



Published in final edited form as:

Arthritis Care Res (Hoboken). 2012 June ; 64(6): 911–918. doi:10.1002/acr.21610.

Primary Sjögren's Syndrome as a systemic disease: a study of participants enrolled in an international Sjögren's Syndrome registry

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Abstract

Objective—To study the prevalence of extra-glandular manifestations (EGM) in primary Sjögren's Syndrome (pSS) among participants enrolled in the Sjögren's International Collaborative Clinical Alliance (SICCA) registry.

Methods—1927 participants in the SICCA registry were studied, including 886 participants who met the 2002 American-European consensus group (AECG) criteria for pSS, 830 “intermediate” cases who had some objective findings of pSS but did not meet AECG criteria, and 211 control individuals. We studied the prevalence of immunologic and hematologic laboratory abnormalities; specific rheumatologic examination findings; and physician confirmed thyroid, liver, kidney disease and lymphoma among SICCA participants.

Results—Laboratory abnormalities, including hematologic abnormalities, hypergammaglobulinemia and hypocomplementemia, frequently occurred among pSS cases, and were more common among the intermediate cases than among control participants. Cutaneous vasculitis and lymphadenopathy were also more common among pSS cases. In contrast, the frequency of physician confirmed diagnoses of thyroid, liver and kidney disease, and lymphoma was low and only primary biliary cirrhosis was associated with pSS cases status. Rheumatologic and neurologic symptoms were common among all SICCA participants, regardless of case status.

Conclusions—Data from the international SICCA registry support the systemic nature of pSS, manifest primarily in terms of specific immunologic and hematologic abnormalities. The occurrence of other systemic disorders among this cohort is relatively uncommon. Previously reported associations may be more specific to select patient subgroups, such as those referred for evaluation of certain neurologic, rheumatologic or other systemic manifestations.

Sjögren's Syndrome (SS) is one of the most common autoimmune diseases, with an estimated prevalence of approximately 0.6% and a 20:1 female predilection (1, 2). SS may occur in isolation and has been referred to as primary Sjögren's Syndrome (pSS) or in conjunction with another connective tissue disease, most commonly rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE). This association is often termed secondary Sjögren's Syndrome (sSS).

The cardinal features of SS, including keratoconjunctivitis sicca and salivary gland hypofunction, presumably result from progressive lymphocytic inflammation in affected exocrine glands. While the hallmark features of SS are related to exocrine gland dysfunction, there is substantial evidence that pSS is a systemic autoimmune process. Such evidence includes: 1) the frequent presence of auto-antibodies [e.g., anti-nuclear antibodies (ANA), Sjögren's Syndrome A (SSA/Ro) and Sjögren's Syndrome B (SSB/La) antibodies]; 2) the presence of SS in conjunction with other systemic connective tissue diseases; and 3) the reported association of SS with a number of extra-glandular manifestations (EGM).

There is an extensive literature describing EGM in SS. One of the earliest reported associations was the increased incidence of lymphoma in patients with SS (3–7). Several reports describe the occurrence of other EGM such as neurologic, pulmonary and other organ specific diseases. For example, renal tubular acidosis, thyroiditis, primary biliary cirrhosis and autoimmune hepatitis are classically thought to be related to SS. However the prevalence of these disorders among SS patients varies widely between cohorts and the association of these EGM with SS is less well defined.

In the current study, we describe the prevalence of EGM among participants in the Sjögren's International Collaborative Clinical Alliance (SICCA) registry (8) and we examine associations between EGM and specific objective phenotypic features of SS. SICCA participants are recruited worldwide into a registry designed to support studies of etiologic factors and outcomes in SS. The registry also provides an opportunity to study EGM prevalence in individuals suspected to have SS, but who fail to meet the 2002 American-European Consensus Group (AECG) criteria for SS. The diversity of the collection in terms of ethnicity, recruitment source, and disease severity, in conjunction with the extensive data collected on each participant, provide a valuable resource for studying EGM in SS.

Patients and Methods

At the time of this study 2,090 participants were enrolled in the SICCA registry. Complete details related to this registry have been described previously (8). In brief, inclusion in the SICCA registry requires at least one of the following: symptoms of dry eyes or dry mouth; prior suspicion/diagnosis of SS; positive serum anti-SSA, anti-SSB, rheumatoid factor (RF) or ANA; increase in dental caries; bilateral parotid gland enlargement; or a possible diagnosis of secondary SS. These broad inclusion criteria have resulted in a cohort of individuals with a wide range of symptoms and signs related to SS. Participants in the current study were enrolled at 9 SICCA sites within 7 countries, including Argentina (University of Buenos Aires and German Hospital, Buenos Aires), China (Peking Union Medical College Hospital, Beijing), Denmark (Rigshospitalet, Copenhagen), Japan (Kanazawa Medical University, Ishikawa), the United Kingdom (King's College London, London), India (Aravind Eye Hospital, Madurai) and the United States (University of California, San Francisco; University of Pennsylvania, Philadelphia; and Johns Hopkins University, Baltimore) (collaborators for the SICCA sites are shown in Appendix A). Because the presence of another connective tissue disease may confound findings related to EGM, we excluded from this analysis participants with a diagnosis of SLE, RA, scleroderma, or other connective tissue diseases ($n = 132$). We also excluded participants with incomplete key data required to determine their pSS case status at the time of this study ($n = 31$), thereby leaving 1,927 participants included in the current study.

Every participant in the SICCA cohort undergoes a systematic and extensive assessment of symptoms and signs related to SS. Uniform protocol-driven data collection methods are used at each SICCA site for the completion of questionnaires, recording of findings from detailed rheumatologic, ocular, and oral examinations, and the acquisition of biospecimens.

Complete details of SICCA enrollment forms, protocols and methods for physical examinations and biospecimen collection may be found at: <http://sicca.ucsf.edu/>.

Assessment of ocular and oral involvement

Ocular and oral symptoms are assessed during an interview and include 18 questions related specifically to oral symptoms and 10 questions related to ocular symptoms. Salivary gland dysfunction is assessed by measurement of unstimulated whole salivary flow (UWS) and by stimulated parotid flow rate. UWS < 0.1 ml in 1 minute is considered to be a positive test for salivary hypofunction as established by Navazesh and colleagues (9). Each participant also undergoes a minor salivary gland biopsy, and the tissue is independently examined by two histopathologists calibrated in this assessment. In the first step, a histopathologic diagnosis is assigned to each specimen under one of six different categories: focal lymphocytic sialadenitis (FLS: with or without evidence of sclerosis), within normal limits, non-specific chronic inflammation, sclerosing chronic sialadenitis, granulomatous inflammation, and MALT (mucosa associated lymphoid tissue) lymphoma (10). Only those specimens with either of the FLS diagnoses are then assessed to determine the focus score, a semi-quantitative measure of FLS noted in minor labial salivary gland biopsy specimens. Diagnoses of FLS with focus scores ≥ 1 focus per 4 mm² represent the salivary component of SS (11) and are strongly associated with the ocular and serologic components of SS and reflect SS autoimmunity (10).

Lacrimal dysfunction is assessed by performing the Schirmer's test (12) (<5 mm of wetting in 5 minutes is considered to be a positive test) and calculating an ocular staining score (OSS). The OSS, which replaces the Rose Bengal score, is a new method of evaluating conjunctival and corneal damage due to keratoconjunctivitis sicca (13). The technique involves fluorescein staining of the cornea and lissamine green staining of the interpalpebral conjunctiva to calculate an OSS. The OSS may have a value ranging from 0 (no corneal or conjunctival staining detected) to 12 for each eye. OSS scores ≥ 3 are considered abnormal and represent keratoconjunctivitis sicca.

Classification of pSS cases

The 2002 American-European Consensus Group (AECG) criteria for pSS (14) were applied to the cohort. The AECG criteria were defined for SICCA participants using the specified oral/salivary, ocular and systemic components, substituting the SICCA OSS for Rose-Bengal staining, and a definition of participant-reported ocular and oral symptoms based on questions most closely matching the corresponding questions used in the AECG criteria. The 886 participants (out of 1,927) who met these criteria were classified as pSS cases. The remaining 1,041 participants who did not meet AECG criteria for pSS were classified into 2 groups on the basis of the presence (vs. absence) of objective SS-related findings. More specifically, participants who met at least one of the following four objective criteria (n = 830) were classified as intermediate cases: 1) anti-SSA/SSB antibodies, 2) FLS with focus score ≥ 1 , 3) OSS ≥ 3 , and 4) UWS < 0.1 ml/min. Participants who met none of these objective criteria (n = 211) were classified as controls.

Assessment of extraglandular manifestations (EGM)

Laboratory Data—Blood is collected from each SICCA participant at the time of enrollment for characterization of autoantibodies and quantification of immunoglobulin and complement levels. The ANA titer is determined by an immunofluorescence staining method. RF, complement C3, C4 and immunoglobulin (IgA, IgG and IgM) levels are determined by immunoturbidimetric assays. Anti-SSA (Ro) and anti-SSB (La) are determined using a fully automated Luminex based pre-coated multi-bead assay (Bioplex 2200 ANA screen). With the exception of the complete blood count (CBC), all laboratory

tests for SICCA enrollees are performed by the same licensed laboratory (Quest Diagnostics, San Jose, CA).

Rheumatologic signs and symptoms—As part of the medical history, participants are asked a series of standardized questions related to rheumatologic symptoms. Rheumatologic questions assess symptoms of morning stiffness lasting more than one hour as well as symptoms of joint pain and swelling. Each participant also undergoes a thorough rheumatologic examination to assess joint tenderness, synovitis, or deformities in the MCP (metacarpophalangeal), PIP (proximal interphalangeal), wrist and elbow joints; cervical, axillary or inguinal lymphadenopathy; and evidence of Raynaud’s phenomenon or cutaneous vasculitis.

Organ specific diseases—As part of the medical history questionnaire that each participant completes upon entry, participants are asked about thyroid, liver or kidney disease, and lymphoma. If a participant reports one or more of these conditions, details are sought from his/her treating physician. More specifically, information is requested from physicians about the following eight disorders: Graves’ disease, Hashimoto’s thyroiditis, interstitial nephritis, primary biliary cirrhosis, autoimmune hepatitis, renal tubular acidosis, glomerulonephritis, and lymphoma. Treating physicians are also asked to provide information about any other systemic disorders present.

Statistical Analysis

Descriptive statistics were used to define the prevalence of EGM among SICCA participants. Fisher’s Exact test was used to assess association between presence of specific EGM and pSS status (pSS versus intermediate cases versus controls). Odds ratios and 95% confidence intervals were calculated to describe the magnitude of the observed associations between case status and specific EGM. All statistical analyses were performed using STATA 11, StataCorp LP, College Station, TX.

Results

Demographic characteristics of the 886 pSS cases, 830 intermediate cases and 211 controls are summarized in Table 1. In the pSS group, as expected, most participants were female (95%), with a mean age at SICCA enrollment of 52 years. The ethnic distribution of the study sample reflects the geographic locations of the nine international recruitment sites. There were fewer females and more current smokers in the intermediate case and control groups.

In Table 2 we summarize SS related characteristics among participants, according to case status. The frequency of dry eye and dry mouth symptoms was high in each of the three groups, but the duration of dry eye and dry mouth symptoms was higher among pSS cases. As expected based on our case definitions, the frequency of autoantibodies or abnormalities of objective ocular or oral test results was much higher in the pSS group and lowest in the control group. In the intermediate group, an abnormal OSS was the most common finding (74%), followed by decreased unstimulated whole salivary flow rate (52%).

Table 3 reports the frequency of each histopathologic category among the 3 groups of participants. Among the 1,160 (60%) participants with either of the diagnoses of focal lymphocytic sialadenitis, 777 (67%) had a focus score ≥ 1 . In 25 cases we were unable to calculate the focus score due to inadequate size of the glandular tissue biopsy sample.

Table 4 summarizes the frequency of EGM assessed in this study, according to case status. Laboratory abnormalities occurred frequently among pSS cases, and were more common

among the intermediate cases than the controls. Most of the differences in laboratory abnormalities were highly statistically significant and easily surpass even a very conservative Bonferroni correction for multiple comparisons. Among the 64% of pSS cases with an ANA titer $\geq 1:320$, the most common pattern was speckled (59%), followed by SSA (21%) and centromere patterns (10%). Among the 60% of pSS cases with a positive RF test, the mean titer was 109 IU/ml.

Joint symptoms occurred commonly among all SICCA participants, regardless of case status, with approximately one third of SICCA participants reporting joint stiffness lasting more than one hour and 60% reporting joint pain and/or swelling (data not shown). Among individuals with synovitis documented on rheumatologic examination, the most common sites were the wrists (30%), proximal interphalangeal (28%), metacarpophalangeal (22%) and elbow joints (20%). Cutaneous vasculitis ($p < 10^{-5}$) and lymphadenopathy ($p = 0.022$) were more commonly observed among pSS cases, although the association with lymphadenopathy should be interpreted with caution given the number of exam findings compared (Table 4).

Prevalence of extraglandular disorders

The prevalence of physician-confirmed diagnoses of eight specific extraglandular disorders assessed is summarized in Table 4. Among all SICCA participants at the time of study entry, 450 participants reported a diagnosis of thyroid, liver, kidney disease and/or lymphoma. Of these, we were able to obtain either confirmation or rejection of the reported diagnosis from the treating physicians for 365 (81%) participants. Although the overall frequency of these disorders was low, we observed significant differences in the frequency of primary biliary cirrhosis among the three case groups ($p = 0.033$). However, given the number of EGM assessed, this association should be interpreted with caution.

Associations between EGM and objective SS-related manifestations

To determine whether certain EGM among the pSS cases were associated with specific SS-related objective criteria, we compared the prevalence of EGM among the 886 pSS cases defined on the basis of presence (vs. absence) of the four SS-related objective findings that are included in the AECG criteria (SSA and/or SSB antibodies, focus score ≥ 1 , OSS ≥ 3 and UWS < 0.1 ml/min). The results of these analyses are shown in Table 5.

Overall, the pattern of association results suggests that a decreased UWS flow rate is less strongly associated with the presence of EGM than the other three objective criteria assessed. The similarity in association results across these 3 objective findings is not unexpected given the strong associations among these objective findings, as reported previously (8). Among all participants in the SICCA cohort, the odds ratio (OR) describing the association of an OSS ≥ 3 with the presence of SSA and/or SSB antibodies is 4.3 (95% CI 3.3–5.6, $p = 9.1 \times 10^{-33}$). Similarly, the OR describing the association between the presence of focal lymphocytic sialadenitis (i.e., focus score ≥ 1) and the presence of these antibodies is 10.0 (95% CI 8.1–12.4, $p = 1.6 \times 10^{-116}$). In contrast, associations between these objective criteria and symptoms of dry eyes or mouth are much weaker and not statistically significant with the exception of an association of dry eye symptoms with an OSS ≥ 3 .

Association between EGM and focus score

To determine whether specific EGM were associated with high focus score values, we classified each SICCA participant with FLS according to the value of the focus score (low: 1–3, moderate: 3–6, high: ≥ 6) and examined associations with EGM. We found that

higher focus score values were associated with RF positivity, ANA titers 1:320, hypergammaglobulinemia (IgG), hypocomplementemia (low C4) and anemia.

Analysis of EGM and symptom duration among pSS cases

To evaluate the relationship between duration of dry eye or mouth symptoms and EGM, we compared the frequency of EGM between pSS cases with self-reported symptom duration (either dry eye or dry mouth symptoms) greater than 10 years (n = 224) versus those reporting symptoms for less than 10 years (n = 492). Patients with symptom duration greater than 10 years were more likely to have a positive ANA with titer 1:320 (71% vs 61%, p=0.008) and joint stiffness for greater than one hour in the morning (35% vs 28%, p=0.041), even after controlling for age. However, we did not observe significant differences in other immunologic or hematologic laboratory values, physical examination findings or other rheumatic complaints based on symptom duration. Among the SS-related objective findings, participants with symptom duration greater than 10 years were more likely to have a decreased UWS compared to those with symptoms duration less than 10 years (82% vs 68% p<0.005). The other three objective SS-related criteria, SSA/B positivity, lymphocytic sialadenitis (focus score 1) and OSS 3, were not associated with symptom duration greater than 10 years.

Analysis of EGM and age among pSS cases

To assess the relationship between the presence of EGM and age, we compared the frequency of EGM between pSS cases who were older than 65 years (n = 149) and those who were 65 years old or younger (n = 734) at study entry. We found that pSS patients who were older than 65 were less likely to be RF positive (52% vs 61%, p = 0.05), less likely to have hypergammaglobulinemia (IgG) (31% vs. 41%, p=0.020) and less likely to have leukopenia, defined as white blood cell count < 3800/mm² (11% vs 18%, p = 0.035). These patients were also less likely to have anti-SSA or anti-SSB auto-antibodies (68% vs 80%, p=0.001) but they were more likely to have a decreased UWS flow rate (87% vs 67%, p=<0.005). We did not find significant differences in other laboratory abnormalities, physical examination findings, joint symptoms or other SS-related characteristics according to age.

Neurologic Symptoms

Participants in SICCA do not undergo objective neurologic testing. However, each participant is asked a series of questions related to neurological symptoms during the medical interview. Forty four percent of pSS cases reported neurological motor symptoms and 53% of pSS cases reported neurological sensory symptoms. In the control group, 60% of participants reported neurological motor symptoms and 75% reported neurological sensory symptoms, suggesting that these symptoms do not help distinguish pSS cases from control individuals.

Discussion

Sjögren's syndrome is a systemic autoimmune disease characterized by lymphocytic infiltration of exocrine glands and a range of extra-glandular features. In this study, we analyzed data collected systematically from 1,927 participants enrolled in the international SICCA registry. The depth and breadth of data collected on both pSS and non-pSS participants allowed us to study many extra-glandular disease manifestations (EGM) reportedly associated with SS based on application of the AECG criteria as well as by specific objective features of SS.

Our results document a strong association between pSS and certain immunologic findings such as hypergammaglobulinemia, low C4 levels and certain autoantibodies. We also find that hematologic abnormalities (leukopenia, anemia and thrombocytopenia) are common and significantly associated with pSS case status, as was the physical exam finding of cutaneous vasculitis. These findings highlight clinically important extra-glandular manifestations in pSS. However, our results also suggest that the prevalence of EGM such as thyroid, liver and kidney disease may be lower than reported previously. Further, while rheumatologic symptoms may be common among pSS patients, these symptoms were not significantly more frequent among individuals with pSS, at least when compared to non-pSS individuals who underwent the same extensive process of phenotypic characterization but did not meet AECG or other objective criteria for pSS.

This study provides an opportunity to examine EGM in the context of salivary gland histopathology. In those patients with a diagnosis of focal lymphocytic sialadenitis, we examined the relationship between the degree of salivary gland inflammation, measured by the focus score, and the presence of EGM. Individuals with higher focus scores were more likely to have anemia and certain immunologic abnormalities. Additional details of relationships between salivary gland histopathology and phenotypic characteristics of SS among this cohort were recently reported (10).

Prior reports of EGM in SS have consisted primarily of descriptions of case cohorts comprised exclusively of pSS patients. For example, Ramos-Casals et al. (15) described the presence of certain EGM among a collection of 1,010 Spanish patients with SS. They employed laboratory studies and detailed objective tests to document the frequency of immunologic, lung, peripheral nerve and renal abnormalities. Similarly, Skopouli et al. (16) characterized specific lung, peripheral nerve, renal and liver abnormalities in a collection of 261 Greek patients with pSS seen between 1981 and 1995 and studied at six month intervals. These studies lacked comparative or control data and therefore are limited in their ability to quantify associations of specific abnormalities with SS.

Comparison of EGM reported for different pSS cohorts also reveals substantial variability. For example, Raynaud's phenomenon was described in 48% of the Greek cohort, 18% of the Spanish cohort and 14% of the SICCA pSS cases. Similarly, arthritis was detected in 23% of Greek, 15% of Spanish, and only 9% of SICCA pSS cases. Possible reasons for these differences include variation in the specific populations studied, recruitment sources, and methods for assessing EGM. Further, the definition of SS has been evolving over the past several decades, introducing another potentially important source of variation in prior studies of EGM in pSS. The various criteria employed in these and other studies encompass a wide range of symptoms, signs, and disease severity. Thus, it is difficult to assess the comparability of SS case groups without additional details of specific disease features. Indeed, this lack of specificity led us to examine the association between EGM and more specific, objective disease features (Table 5).

The association of neurologic disorders with pSS has attracted a lot of attention as a result of prior reports, such as those by Delalande et al (17) and Kieko Mori et al (18). Data from the SICCA registry indicate a very high frequency of neurological motor and sensory symptoms in pSS patients. However, we noted a similarly high frequency of neurological symptoms among non-pSS participants. A limitation of the SICCA collection is the lack of objective neurological testing on participants. Thus, the prevalence of neurologic involvement in pSS remains unclear.

Strengths of the current study include the large size and international nature of the SICCA cohort. Participants are recruited from a wide range of clinical and non-clinical sources,

including rheumatologic, ophthalmologic, oral medicine and various lay and patient organizations. The availability of a subset of participants with a high prevalence of non-specific symptoms of dry eyes and dry mouth but absence of objective findings to support SS is a unique feature of the SICCA collection.

A limitation of the current study is the lack of a completely healthy (asymptomatic) control group of individuals. Although it would be of interest to study such a group, it is not feasible to assemble a sufficiently large, population-based control group characterized by the breadth of relevant variables, including the objective serologic, ocular and oral measures obtained as part of this study. On the other hand, the diversity of the SICCA cohort should enhance the representativeness of the pSS cases because it minimizes the selection bias that can result from enrolling patients only at certain sites or based on specific criteria, such as presence of neurologic or other systemic manifestations.

The large size and international nature of the SICCA registry strengthened our analysis, but also limited our ability to carefully characterize some of the EGM. For example, we were not able to review details of some of the disorders, such as thyroid function tests or antibodies, or results of renal or liver biopsy. Instead, we had to rely on the confirmation of diagnoses by treating physicians. We also did not perform screening tests of serum or urine to identify new diagnoses of renal tubular acidosis or other disorders. For these reasons, we may have underestimated the prevalence of some systemic disorders. In particular, the prevalence of sub-clinical disease such as hypothyroidism may be underestimated because participants were not specifically screened for these conditions. However, the use of self-report diagnoses of thyroid and other disorders is common in large studies such as the National Health and Nutrition Examination Study (NHANES) (19), and a strength of the current study was the systematic effort to confirm all reported diagnoses of thyroid and other conditions by treating physicians.

Although the duration of symptoms at the time of SICCA enrollment was substantial (6 to 7 years on average), the current analyses were limited to prevalent data at the time of enrollment. Some of these individuals may still develop one or more of these EGM in the future. Previous studies suggest that at least some of these disorders, such as lymphoma, may not occur until many years of disease have elapsed (6, 20). Although follow-up data on SICCA participants is currently limited, a subset of patients is being recalled after two years for a complete reevaluation. These follow up data may improve our ability to capture incident cases of rare conditions such as lymphoma and primary biliary cirrhosis.

In conclusion, data from the international SICCA registry support the systemic nature of pSS, manifest primarily in terms of specific autoantibody production and various immunologic and hematologic abnormalities. The concurrence of other systemic disorders among this cohort is relatively uncommon and previously reported associations may be more specific to select patient subgroups, such as those referred for evaluation of neurologic, rheumatologic or other systemic manifestations. Longer term follow up of patients in the SICCA registry and other pSS populations will increase our understanding of rarer extra-glandular features in pSS.

Significance and Innovation

Although the hallmark features of primary Sjögren's Syndrome (pSS) include glandular manifestations, there is convincing evidence that pSS is a systemic disease with various extra-glandular manifestations (EGM).

We assess the prevalence of specific EGM among over 1,900 participants in the Sjögren's International Collaborative Clinical Alliance (SICCA) registry.

Our results support the systemic nature of pSS, primarily based on the presence of several immunologic and hematologic abnormalities. We also find that the prevalence of specific organ manifestations in pSS is relatively low and these abnormalities may be more common among select patient subgroups.

Acknowledgments

Grant support: This work was supported by a contract from the NIH/NIDCR/NEI NO1-DE-32636, NIH Training Grant T32 AR007304, and the Arthritis Foundation Northern California Chapter

Appendix A: Collaborators of the Sjögren's International Collaborative Clinical Alliance

Acknowledgments:

In addition to the listed authors, many other professional collaborators in the Sjögren's International Collaborative Clinical Alliance have been essential to the conduct of this project. Their names and roles follow: University of California, San Francisco, USA: Oral Pathology D Cox and R Jordan, Oral Medicine D. Greenspan and A. Wu, Ophthalmology T Leitman, N McNamara and J Whitcher, Rheumatology D Lee, Operations Director Y DeSouza, Clinical Coordinator / Phlebotomy D Drury, Clinical Coordinator A Do, Clinical Assistant L Scott, Statistician/Programmer M Lam, Data Manager J Nespeco, Finance Director J Whiteford, Administrative Assistant M Margaret; University of Buenos Aires and German Hospital, Buenos Aires, Argentina: Oral Medicine H. Lanfranchi, Ophthalmology A.M. Heidenreich, Stomatology I Adler, AC Smith, AM Bisio, MS Gandolfo, Oral Pathology AM Chirife, A Keszler, Specimen processing S Daverio, Group Coordinator V Kambo; Peking Union Medical College Hospital, Beijing, China: Rheumatology Y Jiang, D Xu, J Su, Stomatology/ Pathology D Du, Stomatology/ LSG biopsies H Wang, Z Li, J Xiao, Specimens / Rheumatology Q Wu, Ophthalmology S Zhang, Phlebotomy C Zhang, W Meng, Project Assistant J Zhang; Rigshospitalet, Copenhagen, Denmark: Oral Medicine M Schiødt, J Schiødt, H Holm, Oral Pathology P Ibsen, Ophthalmology S Johansen, S Hamann, J Lindegaard, Group Coordinators/Specimen Handling AM Manniche, SP Kreuzmann; Kanazawa Medical University, Ishikawa, Japan: Rheumatology Y Masaki, T Sakai, Ophthalmology N Shibata, K Kitagawa, Stomatology M Honjo, Oral Pathology N Kurose, T Nojima, Specimen processing T Kawanami, Hematology/Immunology T Sawaki, Group Coordinator K Fujimoto; King's College London, UK: Oral Medicine S Challacombe, P Shirlaw, B Varghese-Jacob, Ophthalmology G Larkin, Pathology E Odell, P Morgan, Specimen processing L Fernandes-Naglik; University of Pennsylvania, Philadelphia, USA: Rheumatology S Seghal, R Mishra, Ophthalmology V Bunya, M. Massaro-Giordano, Otolaryngology SK Abboud, Oral Medicine A Pinto, YW Sia, Group Coordinator K. Dow; Johns Hopkins University, Baltimore, Maryland, USA: Ophthalmology E Akpek, S Ingrodi, Oral Medicine W Henderson, Otolaryngology C Gourin, Group Coordinator A Keyes; Aravind Eye Hospital, Madurai, India: Group Director M Srinivasan, co-Directors J Mascarenhas, M Das, A Kumar, Ophthalmology Pallavi Joshi, Surgeon U Kim, Oral Medicine B Babu, Administration A Ram, Saravanan, Kannappan, Group Coordinator N Kalyani;

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Table 1

Demographic characteristics of 1,927 SICCA participants *

	pSS (n = 886)	Intermediate (n = 830)	Control (n = 211)
Age in Years (mean, range)	52 (21–89)	55 (21–90)	52 (22–87)
Female, N (%)	838 (95)	747 (90)	181 (86)
Ethnicity, N (%)			
African	19 (2)	15 (2)	1 (0.5)
Asian/Pac Islander	367 (41)	212 (26)	37 (18)
Caucasian	354 (40)	453 (55)	135 (64)
Hispanic	91 (10)	89 (11)	23 (11)
Native American	10 (1)	9 (1)	4 (2)
Other	45 (5)	52 (6)	11 (5)
Smoking, N (%):			
Current smoker	30 (3)	115 (14)	32 (15)
Prior smoker	239 (27)	262 (32)	60 (29)

* pSS cases defined as participants in the SICCA cohort who meet 2002 AECG criteria for primary Sjögren's Syndrome. Intermediate cases are defined as participants who do not meet 2002 AECG criteria but have at least one positive objective SS-related finding (see below for details). Controls are defined as participants who have normal or negative results for all 4 SS-related objective findings (negative anti-SSA and -SSB, FS < 1, OSS < 3, UWS > 0.1 ml/1 minute).

Table 2

SS-related characteristics of 1,927 SICCA participants *

	pSS (n = 886)	Intermediate (n = 830)	Control (n = 211)
Symptoms:			
Symptoms of dry mouth	827 (93)	729 (88)	187 (89)
Symptoms of dry eyes	773 (87)	688 (83)	176 (83)
Duration of dry mouth symptoms (yrs, range)	6.6 (0 – 66.5)	5.9 (0–60)	4.5 (0–54)
Duration of dry eye symptoms (yrs, range)	7.2 (0.1 – 66.5)	6.7 (0.1 – 60.4)	5.3 (0–47.6)
Serologic Results:			
Anti-SSA (Ro)	676 (76)	49 (6)	0
Anti-SSB (La)	435 (49)	26 (3)	0
Rheumatoid factor	528 (60)	121 (15)	19 (9)
Antinuclear Antibody titer (1:320)	567 (64)	131 (16)	18 (9)
SS-related objective findings:			
Ocular Staining Score 3	809 (91)	615 (74)	0
Schirmer's test 5mm/5 min (mean)	385 (43)	194 (23)	23 (11)
Unstimulated salivary flow rate < 0.1 ml/1 min	626 (71)	432 (52)	0
Focus Score 1 **	722 (81)	56 (7)	0

* Refer to footnote from Table 1 for definition of pSS case, intermediate and control groups.

** Focal lymphocytic sialadenitis based on labial salivary gland biopsy with focus score 1 (10).

Table 3

Histopathologic patterns in minor salivary gland biopsy tissue among 1,927 SICCA participants. Cells show numbers and percent (column) of participants.

Histopathologic pattern *	pSS Cases n=858	Intermediate n=828	Controls n=211	Total
Focal and focal/sclerosing lymphocytic sialadenitis				
Focus score = 1	721 (84)	56 (7)	0 (0)	777 (40)
Focus score <1	62 (7)	232 (28)	64 (30)	358 (19)
Within normal limits	3 (<1)	20 (2)	6 (3)	29 (2)
Non-specific chronic inflammation/Sclerosing chronic sialadenitis	71 (8)	520 (63)	141 (67)	732 (38)
MALT	1 (<1)	0	0	1 (<1)

* At the time of this report, there were 25 FLS cases with insufficient glandular tissue to determine a focus score. There were 3 cases with granulomatous inflammation. There were 2 cases with missing biopsy tissue.

Table 4

Extra-glandular manifestations among 1,927 SICCA participants*.

Characteristic	pSS (n = 886)	Intermediate (n = 830)	Control (n = 211)	Fisher's Exact p value
Laboratory tests:				
RF positive	528 (60)	121 (15)	19 (9)	1.4×10^{-03}
ANA titer 1:320	567 (64)	131 (16)	18 (9)	1.5×10^{-117}
IgG > 1760 mg/dL	347 (39)	38 (5)	3 (1.4)	3.7×10^{-89}
IgA > 463 mg/dL	77(9)	18 (2)	4 (2)	3.4×10^{-10}
IgM > 368 mg/dL	28(3)	20 (2)	3 (1)	0.359
Complement 3 < 90 mg/dL	139 (16)	118 (14)	34 (16)	0.632
Complement 4 < 16 mg/dL	163 (18)	80 (10)	21 (10)	2.6×10^{-7}
WBC < 4000/mm ³	197 (22)	53 (6)	8 (4)	6.1×10^{-26}
Anemia [†]	178 (20)	78 (9)	15 (7)	8.3×10^{-12}
Platelet count < 140,000/uL	48 (5)	23 (3)	3 (1)	0.003
Physical exam findings:				
Joint synovitis on exam	74 (8)	80 (10)	15 (7)	0.453
Raynaud's phenomenon	127 (14)	91 (11)	23 (11)	0.089
Cutaneous vasculitis	34 (4)	5 (1)	3 (1)	9.3×10^{-6}
Lymphadenopathy	66 (8)	37 (5)	9 (4)	0.022
Confirmed diagnoses:				
Graves' disease	21 (2.4)	10 (1.0)	1 (0.5)	0.075
Hashimoto's thyroiditis	47 (5.3)	46 (6.0)	7 (3.0)	0.451
Interstitial nephritis	2 (0.2)	1 (0.1)	0	1.0
Primary biliary cirrhosis	17 (1.9)	5 (1.0)	1 (0.5)	0.033
Autoimmune hepatitis	9 (1.0)	5 (1.0)	0	0.312
Renal tubular acidosis	4 (0.5)	1 (0.1)	0	0.521
Glomerulonephritis	3 (0.3)	4 (0.5)	1 (0.5)	0.782
Lymphoma	5 (0.6)	3 (0.4)	0	0.679

* Refer to footnotes from Table 1 for definition of pSS case, intermediate and control groups.

[†] Anemia is defined as hemoglobin <12g/dL in female and <13g/dL in male participants

Table 5

Association of EGM with SS-related objective criteria in 886 pSS cases. (Odds Ratios with 95% confidence intervals shown if $p < 0.05$).

	SSA/B positive	FS 1	OSS 3	UWS < 0.1 ml/1 minute
Number (%)	693 (78%)	720 (81%)	809 (91%)	626 (71%)
Laboratory tests:				
RF positive	5.6 (3.9–8.1)	3.1 (2.1–4.6)	3.6 (2.1–6.2)	1.6 (1.2–2.2)
ANA titer 1:320	2.3 (1.6–3.2)	2.7 (1.8–4.0)	3.2 (1.9–5.4)	1.6 (1.2–2.2)
IgG > 1760 mg/dL	5.8 (3.7–9.6)	3.8 (2.3–6.4)	3.4 (1.8–6.8)	ns
IgA > 463 mg/dL	2.0 (1.0–4.4)	2.8 (1.1–9.1)	ns	ns
IgM > 368 mg/dL	0.3 (0.1–0.6)	ns	ns	3.5 (1.1–18.4)
C3 < 90 mg/dL	2.2 (1.3–4.0)	ns	2.3 (1.0–6.6)	ns
C4 < 16 mg/dL	1.9 (1.2–3.2)	ns	2.8 (1.2–8.0)	ns
WBC < 4000/mm ³	4.6 (2.6–8.8)	ns	ns	ns
Anemia [†]	2.6 (1.5–4.4)	ns	2.7 (1.2–7.0)	ns
Platelets < 140,000/ μ L	ns	4.6 (1.2–39.7)	ns	ns
Physical exam findings:				
Joint synovitis	0.5 (0.3–0.9)	ns	ns	ns
Raynaud's phenomenon	0.5 (0.3–0.8)	2.1 (1.1–4.5)	ns	ns
Cutaneous vasculitis	ns	ns	ns	ns
Lymphadenopathy	ns	ns	ns	ns

* FS = focus score; OSS = ocular staining score; UWS = unstimulated whole salivary flow rate.

[†] Anemia is defined as hemoglobin <12 g/dL in female and <13 g/dL in male participants