

# Primary Sjögren's syndrome prevalence in a major metropolitan area in Brazil

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## ABSTRACT

There has been no previous prevalence study about of Sjögren's syndrome (SS) in Brazil. The aim was to evaluate the SS prevalence in a general population in Vitória, ES, Brazil. This was an epidemiological, observational, and cross-sectional study conducted on 1,205 randomized people, aged 18–65 years, who lived in Vitória. The subjects were screened for xerostomia and xerophthalmia through home interviews. Those with sicca symptoms were asked to report to a hospital for further medical evaluation, unstimulated salivary flow, Schirmer I test, blood analysis and minor labial salivary biopsy. Sicca symptoms were found in 18% (217 subjects) of the sample. Of the 217 subjects with sicca symptoms, 127 (58%) were available for examination. In this sample, 61.7% were female and 46.8% were under medication. Sicca syndrome was confirmed in 12% by at least one examination (salivary flow or Schirmer I). Two patients (0.17%) matched four criteria according to American-European Criteria (95% CI = 0.020–0.5983).

**Keywords:** primary Sjögren syndrome, prevalence, minor salivary biopsy, epidemiology.

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## INTRODUCTION

Primary Sjögren's syndrome (pSS) is an autoimmune systemic disease characterized not only by lymphocytic infiltration of exocrine glands, but also by its effect on some organs like lungs, nerves, blood, and kidneys.<sup>1</sup> Its symptom is usually presented by dryness of the mouth and eyes.<sup>2</sup> The pSS is one of the most common autoimmune diseases. But it has a low rate of diagnosis because dry complaints are not systematically investigated by physicians.<sup>3</sup>

Published studies of pSS prevalence have shown different results, ranging from 0.04% to 4.8%.<sup>4–14</sup> These differences can be explained because of the use of different diagnostic criteria, tests, and reference values to assess the dysfunction of lachrymal and salivary glands. Another reason could be that

many studies were performed in different countries including those on specific populations.

Over the years, many different criteria have been proposed: Boston (1965), Japanese (1971), San Francisco (1975), Copenhagen (1976), San Diego (1986), Greek (1986), and European (1993). The currently accepted criteria are those of the American-European Consensus Group (2002).<sup>15</sup> The main contributions and differences of those criteria include: the San Francisco Criteria, which proposed histological criteria for salivary biopsy; the San Diego Criteria, which included SS-A and/or SS-B autoantibodies as required criteria, the European Criteria, which considered antinuclear antibodies, rheumatoid factor, and lachrymal biopsy as criteria. In general, the criteria developed by the American scientific committee took into account specific and objective tests like biopsy and autoantibodies. On the other hand, the European

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criteria emphasized on clinical dryness symptoms. Based on the European criteria, it was possible to classify people with only sicca symptoms and dysfunctional lachrymal and salivary tests as SS. The American-European classification criteria maintained the same clinical questions and tests for glandular dysfunction for screening of dryness. Also, it included requirement of positive biopsy or anti-SS-A/SS-B to fulfill diagnosis.<sup>15</sup>

Using the preliminary European criteria,<sup>16</sup> the estimated prevalence in women living in a rural community in Greece was 0.6%.<sup>4</sup> Similar results were found for those in Slovenia (0.6%) and Denmark (0.6%–2.1%).<sup>10,11</sup> Using the Copenhagen criteria, the prevalence was 2.7% in Sweden and 0.7% in China.<sup>6,12</sup> In a study conducted in the USA by Hochberg (1996), the prevalence was 0.04% for those aged between 65 and 84 years. This low rate is because autoantibodies were used to classify the patients.<sup>13</sup> In others studies the prevalence of SS was between 2% and 4.8%.<sup>5,12,15</sup> In the United Kingdom, the prevalence was estimated to be 3%–4%, using the preliminary European criteria.<sup>8</sup> Using the American-European consensus, the prevalence rates are ranging from 0.1% to 0.4%.<sup>9</sup>

There has been no previous study about SS prevalence in Brazil. Hence, the objective of this study was to determine the pSS prevalence in a Brazilian city, using a randomized sample.

## MATERIAL AND METHODS

This study was an epidemiological, observational, and cross-sectional one on 1,205 randomized subjects, aged 18–65 years, who lived in Vitória, the capital of Espírito Santo State, located in the southeast region of Brazil. Vitória is an island, with an area of 93,381 km<sup>2</sup> surrounded by mangroves; 40% is mountainous with tropical climate, and has an annual average temperature of around 23 °C. In 2010, the population was around 320,156 inhabitants and 95% of adults were literate. There is a mix of different ethnic groups in Brazil, including indigenous, blacks, and Caucasians (Portuguese, French, German, and Italian people).

The sample was proportional to the 2000 demographic census data of the Brazilian Institute of Geography and Statistics (IBGE, in Portuguese). It was probabilistic, by conglomerates, multiple stages within homogeneous strata with the sampling unit being the domicile. In the socioeconomic class definition, the monthly revenue of the head of the household is expressed in ranges based on minimum wage (MW). These ranges are the following: up to 2 MW (US\$ 318.00), from 2 to 5 MW (US\$ 318.00 to 795.00),

from 5 to 10 MW (US\$ 795.00 to 1,590.00), and more than 10 MW (US\$ 1,590.00). The average obtained was 7.5 MW (US\$ 1,193.18) with a standard deviation of 4.55 MW (US\$ 723.86). Adopting a procedure where the size of the sample is proportional to the population, and considering the population size as infinite (large), the desired precision of 0.7%, and a significance level of 5%, the sample size was calculated to be 1,158 individuals. At the end of the study, the confidence interval was calculated on the basis of the derived result.

During the first part of the study, randomized home visits were performed. About six standard questions (sicca symptoms) from the American-European criteria<sup>15</sup> were asked. The interviewers were undergraduate health-care students who were trained to conduct these interviews.

The choice of households was randomized according to the following criteria: domiciled unit located on the farthest right side of the map, on the right side of the street. The way to be followed was always by the right, clockwise, and then skipping three houses between each visited one. The choice of the person in the house to be included in the interview was also randomized according to gender, age, and date of birth.

In the second phase, all patients were evaluated by a rheumatologist medical doctor. Complementary exams were performed to investigate rheumatic disease, including Schirmer test, unstimulated salivary flow, rheumatoid factor, antinuclear antibodies (ANA), anti-SS-A/Ro, anti-SS-B/La, and salivary lip biopsy. Patients with positive HIV/HTLV tests and lymphoma were excluded.

Unstimulated whole salivary flow in 15 min was collected in the morning (8–10 h) and stored in clean plastic containers. The sample was weighed in a precision balance. It was considered that saliva has 1 mg to each 1 mL. Patients were instructed not to eat food or drink beverages with caffeine, or smoke, or chew bubble gum on the day of the examination. Room temperature was maintained between 20 °C and 30 °C, and air conditioning was turned off.

Blood samples were collected and stored at –20 °C for autoantibody identification, virus C, and HIV analysis. All individuals were asked to undergo salivary lip biopsy.<sup>17</sup> The salivary glands were formalin-fixed until histopathological analysis was performed by an expert pathologist. In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, with a focus score  $\geq 1$ , defined as a number of lymphocytic foci (which contain more than 50 lymphocytes) per 4 mm<sup>2</sup> of glandular tissue was considered as SS. Patients who had dry eyes or dry mouth symptoms plus positive autoantibody (SS-A or SS-B) or  $\geq 1$  focus score

were considered positive for SS. Also, patients who fulfilled four-criteria (out of the six) were classified as SS according to the American-European criteria.<sup>15</sup>

Characteristics of the population were described. The chi-square test was used to compare patients with and without dryness symptoms. For the quantitative variables, Student *t*-test was used. For the ones with non-normal distributions, Mann-Whitney test was used. For all tests, the significance level was 5%. To evaluate data normal distribution, Kolmogorov-Smirnoff test was performed.

The study had approval from the Research Ethics Committee of the Universidade Federal do Espírito Santo, and all participants were informed about the research and had given their written informed consent.

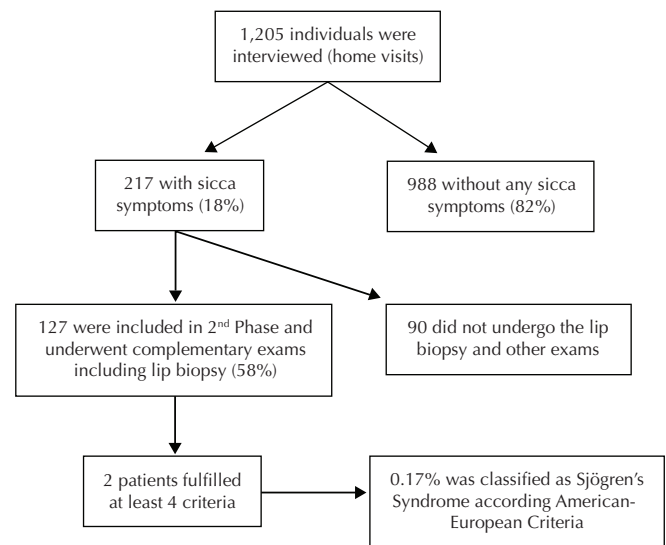
## RESULTS

A total of 1,205 participants were interviewed and were representative of the general population of Vitória city. All individuals accepted to answer questionnaires and to complete the first stage (Figure 1). In this sample, 50.8% were women, 45.3% were married, 47.5% were Caucasian, aged 36.2 (13.6) years (Table 1). After home screening for sicca syndrome, 18% (217) of the participants showed oral or visual dryness. The most common complaint was the sensation or feeling of having sand or gravel in the eyes followed by dry mouth. Out of the 217 individuals, 58% (127) were evaluated for Schirmer test, unstimulated whole salivary flow, blood analysis, and minor labial salivary biopsy. Several reasons for nonperformance of the examinations were observed: forgot to follow up, change of address, lack of time, or had given up on examinations. Only one patient disagreed to undergo all.

Trying to understand any bias that could have happened, the 90 individuals with sicca symptoms who were not available for examinations (second phase) were compared with those 127 who had undergone tests, including salivary lip biopsy. Participants who came to examination were older ( $44.77 \pm 13.1$  vs.  $36.1 \pm 13.5$ ;  $P = 0.001$ ; *t* test). No other statistical difference was found (Table 2).

At least one positive test for dryness was observed in 12% of the participants. Visual dryness without oral manifestation was observed in 41.1% and isolated oral dryness in only 24.4%.

In the final analysis, two individuals have achieved at least four criteria and could be classified as SS according American-European criteria. Thus, the prevalence observed was 0.17% (CI = 0.0201–0.05983) (Figure 1). Both Sjögren patients were female, non-white, and married; one was 41



**Figure 1**  
Flowchart of the sample.

**Table 1**  
Demographic characteristics of the sample

Variable	Category	Count	%
Gender	Female	614	51.0
	Male	591	49.0%
Ethnicity*	Caucasian	554	47.5
	Black	207	17.8
	Indigenous	2	0.2
	Mixed origin	403	34.6
Marital status*	Single	513	43.5
	Married	534	45.3
	Widow	42	3.6
	Divorced	90	7.6
Social class*	A	359	30.3
	B	322	27.2
	C	445	37.5
	D	60	5.0
Variable	Mean	SD	Min-max
Age	36.2	13.6	18–65

n = 1,205. The differences correspond to information loss. SD = standard deviation.

years old and the other, 46 years old. One was using medication and both did not have comorbidities (Table 3).

## DISCUSSION

This study provided the first Brazilian data about pSS prevalence. Brazil has a continental extension and it would be very hard to perform this methodology and design for all states. The mixed-race ethnic groups of Vitória city represent the most important ethnicities of Brazilian population.

**Table 2**

Demographic and sicca symptoms comparisons between individuals that have performed exams in second phase compared to others who did not perform tests (non-participants second phase)

Variable	Category	Non-participants 2 <sup>nd</sup> phase		Performed tests		P*
		n	Col %	n	Col %	
Gender	Female	57	62	79	63.7	0.903
	Male	35	38	45	36.3	
Ethnicity	Caucasian	34	37.4	51	42.9	0.307
	Black	24	26.4	21	17.6	
	Mixed origin	33	36.3	47	39.5	
Marital status	Single	24	26.4	49	40.5	0.115
	Married	52	57.1	61	50.4	
	Widow	7	7.7	6	5	
	Divorced	8	8.8	5	4.1	
Sicca symptom (answer yes)	- Have you had daily, persistent, troublesome dry eyes for more than 3 months?	35	37.6	38	30.6	0.281
	- Do you have a recurrent sensation of sand or gravel in the eyes?	29	31.2	48	38.7	0.251
	- Do you use tear substitutes more than 3 times a day?	13	14	16	12.9	0.818
	- Have you had a daily feeling of dry mouth for more than 3 months?	48	51.6	55	48.4	0.289
	- Have you had recurrently or persistently swollen salivary glands as a3?	5	5.4	7	5.7	0.920
	- Do you frequently drink liquids to aid in swallowing dry food?	19	20.4	30	24.4	0.512

\*Chi-square test.

**Table 3**

Classification criteria for primary Sjögren's syndrome in patients

Criteria number	Ocular dryness	Mouth dryness	Schirmer test	Salivary flow	Medicine	Ro/La	≥ 1 focus score/4 mm <sup>2</sup>
4	Yes	Yes	Pos	4,269	Yes	Neg	Yes
4	Yes	Yes	Pos	2,868	No	Neg	Yes

Medicine = antihypertensives, antidepressants, diuretics. Schirmer (mm/5 min); Salivary flow (mL/15 min).

Many studies were performed in different countries, including specific populations, like old people and patients of outpatient rheumatology clinic.<sup>4-9,13,14</sup> However, there has been no previous study in the Brazilian population. Prevalence studies have shown different results. The large variability could be explained by differences in genetic and environmental factors, but primarily it may also reflect on differences in the methodology. The prevalence found, of 0.17%, agrees with that observed in other studies that have used American-European criteria.<sup>9</sup>

Many classification criteria for SS had been proposed, modified, and revised before and during the International Symposia in Copenhagen in 1986.<sup>13</sup> Nowadays, in spite of some limitations, the American-European Consensus is used widely to classify SS.<sup>15</sup> These criteria have included oral and visual dryness associated with sialoadenitis or positive autoantibodies (SS-A/Ro and SS-B/La).

In the sample, only two individuals fulfilled at least four criteria classified as SS. It is possible that patients with three or two criteria including positive lip biopsy can be classified as SS in the future. Being strict in requiring four positive findings to diagnose pSS, according to the American-European consensus, those mild, atypical, and initial diseases might have been excluded. The rigor of the current criteria, insidious disease onset, and wide spectrum of systemic clinical manifestation could underestimate the prevalence.

It was a limitation of the study not performing all complementary exams included in the American-European consensus. Perhaps, individuals with negative Schirmer test or normal salivary flow could present other positive dry tests like Bengal Rose, scintigraphy, and sialography. Unstimulated salivary flow and Schirmer test were chosen because they are easy and cheap to perform. In addition, these tests have shown good correlation and sensitivity for SS diagnosis.<sup>18</sup>

Among the interviewed patients without dryness symptoms (988 from 1,205), it could be possible to find SS because the sicca syndrome cannot be present in early SS and in patients with a predominance of systemic symptoms. However, this difficulty is related to aspects of SS disease and limitation of classification criteria, which explains how hard it is to carry out randomized clinical trials.

Another limitation of the study was that only 58% of the invited individuals came to the second phase, i.e., for salivary biopsy and autoantibody evaluation. A prevalence of SS considering only participants of second phase that came to complementary exams could result in an under-estimate of SS in the population as a whole. This limitation is also present in other studies.<sup>5-9</sup> People who performed exams were older than nonparticipants of the second phase of the study. Perhaps, older people are more responsible or have a

better understanding of the importance of the study. Also, it is possible and expected that the nonparticipants have had milder dryness. That's why we believe that the prevalence would not be so higher if all individuals with dryness were included in the second phase of the study.

Previous studies failed to determine histological abnormalities because many patients disagreed to submit for biopsy.<sup>4-14</sup> However, disagree to invasive exams is common in large population studies. A positive point of this study was that biopsy was done for all participants with dryness symptoms, who came back for tests, and not just for those with positive tests for glandular dysfunction or positive autoantibodies.

In conclusion, the prevalence of pSS in Vitória, ES, Brazil, was 0.17% according to American-European criteria. It is possible that it could be underestimated.

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