high-risk participants, WUS as a screening test was unable to differentiate between SS and Sicca (overlapping 95% CIs, Table 2A) and test diagnostics for ISS were low. For IUS, sensitivity was 76% and specificity was 46.9% for detecting SS and SS participants were nearly 3 times more likely to have xerostomia compared to other high-risk groups (OR = 2.80, 95% CI: 2.17–3.62). The inability of
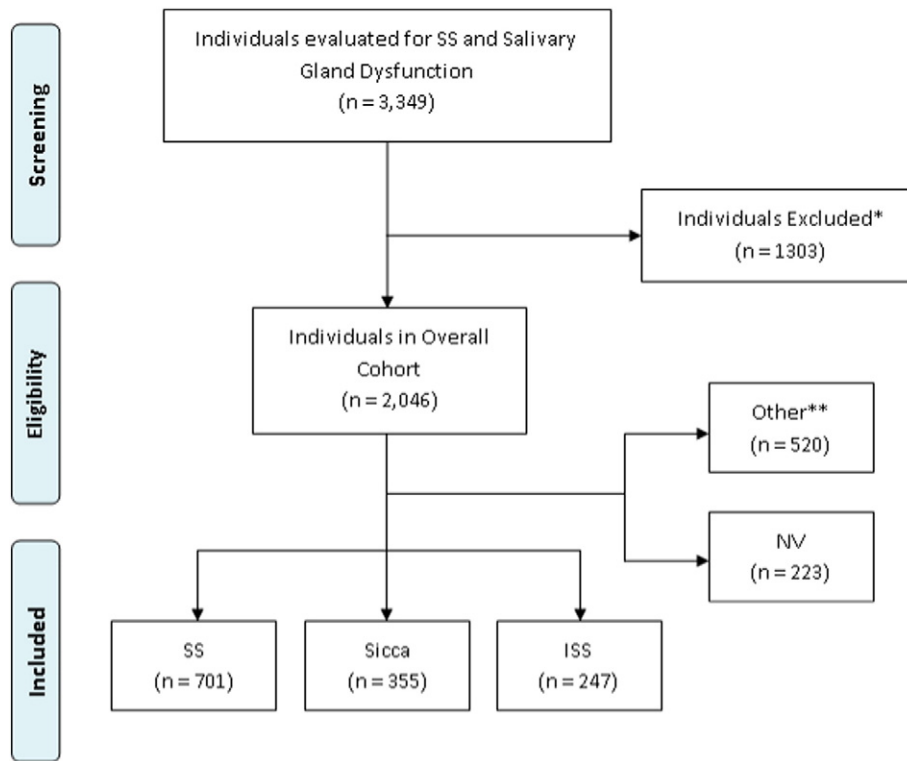
Fig. 1. Enrollment flow diagram. *Based on study's exclusion criteria: those under 4 years of age, diagnosed with drug-related xerostomia, unable or unwilling to comply with follow-up requirements, with any medical or psychological/psychiatric condition or treatment that would exclude them from the research, and unable to give consent/assent or parental/guardian consent. **Includes those who meet AE classification exclusion criteria and those who have incomplete information to date to classify. SS: Sjögren's Syndrome | ISS: Incomplete Sjögren's Syndrome | NV: Normal Volunteers. Participants, though not restricted to enroll based on geographic region or countries, were predominately from the Eastern US of varied races and ethnicities. They were referred by private physicians and dentists, the National Institutes of Health (NIH) Clinical Center, or self- referred. All participants were enrolled in NIH Institutional Review Board approved Clinical Protocols and had provided Informed Consent prior to the initiation of any study procedures.
Adapted from PRISMA Statement.

WUS to distinguish between SS and Sicca demonstrated by test diagnostics was corroborated by the non-statistically significant difference in median WUS between the SS and Sicca groups (Figs. 2, 3). As the test diagnostics of IUS were better than that of WUS, we also found that the median IUS was significantly different among all 3 high-risk groups. The SS group had the lowest median IUS and TSS compared to Sicca and ISS groups.

Correlations between WUS, IUS, TSS, and Xerostomia are shown in Table 2B. In the overall pool of high-risk participants, both unstimulated and stimulated salivary flow rates were negatively correlated with xerostomia, with WUS possessing the strongest point-biserial correlation coefficient compared to IUS and TSS (-0.49, -0.42, -0.21

respectively, p-value < 0.001, without outliers). However, when stratified by high-risk groups, WUS was only significantly correlated with xerostomia in SS and Sicca groups, while IUS was significantly correlated with xerostomia in all three groups. Correlation of TSS with xerostomia was only noted in the SS group, and was weaker than that of WUS and IUS. Correlation coefficients are influenced by outliers, yielding weak correlations. In this analysis, even with the removal of outliers salivary flow rates remained weakly correlated with xerostomia in all three high-risk groups.

Table 3 compares the phenotypic characteristics of those with and without xerostomia. Compared to SS participants without xerostomia (SS+X−), SS participants with xerostomia (SS+X+) had a significantly

Table 1
Comparison of demographic characteristics of high-risk groups by xerostomia status.
[a]Wilcoxon rank-sum (Mann-Whitney) test | [b]Fisher exact test | [c]American Indian or Alaskan Native, Native Hawaiian and other Pacific Islander, multiple races, other, and unknown | Percentages rounded to one decimal place.

Demographic characteristic	SS+X+ N = 613	SS+X− N = 88	p-Value	Sicca + X+ N = 257	Sicca + X− N = 98	p-Value	ISS + X+ N = 94	ISS + X− N = 153	p-Value
Age (median, range)	53 (7–81)	48 (16–83)	0.001[a]	52 (17–84)	52 (21–88)	0.50[a]	50 (11–86)	46 (9–81)	0.06[a]
Gender (n, %)									
Male	48 (7.8)	9 (10.2)	0.41[b]	37 (14.4)	26 (26.5)	0.007[b]	10 (10.6)	27 (17.7)	0.09[b]
Female	565 (92.2)	79 (89.8)		220 (85.6)	72 (73.5)		84 (89.4)	126 (82.4)	
Race (n, %)									
White	455 (74.2)	50 (56.8)	0.01[b]	225 (87.6)	77 (78.6)	0.11[b]	75 (79.8)	100 (65.4)	0.10[b]
Black or African American	73 (11.9)	20 (22.7)		15 (5.8)	9 (8.2)		7 (7.5)	25 (16.3)	
Asian	44 (7.2)	11 (12.5)		9 (3.5)	4 (4.1)		5 (5.3)	12 (7.8)	
Other[c]	41 (6.7)	7 (8.0)		8 (3.1)	8 (8.2)		7 (7.5)	16 (10.5)	
Ethnicity (n, %)									
Not Latino or Hispanic	564 (92.0)	79 (89.8)	0.03[b]	253 (98.4)	91 (92.9)	0.02[b]	86 (91.5)	143 (93.5)	0.66[b]
Latino or Hispanic	37 (6.0)	3 (3.4)		2 (0.8)	4 (4.1)		8 (8.5)	9 (5.9)	
Unknown	12 (2.0)	6 (6.8)		2 (0.8)	3 (3.1)		0 (0.0)	1 (0.7)	

Table 2

Xerostomia and hyposalivation (WUS, IUS) by high-risk group.

A.[*]Statistically significant. B. In Overall, WUS had the strongest point-biserial correlation coefficient ($r_{pb} = -0.49$, $p < 0.001$) than IUS and TSS. Stratified by groups, WUS is significantly correlated with xerostomia in SS and Sicca groups; ISS is significantly correlated with xerostomia in SS ($r_{pb} = -0.17$, $p < 0.001$), Sicca ($r_{pb} = -0.20$, $p = 0.002$), and ISS ($r_{pb} = -0.18$, $p = 0.01$) groups. Among SS participants, both unstimulated and stimulated salivary flow rates were weakly correlated with xerostomia reaching statistical significance only after the removal of outliers (WUS: $r_{pb} = -0.19$, $p = 0.02$; IUS: $r_{pb} = -0.17$, $p < 0.001$; TSS: $r_{pb} = -0.13$, $p = 0.002$), with the exception of IUS which exhibited borderline significance even in the presence of outliers ($r_{pb} = -0.08$, $p = 0.04$). Among Sicca participants, only unstimulated salivary flow rates (WUS, IUS) showed a statistical significant correlation, albeit weak, with xerostomia (WUS: $r_{pb} = -0.22$, $p = 0.03$; IUS: $r_{pb} = -0.20$, $p = 0.002$). Among ISS participants, only IUS was statistically significantly correlated with xerostomia, which too was a weak correlation ($r_{pb} = -0.18$, $p = 0.01$). Correlation of TSS with xerostomia was of statistical significance in the SS group ($r_{pb} = -0.13$, $p = 0.002$).

A. Test Diagnostics of Xerostomia and Hyposalivation

Test Result	Disease Status						Overall Total
	SS+	SS−	Sicca+	Sicca−	ISS+	ISS−	
Xerostomia+[*]	613	351	257	707	94	870	964
Xerostomia−	88	251	98	241	153	186	339
Total	701	602	355	948	247	1056	1303

Test Diagnostics - Xerostomia	SS+ (N = 701)		Sicca+ (N = 355)		ISS+ (N = 247)	
	ES	95% CI	ES	95% CI	ES	95% CI
Prevalence (%)	53.8	51.0–56.5	27.2	24.8–29.8	19	16.9–21.2
Sensitivity (%)	87.5	84.8–89.8	72.4	67.4–77.0	38.1	32.0–44.4
Specificity (%)	41.7	37.7–45.7	25.4	22.7–28.3	17.6	15.4–20.0
Likelihood ratio (+)	1.50[*]	1.39–1.61	0.97	0.90–1.05	0.46[*]	0.39–0.54
Likelihood ratio (−)	0.30[*]	0.24–0.37	1.09	0.89–1.33	3.52[*]	2.99–4.14
Odds ratio LR(+)/LR(−)	4.98[*]	3.78–6.56	0.89	0.68–1.18	0.13[*]	0.10–0.18
Positive Predictive Value (%)	63.6	60.5–66.6	26.7	23.9–29.6	9.8	8.0–11.8
Negative Predictive Value (%)	74	69.0–78.6	71.1	65.9–75.9	54.9	49.4–60.2

Test Diagnostics - Hyposalivation (WUS)	SS+ (N = 177)		Sicca+ (N = 104)		ISS+ (N = 50)	
	ES	95% CI	ES	95% CI	ES	95% CI
Prevalence (%)	53.5	47.9–58.9	31.4	26.5–36.7	15.1	11.4–19.4
Sensitivity (%)	63.8	56.3–70.9	67.3	57.4–76.2	10	3.3–21.8
Specificity (%)	51.3	43.1–59.4	48	41.4–54.7	34.9	29.3–40.8
Likelihood ratio (+)	1.31[*]	1.08–1.60	1.29[*]	1.08–1.56	0.15[*]	0.07–0.35
Likelihood ratio (−)	0.70[*]	0.55–0.90	0.68[*]	0.50–0.93	2.58[*]	2.15–3.10
Odds ratio LR(+)/LR(−)	1.86[*]	1.20–2.89	1.90[*]	1.17–3.08	0.06[*]	0.02–0.15
Positive Predictive Value (%)	60.1	52.7–67.2	37.2	30.3–44.6	2.7	0.9–6.1
Negative Predictive Value (%)	55.2	46.7–63.6	76.2	68.4–82.9	68.5	60.2–76.0

Test Diagnostics - Hyposalivation (IUS)	SS+ (N = 667)		Sicca+ (N = 257)		ISS+ (N = 199)	
	ES	95% CI	ES	95% CI	ES	95% CI
Prevalence (%)	59.4	56.5–62.3	22.9	20.5–25.5	17.7	15.5–20.1
Sensitivity (%)	76	72.6–79.2	71.6	65.7–77.0	29.1	22.9–36.0
Specificity (%)	46.9	42.3–51.6	34.8	31.6–38.0	25.2	22.4–28.1
Likelihood ratio (+)	1.43[*]	1.30–1.58	1.1	1.00–1.20	0.39[*]	0.31–0.49
Likelihood ratio (−)	0.51[*]	0.43–0.60	0.82	0.66–1.01	2.81[*]	2.44–3.24
Odds ratio LR(+)/LR(−)	2.80[*]	2.17–3.62	1.34	0.99–1.82	0.14[*]	0.10–0.19
Positive Predictive Value (%)	67.7	64.2–71.0	24.6	21.5–27.8	7.7	5.9–9.9
Negative Predictive Value (%)	57.2	52.0–62.3	80.5	76.1–84.4	62.3	57.2–67.2

B. Point Biserial Correlation of Xerostomia and Hyposalivation

|	SS+	Sicca+	ISS+	Overall
	Whole Unstimulated Salivary Flow Rate (WUS, ml/15min)			
Xerostomia	$r_{pb} = -0.09$ p = 0.25 n = 177	$r_{pb} = -0.20$ p = 0.05 n = 104	$r_{pb} = -0.16$ p = 0.27 n = 50	$r_{pb} = -0.33$ p < 0.001 n = 331
Xerostomia, without outlier influence	$r_{pb} = -0.19$ p = 0.02 n = 166	$r_{pb} = -0.22$ p = 0.03 n = 99	$r_{pb} = -0.23$ p = 0.12 n = 48	$r_{pb} = -0.49$ p <0.001 n = 306
	Imputed Unstimulated Salivary Flow Rate (IUS, ml/15min)			
Xerostomia	$r_{pb} = -0.08$ p = 0.04 n = 667	$r_{pb} = -0.13$ p = 0.04 n = 257	$r_{pb} = -0.09$ p = 0.23 n = 199	$r_{pb} = -0.22$ p < 0.001 n = 1123
Xerostomia, without outlier influence	$r_{pb} = -0.17$ p <0.001 n = 613	$r_{pb} = -0.20$ p = 0.002 n = 242	$r_{pb} = -0.18$ p = 0.01 n = 192	$r_{pb} = -0.42$ p < 0.001 n = 1013
	Total Stimulated Salivary Flow Rate (TSS, ml/15min)			
Xerostomia	$r_{pb} = -0.06$ p = 0.17 n = 575	$r_{pb} = -0.11$ p = 0.08 n = 230	$r_{pb} = -0.12$ p = 0.13 n = 169	$r_{pb} = -0.15$ p < 0.001 n = 974
Xerostomia, without outlier influence	$r_{pb} = -0.13$ p = 0.002 n = 557	$r_{pb} = -0.13$ p = 0.06 n = 218	$r_{pb} = 0.13$ p = 0.08 n = 168	$r_{pb} = -0.21$ p < 0.001 n = 934
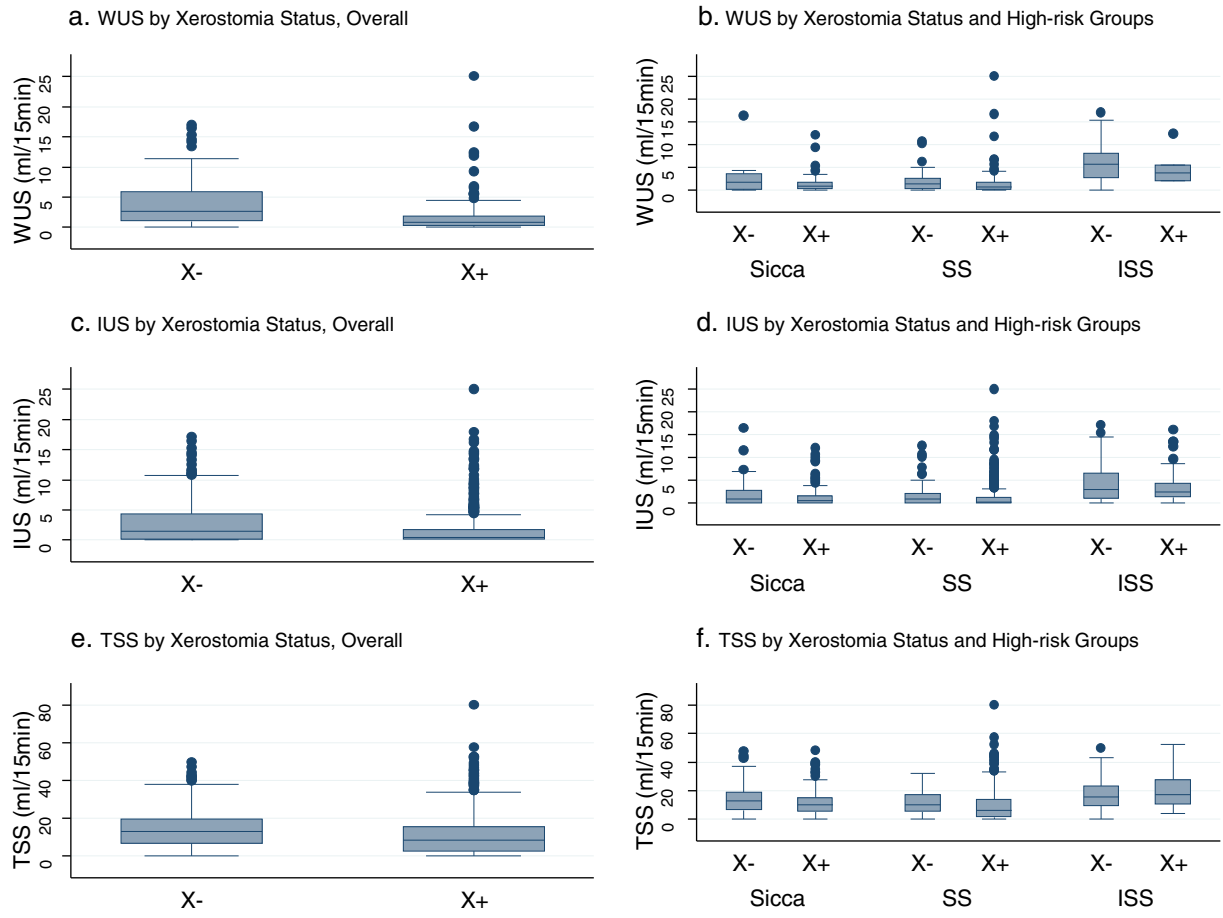
Fig. 2. Salivary flow rates in high-risk groups by xerostomia status. Box represents 25th, 50th (median) and 75th percentile of salivary flow rate. Whiskers drawn to the smallest and largest observations within the calculated fences. Dots represent outliers. WUS: Whole Unstimulated Salivary Flow Rate | IUS: Imputed Unstimulated Salivary Flow Rate | TSS: Total Stimulated Salivary Flow Rate | SS: Sjögren's Syndrome | ISS: Incomplete Sjögren's Syndrome | X+: Presence of xerostomia | X−: Absence of xerostomia | Panels a, c, and e represent salivary flow rates by xerostomia status in the three high-risk groups combined. Panels b, d, and f represent salivary flow rates by xerostomia status stratified by high-risk group.

Fig. 3. Median salivary flow rates by disease groups. Salivary flow rates expressed in ml//15 min. ***Statistically significantly different from other disease groups, p < 0.001. WUS: Whole Unstimulated Salivary Flow Rate | IUS: Imputed Unstimulated Salivary Flow Rate | TUS: Total Unstimulated Salivary Rate | TSS: Total Stimulated Salivary Flow Rate | SS: Sjögren's Syndrome | ISS: Incomplete Sjögren's Syndrome. Median WUS of SS and Sicca groups were comparable (p = 0.78) but lower than that of ISS group (p < 0.001 in both Mann-Whitney tests). Median IUS, TUS, and TSS were lowest in SS group compared to Sicca and ISS groups (p < 0.001 in each comparison). Sicca group had lower median IUS, TUS, and TSS compared to ISS group (p < 0.001 in each comparison).

higher proportion of reporting ocular dryness lasting >3 months, hyposalivation with respect to both unstimulated and stimulated salivary flow rates, and salivary gland swelling. Although subjective ocular dryness was significantly different, the proportion of objective ocular signs was similar between subgroups. In addition, though the proportion of hyposalivation (IUS, TSS) was higher in SS + X+ subgroup,

the proportions of positive focus scores (≥1 per 4 mm²) and autoantibodies SSA/SSB were not different between subgroups. Diabetes mellitus, thyroid disease, and other autoimmune disorders and extraglandular manifestations such as fatigue, anxiety, and pain were comparable between subgroups. Potential confounders such as cigarette smoking, alcohol intake and caffeine intake were similar in both subgroups. Various classes of medications were also similar between subgroups. Among Sicca participants, the proportions of symptomatic dry eye, salivary gland pain, thyroid disease, and caffeine intake were significantly higher among those with xerostomia than those without. Among ISS participants, the proportions of symptomatic dry eye and thyroid disease were significantly higher among those with xerostomia than those without.

The results of multivariable regression analyses for independent predictors of xerostomia in SS participants are presented in Table 4. In a model adjusting for all potential confounders, Black/African Americans (OR: 0.40, 95% CI: 0.23–0.68, p-value = 0.001) and Asians (OR: 0.49, 95% CI: 0.25–0.96, p-value = 0.038) were less likely to have xerostomia compared to whites. Those with dry eye symptoms of >-3 months were almost 6 times more likely to have xerostomia than those without dry eye symptoms of this duration (OR: 5.80, 95% CI: 3.62–9.28, p-value <0.001). Paradoxically, those with a Van Bijsterveld score ≥ 4 were less likely to have xerostomia (OR: 0.55, 95% CI: 0.34–0.90, p-value = 0.017); however, the crude odds ratio was not statistically significant. Presence of hyposalivation based on unstimulated salivary flow rate (IUS), although highly significant in the simple logistic regression model (OR: 2.02, 95% CI: 1.24–3.27, p-value = 0.004) was only of borderline significance when adjusted for confounders (OR:
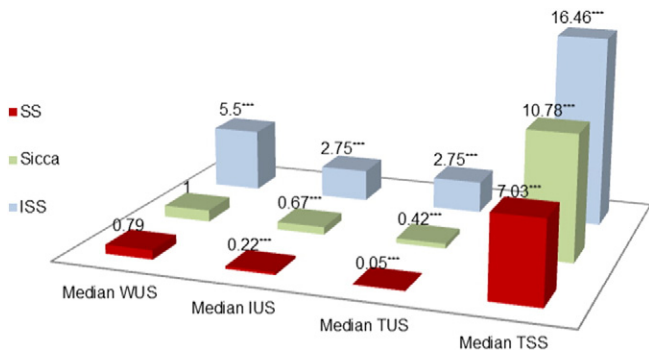
Table 3

Comparison of characteristics of SS, Sicca and ISS participants with and without xerostomia.

*Statistically significant variables | Two-sample test of proportions | Percentages rounded to one decimal place.

Independent variable	SS+X+ n	%	95% CI	SS+X− n	%	95% CI	p-Value	Sicca+X+ n	%	95% CI	Sicca+X− n	%	95% CI	p-Value	ISS+X+ n	%	95% CI	ISS+X− n	%	95% CI	p-Value
Focus score ≥ 1 per 4 mm	574	97.8	96.6–99.0	84	100	–	0.17	–	–	–	–	–	–	–	82	93.2	87.9–98.4	137	94.5	90.8–98.2	0.69
SSA/SSB positive	282	73.8	69.4–78.2	59	84.3	75.8–92.8	0.06	–	–	–	–	–	–	–	14	32	21.4–42.6	24	43.8	26.6–60.9	0.24
Dry eye > 3months	527	86.4	83.7–89.1	47	62.7	51.7–73.6	<0.001*	216	84	79.6–88.5	27	45	32.4–57.6	<0.001*	63	67	57.5–76.5	25	28.1	18.8–37.4	<0.001*
Schirmer's positive	296	50	46.0–54.0	46	54.8	44.1–65.4	0.41	101	41.9	35.7–48.1	49	60.5	49.8–71.1	<0.001*	2	2.8	0–6.7	17	17.5	10.0–25.1	<0.001*
Van B positive	233	50	45.4–54.4	41	50.6	39.7–61.5	0.9	36	21.6	15.3–27.8	18	31.6	19.5–43.6	0.13	1	1.7	0–5.1	5	7.9	1.3–14.6	0.12
Oxford positive	183	48.2	43.1–53.2	26	42.6	30.2–55.0	0.42	32	22.2	15.4–29.0	14	29.2	16.3–42.0	0.33	4	9.3	0.6–18.0	3	6.8	0–14.3	0.67
Any one ocular sign positive	387	74.3	70.5–78.0	64	82.1	73.5–90.6	0.14	130	62.8	56.2–69.4	56	77.8	68.2–87.4	0.02*	5	12.2	2.2–22.2	21	36.2	23.8–48.6	0.01*
WUS ≤1.5 ml/15 min	93	66.4	58.6–74.3	20	54.1	38.0–70.1	0.16	62	70.5	60.9–80.0	8	50	25.5–74.5	0.12	0	0	–	5	12.5	2.3–22.7	0.24
IUS ≤1.5 ml/15 min	453	77.8	74.5–81.2	54	63.5	53.3–73.8	<0.001*	142	72.8	66.6–79.1	42	67.7	56.1–79.4	0.44	19	25.3	15.5–35.2	39	31.5	23.3–39.6	0.36
TUS ≤1.5 ml/15 min	394	80.2	76.7–83.8	59	71.1	61.3–80.8	0.06	131	75.7	69.3–82.1	39	69.6	57.6–81.7	0.37	11	18.6	8.7–28.6	34	30.9	22.3–39.5	0.09
Any one unstimulated salivary flow ≤1.5 ml/15 min	483	96.6	95.0–98.2	62	87.3	79.6–95.1	<0.001*	156	92.9	89.0–96.8	45	90	81.7–98.3	0.51	20	69	52.1–85.8	46	62.2	51.1–73.2	0.52
TSS ≤7.5 ml/15 min	263	53.5	49.0–57.9	32	38.6	28.1–49.0	0.01*	61	35.1	28.0–42.1	16	28.6	16.7–40.4	0.37	7	11.9	3.6–20.1	22	20	12.5–27.5	0.18
Salivary gland swelling	71	98.6	95.9–100.0	9	81.8	59.0–100.0	<0.001*	15	93.8	81.9–100.0	5	100	–	0.57	–	–	–	–	–	–	–
Salivary gland pain	31	81.6	69.3–93.9	4	57.1	20.5–93.8	0.15	18	94.7	84.7–100.0	1	50	0–100.0	0.04*	0	0	–	3	100	–	0.05
Fatigue	104	92.9	88.1–97.6	11	78.6	57.1–100.0	0.07	58	93.5	87.4–99.7	7	87.5	64.6–100.0	0.53	5	100	–	9	64.3	39.1–89.4	0.12
Anxiety	77	70	61.4–78.6	8	57.1	31.2–83.1	0.33	47	75.8	65.1–86.5	4	50	15.3–84.6	0.12	5	100	–	8	57.1	31.2–83.1	0.08
Pain	92	90.2	84.4–96.0	24	88.9	77.0–100.0	0.84	20	83.3	68.4–98.2	4	66.7	28.9–100.0	0.36	1	100	–	16	72.7	54.1–91.3	0.54
Thyroid disease	151	24.6	21.2–28.0	17	19.3	11.1–27.6	0.27	46	17.9	13.2–22.6	3	3.1	0–6.5	<0.001*	17	18.1	10.3–25.9	8	5.2	1.7–8.8	<0.001*
Diabetes mellitus	13	2.1	0.9–3.3	1	1.4	0–3.4	0.54	9	3.5	1.3–5.7	4	4.1	0.2–8.0	0.79	2	2.1	0–5.0	3	2	0–4.2	0.93
Hx of other autoimmune disorder	17	2.8	1.5–4.1	5	5.7	0.8–10.5	0.14	2	0.8	0–1.9	1	1	0–3.0	0.82	2	2.1	0–5.0	7	4.6	1.2–7.9	0.32
Cigarette smoking	49	31.2	24.0–38.5	9	34.6	16.3–52.9	0.73	17	24	14.0–33.9	4	40	9.6–70.4	0.28	2	40	0–82.9	5	19.2	4.1–34.4	0.31
Alcohol intake	82	50.9	43.2–59.0	16	57.1	38.8–75.5	0.54	40	55.6	44.1–67.0	6	66.7	35.9–97.6	0.53	4	80	44.9–100.0	12	44.4	25.7–63.2	0.14
Caffeine intake >1 drink/day	99	61.5	54.0–69.0	18	62.1	44.4–79.7	0.95	46	63.9	52.8–75.0	3	30	1.6–58.4	0.04*	2	40	0–82.9	11	40.7	22.2–59.3	0.98
Medications - reduce salivary flow	22	3.6	2.1–5.1	1	1.1	0–3.4	0.23	2	0.8	0–1.9	0	–	–	0.38	–	–	–	–	–	–	–
Medications - sialagogues	15	2.4	1.2–3.7	1	1.1	0–3.4	0.44	3	1.7	0–2.5	0	–	–	0.28	1	1.1	0–3.1	0	0	–	0.2
Medications - extraglandular manifestations	85	14	11.1–16.6	15	17	9.2–24.9	0.43	13	5.1	2.4–7.7	3	3.1	0–6.5	0.42	1	1.1	0–3.1	6	3.9	0.8–7.0	0.19
Medications - combinations	30	5	3.2–6.6	2	2.3	0–5.4	0.27	2	0.8	0–1.9	0	–	–	0.38	0	0	–	2	1.3	0–3.1	0.27
Medications - other	34	5.5	3.7–7.4	6	6.8	1.6–12.1	0.63	5	1.9	0.3–3.6	0	–	–	0.16	4	1.1	0–4.8	1	2.6	0.1–5.1	0.4

Table 4

The association between key characteristics of SS participants and xerostomia.

[a]Focus score - nonlinear association, spline at 2 based on data | [b]Binary variables with absence of the variable as reference | [c]TSS - from multiple logistic regression model replacing IUS | OR - odds ratio | NA - variable not selected by model due to non-significance/collinearity | [*]Statistically significant variables. Independent predictors of xerostomia among SS participants: those with xerostomia of >3 months duration are more likely to be white, have dry eye symptoms for >3 months, but have a lower Van Bijsterveld score (<4), have a lower stimulated salivary flow rate (≤7.5 ml/15 min), have a higher focus score (>2), and have salivary gland swelling. Non-predictors of xerostomia among SS participants: there was no statistically significant difference in age, gender, autoantibodies SSA/SSB, Schirmer's test, Oxford score, unstimulated parotid (OR: 1.01, 95% CI:0.87–1.16, p-value = 0.941) and submandibular (OR: 0.78, 95% CI: 0.36–1.69, p-value = 0.526) salivary flow rates (not shown in the table), extraglandular manifestations such as fatigue, anxiety, pain, past history of thyroid disease, diabetes mellitus, other autoimmune disorders, cigarette smoking, alcohol intake, and caffeine intake between those with and without xerostomia.

	SS+					
	Unadjusted models		p-Value	Adjusted model		p-Value
Independent variable	OR	95% CI		OR	95% CI	
Age	1.02	1.01–1.04	0.004[*]	1	0.99–1.02	0.405
Gender						
Male	1	—	—	1	—	—
Female	1.34	0.63–2.83	0.443	1.12	0.55–2.27	0.75
Race						
White	1	—	—	1	—	—
Black or African American	0.4	0.23–0.71	0.002[*]	0.4	0.23–0.68	0.001[*]
Asian	0.44	0.21–0.91	0.026[*]	0.49	0.25–0.96	0.038[*]
Other	0.64	0.27–1.51	0.311	0.62	0.27–1.39	0.243
Ethnicity						
Not Latino/not Hispanic	1	—	—	NA	—	—
Latino/Hispanic	1.73	0.52–5.74	0.372	—	—	—
Unknown	0.28	0.10–0.77	0.013[*]	—	—	—
Focus score[a]						
Spline at 2 (crude)						
Focus score ≤ 2	0.45	0.24–0.82	0.009[*]	1	—	—
Focus score > 2	1.16	1.06–1.26	0.001[*]	NA	—	—
Focus score > 2 (binary, ref ≤2)	2.59	1.36–4.93	0.004[*]	1.92	1.20–3.09	0.007[*]
Autoantibodies						
Neither SSA or SSB	1	—	—	1	—	—
Either one present	0.41	0.19–0.89	0.023[*]	0.78	0.38–1.63	0.514
Both present	0.61	0.29–1.25	0.177	1.1	0.55–2.23	0.784
Dry eye >3 months[b]	5.35	3.32–8.61	<0.001[*]	5.8	3.62–9.28	<0.001[*]
Schirmer's test positive[b]	0.83	0.52–1.31	0.414	NA	—	—
Van B test positive[b]	0.97	0.61–1.56	0.904	0.55	0.34–0.90	0.017[*]
Oxford test positive[b]	1.25	0.72–2.16	0.422	NA	—	—
Hyposalivation	1.68	0.81–3.51	0.166	1.34	0.53–3.39	0.543
WUS ≤1.5 ml/15 min[b]						
Hyposalivation	2.02	1.24–3.27	0.004[*]	1.68	1.01–2.79	0.046[*]
IUS ≤1.5 ml/15 min[b]						
Hyposalivation	1.65	0.98–2.79	0.06	NA	—	—
TUS ≤1.5 ml/15 min[b]						
Hyposalivation	1.83	1.14–2.95	0.004[*]	1.67	1.06–2.65	0.028[*]
TSS ≤7.5 ml/15 min[c]						
Salivary gland swelling[b]	15.78	1.30–191.94	0.030[*]	49.39	2.02–1206.3	0.017[*]
Salivary gland pain[b]	3.32	0.60–18.31	0.168	2.55	0.39–16.64	0.327
Fatigue[b]	3.55	0.82–15.35	0.09	2.6	0.57–11.92	0.218
Anxiety[b]	1.75	0.56–5.44	0.334	NA	—	—
Pain[b]	1.15	0.29–4.51	0.841	0.88	0.18–4.23	0.87
Thyroid disease[b]	1.37	0.78–2.39	0.276	NA	—	—
Diabetes mellitus[b]	1.89	0.24–14.59	0.544	NA	—	—
Hx of other autoimmune disorder[b]	0.47	0.17–1.32	0.152	NA	—	—
Cigarette smoking[b]	0.86	0.36–2.06	0.73	NA	—	—
Alcohol intake[b]	0.78	0.35–1.75	0.544	NA	—	—
Caffeine intake >1 drink/day[b]	0.96	0.43–2.20	0.953	NA	—	—
Medications						
None	1	—	—	1	—	—
Medications that reduce salivary flow	3.25	0.43–24.50	0.254	11.25	1.64–77.01	0.014[*]
Medications - sialagogues	2.21	0.29–17.04	0.446	5.32	0.86–32.89	0.072
Medications - extraglandular manifestations	0.84	0.45–1.54	0.565	1.77	0.92–3.42	0.087
Medications - combinations	2.21	0.52–9.49	0.285	6.95	1.75–27.63	0.006[*]
Medications - other	0.84	0.34–2.07	0.699	2.05	0.80–5.28	0.135

1.68, 95% CI: 1.01–2.79, p-value = 0.046). Hyposalivation based on TSS was significantly associated with xerostomia (OR: 1.67, 95% CI: 1.06–2.65, p-value = 0.028). Those with a focus score > 2 were twice as likely to have xerostomia as those with a focus score of ≤2 (OR: 1.92, 95% CI: 1.20–3.09, p-value = 0.007). Salivary gland swelling was strongly associated with xerostomia in this group (OR: 49.39, 95% CI: 2.02–1206.30, p-value = 0.017). Those on medications that reduce salivary flow (OR: 11.25, 95% CI: 1.64–77.01, p-value = 0.014) or on a combination of medications (OR: 6.95, 95%CI: 1.75–27.63, p-value = 0.006) were

more likely to have xerostomia than those not on any medications. Modeling for Sicca and ISS groups are reported as SI.

4. Discussion

Xerostomia is a chief complaint of SS patients. Since dry mouth can affect adversely oral health, overall well-being, and patient's quality of life, it is a patient-centered outcome that should be considered in SS research and disease management. In this study, we examined the

importance of patient-reported xerostomia of >3 months duration in individuals with SS, Sicca, and ISS. In our study population, the prevalence of xerostomia was highest in the SS group followed by the Sicca and ISS groups. We also found that the ability of xerostomia to screen for SS was greater than its ability to screen for Sicca or ISS. Furthermore, when compared with the objective sign of hyposalivation, xerostomia had comparable if not superior screening test utility. These screening test diagnostics of xerostomia are only applicable to a high risk population (those with salivary gland dysfunction) since screening tests are more effective herein than when applied to the general population (Gordis, 2009). These results indicate that subjective and objective measurements of salivary gland dysfunction are both important in the diagnosis and classification of SS. The findings suggest that xerostomia may be reflective of a different domain of salivary gland dysfunction in SS, namely one that comprises compositional changes of saliva.

As xerostomia of prolonged duration was associated with objective clinical findings such as higher focus score, lower salivary flow, and salivary gland swelling, it could be considered a surrogate marker of the poorly understood disease progression of SS. We found that xerostomia in SS participants was not attributable to age, gender, extraglandular manifestations, or other comorbidities. In addition, autoantibodies SSA/SSB failed to be a significant predictor of xerostomia. Medications with a well-documented inhibitory effect on salivary flow, in combination with/without other medications, were included in the regression models to control for their confounding effect (Porter and Scully, 2000, Sreebny and Schwartz, 1997).

It is well known that diagnostic and classification criteria for SS need to be improved, especially as this syndrome encompasses a spectrum of similarly presenting diseases (Goules et al., 2014). However, classification criteria that eliminate both xerostomia and hyposalivation and assess salivary dysfunction solely based on a focus score of ≥1, assume that the pathogenesis takes on a singular pathway of dysfunctional immune response, while ignoring the possibility of other pathways in the etiopathology of salivary dysfunction and disease progression in this complex disorder. Moreover, the diagnostic value of focus score remains unclear. In a systematic review of 9 included studies, a focus score ≥ 1was found to have a high specificity (61.2% to 100%) and a variable sensitivity (63.5% to 93.7%). As a positive focus score is found in healthy aged patients, a specificity of 100% would be an overestimate. The authors concluded that their findings indicate a lack of information about the diagnostic value of minor salivary gland biopsy (Guellec et al., 2013).

Furthermore, such classification criteria that select a highly specific sub-population of SS participants (those with 2 out of 3 objective signs - focus score ≥ 1, positive serology, and ocular staining score ≥ 3) (Shiboski et al., 2012) could challenge external validity. Therefore, clinical trial results based on such limited classification criteria would not be generalizable to the entire SS population but rather to a highly specific sub-population. Moreover, such classification criteria have a potential for information bias leading to differential/non-differential misclassification, and missing cases leading to an immigrative selection bias. Further, as xerostomia is a chief oral complaint of SS participants and is of high prevalence in this group, failure to include xerostomia in SS research studies or to target its mitigation in clinical trials developing therapeutics for SS discounts patient-centered outcomes research. Further, others have pointed out that when symptoms are excluded from classification criteria, there is a higher likelihood of missing cases of early disease who would have had a higher possibility of responding to newer target therapies (Vitali et al., 2013).

However, this study was not designed to develop a classification system for SS rather it was purposed to provide evidence to assist in the process of developing newer classification systems. The development of classification systems requires a balance between sensitivity and specificity in order to minimize misclassification. Furthermore, the net specificity and net sensitivity of the entire classification set needs to be analyzed. This is important, especially when simultaneous testing by individual criteria is being undertaken. Therefore, there is space for improvement in the development of classification criteria and we look forward to the newer classification system (ACR-EULAR) that is in the pipeline which is said to have incorporated both xerostomia and hyposalivation to certain levels.

This study undertook an in-depth evaluation of xerostomia in SS. Sicca and ISS groups were also evaluated for the purpose of a comparative analysis. Various statistical analyses were performed to check for consistency of findings, including regression modeling with the adjustment for confounders; such evidence has been lacking in the literature. Clinical characteristics of those with SS based on xerostomia status were elucidated, which again is novel. Furthermore, this study minimized various biases, described in the SA, that strengthen the analyses. The lack of temporality in associations reported, as a consequence of study design, is a study limitation. Therefore, it should not be assumed that characteristics such as focal lymphocytic sialadenitis (focus score > 2/mm^2) preceded the development of xerostomia in SS. The other limitation is the use of imputed data for whole unstimulated salivary flow rate. However, we analyzed and reported WUS without imputation and total unstimulated salivary flow rate for comparison. To the argument that there may be circularity in SS case definition and xerostomia as a screening aid, it must be acknowledged that xerostomia is neither a sufficient nor necessary criterion in the AE classification. Furthermore, it is not uncommon for screening tests to also be a part of classification criteria, as in the case of diabetes where blood glucose concentrations are utilized for both screening and classification criteria (Harris, 1995).

Studies with longitudinal analyses on changes over time in various key characteristics of SS, Sicca and ISS groups are planned for the future. It is our intention to carry out a detailed and thorough investigation of the trajectories of the various groups over time which is beyond the scope of the current study as it pertains to the baseline analyses of the data.

Our study evaluated patient-reported xerostomia of >3 months and found it to be a significant indicator of SS. In SS, qualitative changes in saliva might be more informative than quantitative salivary flow. Saliva is a complex medium that has many functions and many components with different physical characteristics that cannot be captured by flow measurements alone. In light of our current understanding that xerostomia causes considerable morbidity and quality of life deficit in SS patients, our findings suggest that self-reported xerostomia should be considered in SS classification systems and be a targetable endpoint in SS clinical trials and research.

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Conflicts of Interest

All authors have no competing interests to declare.

Author Contributions

MB - study design, data analysis, data interpretation and writing of manuscript.

IA - principal investigator of protocols, acquisition of clinical data, critical review of study design, data interpretation and revision of manuscript.

BAD, TI - critical review of study design, data interpretation and revision of manuscript.

ANB, MG - acquisition of clinical data and review of manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ebiom.2016.09.005.

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