Epidemiological profile and north-south gradient driving baseline systemic involvement of primary Sjögren syndrome.

Pilar Brito-Zerón[1,2], Nihan Acar-Denizli[3], Wan-Fai Ng[4], Ildiko Fanny Horváth[5], Astrid Rasmussen[6], Raphaele Seror[7], Xiaomei Li[8], Chiara Baldini[9], Jacques-Eric Gottenberg[10], Debashish Danda[11], Luca Quartuccio[12], Roberta Priori[13], Gabriela Hernandez-Molina[14], Berkan Armagan[15], Aike A. Kruize[16], Seung-Ki Kwok[17], Marika Kvarnstrom[18], Sonja Praprotnik[19], Damien Sene[20], Roberto Gerli[21], Roser Solans[22], Maureen Rischmueller[23], Thomas Mandl[24], Yasunori Suzuki[25], David Isenberg[26], Valeria Valim[27], Piotr Wiland[28], Gunnel Nordmark[29], Guadalupe Fraile[30], Hendrika Bootsma[31], Hideki Nakamura[32], Roberto Giacomelli[33], Valerie Devauchelle-Pensec[34], Benedikt Hofauer[35], Michele Bombardieri[36], Virginia Fernandes Moça Trevisani[37], Daniel Hammenfors[38], Sandra G. Pasoto[39], Soledad Retamozo[40], Tamer A Gheita[41], Fabiola Atzeni[42], Jacques Morel[43], Cristina Vollenveider[44], Margit Zeher[5†], Kathy Sivils[6], Bei Xu[8], Stefano Bombardieri[9], Pulukool Sandhya[11], Salvatore de Vita[12], Antonina Minniti[13], Jorge Sánchez-Guerrero[14], Levent Kilic[15], Eefje van der Heijden[16], Sung-Hwan Park[17], Marie Wahren-Herlenius[18], Xavier Mariette[7], Manuel Ramos-Casals[2] for the Sjogren Big Data Consortium*

[1] Autoimmune Diseases Unit, Department of Medicine, Hospital CIMA- Sanitas, Barcelona, Spain.
[2] Sjögren Syndrome Research Group (AGAUR), Laboratory of Autoimmune Diseases Josep Font, IDIBAPS-CELLEX, Department of Autoimmune Diseases, ICMiD, University of Barcelona, Hospital Clínic, Barcelona, Spain.
[3] Department of Statistics, Faculty of Science and Letters, Mimar Sinan Fine Arts University, Istanbul, Turkey.
[4] Institute of Cellular Medicine, Newcastle University, and NIHR Biomedical Research Centre, Newcastle Upon Tyne, UK.
[5] Division of Clinical Immunology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary.
[6] Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, USA.
[7] Center for Immunology of Viral Infections and Autoimmune Diseases, Assistance Publique – Hôpitaux de Paris, Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre, Université Paris Sud, INSERM, Paris, France.
[8] Department of Rheumatology and Immunology, Anhui Provincial Hospital, Hefei, China.
[9] Rheumatology Unit, University of Pisa, Pisa, Italy.
[10] Department of Rheumatology, Strasbourg University Hospital, Université de Strasbourg, CNRS, Strasbourg, France.
[11] Department of Clinical Immunology & Rheumatology, Christian Medical College & Hospital, Vellore, India.
[12] Clinic of Rheumatology, Department of Medical and Biological Sciences, University Hospital "Santa Maria della Misericordia", Udine, Italy.
[13] Department of Internal Medicine and Medical Specialties, Rheumatology Clinic, Sapienza University of Rome, Rome, Italy.
[14] Immunology and Rheumatology Department, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. México City, Mexico.
[15] Department of Internal Medicine, Hacettepe University, Faculty of Medicine, Ankara, Turkey.
[16] Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, The Netherlands.
[17] Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea.
[18] Department of Medicine, Solna, Division of Experimental Rheumatology, Karolinska Institutet, and Karolinska University Hospital, Stockholm, Sweden.
[19] Department of Rheumatology, University Medical Centre, Ljubljana, Slovenia.
[20] Service de Médecine Interne 2, Hôpital Lariboisière, Université Paris VII, Assistance Publique-Hôpitaux de Paris, 2, Paris, France.
[21] Rheumatology Unit, Department of Medicine, University of Perugia, Perugia, Italy.
[22] Department of Internal Medicine, Hospital Vall d'Hebron, Barcelona, Spain.
[23] Department of Rheumatology, The Queen Elizabeth Hospital, Discipline of Medicine, University of Adelaide, South Australia, Australia.
[24] Department of Rheumatology, Skane University Hospital Malmö, Lund University, Lund, Sweden.
[25] Division of Rheumatology , Kanazawa University Hospital, Kanazawa, Ishikawa, Japan.
[26] Centre for Rheumatology, Division of Medicine , University College London, London, UK.
[27] Department of Medicine, Federal University of Espírito Santo, Vitória, Brazil.

[28] Department of Rheumatology and Internal Medicine, Wroclaw Medical Hospital, Wroclaw, Poland
[29] Rheumatology, Department of Medical Sciences, Uppsala University, Uppsala, Sweden.
[30] Department of Internal Medicine, Hospital Ramón y Cajal, Madrid, Spain.
[31] Department of Rheumatology & Clinical Immunology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.
[32] Department of Immunology and Rheumatology, Division of Advanced Preventive Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
[33] Clinical Unit of Rheumatology, University of l'Aquila, School of Medicine, L'Aquila, Italy.
[34] Rheumatology Department, Brest University Hospital, Brest, France.
[35] Otorhinolaryngology, Head and Neck Surgery, Technical University Munich, Munich, Germany.
[36] Centre for Experimental Medicine and Rheumatology, Queen Mary University of London, London, UK.
[37] Federal University of São Paulo, Sao Paulo, Brazil.
[38] Department of Clinical Science, University of Bergen; and Department of Rheumatology, Haukeland University Hospital, Bergen, Norway.
[39] Rheumatology Division, Hospital das Clinicas, Faculdade de Medicina da Universidade de Sao Paulo (HCFMUSP), Sao Paulo, Brazil.
[40] Instituto De Investigaciones En Ciencias De La Salud (INICSA), Universidad Nacional de Córdoba (UNC), Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) - Córdoba - Argentina. Instituto Universitario de Ciencias Biomédicas de Córdoba (IUCBC), Córdoba- Argentina.
[41] Rheumatology Department, Kasr Al Ainy School of Medicine, Cairo University, Cairo, Egypt.
[42] IRCCS Galeazzi Orthopedic Institute, Milan and Rheumatology Unit, University of Messina, Messina, Italy
[43] Department of Rheumatology, Teaching hospital and University of Montpellier, Montpellier, France.
[44] German Hospital, Buenos Aires, Argentina.

**The members of the EULAR-SS Task Force Big Data Consortium are listed in the Acknowledgements section*

Address reprint requests to: Dr Manuel Ramos-Casals, Servei de Malalties Autoimmunes Sistèmiques, Hospital Clínic, C/Villarroel, 170, 08036-Barcelona, Spain. Phone: 34-93-2275774. FAX: 34-93-2271707. E-mail: mramos@clinic.cat

ABSTRACT

OBJECTIVES. To characterize the systemic phenotype of primary Sjögren syndrome (SjS) at diagnosis by analysing the ESSDAI scores.

METHODS. The Big Data Sjögren Project Consortium is an international, multicentre registry based on worldwide data-sharing cooperative merging of pre-existing databases from leading centres in clinical research in SjS from the five continents.

RESULTS. The cohort included 10,007 patients (9,352 female, mean 53 years) with recorded ESSDAI scores available. At diagnosis, the mean total ESSDAI score was 6.1; 81.8% of patients had systemic activity (ESSDAI score ≥1). Males had a higher mean ESSDAI (8.1 vs. 6.0, $p<0.001$) compared with females, as did patients diagnosed at <35 years (6.7 vs. 5.6 in patients diagnosed at > 65 years, $p<0.001$). The highest global ESSDAI score was reported in Black/African Americans (BAA), followed by White, Asian and Hispanic patients (6.7, 6.5, 5.4 and 4.8, respectively; $p<0.001$). The frequency of involvement of each systemic organ also differed between ethnic groups, with BAA patients showing the highest frequencies in the lymphadenopathy, articular, PNS, CNS and biological domains, White patients in the glandular, cutaneous and muscular domains, Asian patients in the pulmonary, renal and haematological domains, and Hispanic patients in the constitutional domain. Systemic activity measured by the ESSDAI, clinESSDAI and DAS was higher in patients from southern countries ($p<0.001$).

CONCLUSION. The systemic phenotype of primary SjS is strongly influenced by personal determinants such as age, gender, ethnicity and place of residence, which are key geoepidemiological players in driving the expression of systemic disease at diagnosis.

KEYWORDS: primary Sjögren syndrome,gender,ethnicity,geoepidemiology,phenotype

KEY MESSAGES

- The great variability of systemic SjS is linked with age, gender, ethnicity and geolocation.
- Both the type of organ affected and the severity are modulated by geoepidemiological factors.
- Personal determinants should be considered when follow-up is planned for a patient newly-diagnosed with SjS.

INTRODUCTION

Primary Sjögren syndrome (SjS) is a systemic autoimmune disease that mainly affects middle-aged women, with a frequency ranging between 0.01 and 0.72% [1]. Etiopathogenically, SjS targets the exocrine glands, which are infiltrated by lymphocytes (focal sialadenitis) [2]. More than 90% of patients present with oral and/or ocular dryness, but may also develop a large number of extraglandular (systemic) manifestations, which may even be the presenting manifestation [3]. The key immunological markers are anti-Ro antibodies, the most specific, and cryoglobulins and hypocomplementaemia, the main prognostic markers [4].

The development of the EULAR-SS disease activity index (ESSDAI) [5] by the EULAR task force on SS represented a step forward in the evaluation of systemic SjS. The ESSDAI includes specific organ-by-organ definitions and allows homogeneous evaluation of systemic disease in large series of patients [6–9]. Some recent studies have linked higher systemic activity scores at disease diagnosis with poor outcomes in multicentre registries from European countries [10–13], making the baseline ESSDAI score a solid prognostic marker. However, no studies have been carried out in patients with non-European backgrounds. Since we have recently reported significant differences in the main SjS-related glandular features between ethnic groups and geographical locations [14], it seems reasonable to analyse how systemic activity at diagnosis could also be modulated by geoepidemiological determinants. The understanding of how these factors influence the systemic phenotype could help physicians to identify which patients may be more prone to develop more-complicated disease at the diagnosis of primary SjS and, therefore, which patients should be followed more closely and/or treated more intensively.

The objective of this study was to characterize the systemic presentation of primary SjS by measuring the ESSDAI scores at diagnosis in a large international, multi-ethnic cohort of patients.

MATERIAL AND METHODS

Patients

The Big Data Sjögren Project Consortium is an international, multicentre registry designed in 2014 to take a "high-definition" picture of the main features of primary SjS using worldwide data-sharing cooperative merging of pre-existing clinical SjS databases from leading centres in clinical research in SjS from the five continents (see reference 14 for additional methodological details). The centres share a harmonized data infrastructure and conduct cooperative online efforts in order to refine already-collected data in each centre. The codebook containing instructions on the variables and data codification was firstly discussed and approved by the Steering Committee members, and was further shared with the consortium partners. Data bases from each centre were harmonized into a single data base by applying the data-cleaning pre-processing techniques. Descriptive statistics and data visualisation methods were used in order to detect outliers, data errors, missing data and influential observations [15]. A double checking process correcting errors and completing missing information was carried out to minimize incomplete and erroneous data. Inclusion criteria were fulfilment of the 2002 classification criteria [16]. Exclusion criteria for considering SjS as a primary disease were chronic HCV/HIV infection, previous lymphoproliferative processes, and associated systemic autoimmune diseases. Diagnostic tests for SjS (ocular tests, oral tests and salivary gland biopsy) were carried out according to the recommendations of the European Community Study Group [17]. The study was approved by the Ethics Committee of the Coordinating Centre (Hospital Clinic, Barcelona, Spain, registry HCB/2015/0869).

Definition of variables

Disease diagnosis was defined as the time when the attending physician confirmed fulfilment of the 2002 criteria. The main disease features at this time were retrospectively collected and analysed. The following clinical variables were selected for harmonization and further refinement: age, gender, ethnicity, country of residence, fulfilment of the 2002 criteria items, antinuclear antibodies, rheumatoid factor, C3 and C4 levels, cryoglobulins, and organ-by-organ ESSDAI scores. By January 2018, the participant centres had included 10,540 valid patients from 22 countries; for this specific study, we excluded 533 patients due to a lack of recorded information on the ESSDAI domains at diagnosis, except for haematological and/or biological domains. The epidemiological variables included in this study were age at diagnosis (continuous variable, also categorized as younger onset <35 years, intermediate 35-65 years and older onset >65 years), gender and ethnicity according to FDA definitions [14]. Geolocation variables were the continent, country and city, with an additional north-south sub-classification (see statistical section). Systemic involvement at diagnosis was retrospectively classified and scored according to the ESSDAI [5], which evaluates 12 domains or organ systems, and the clinESSDAI [18], which evaluates the same domains but excluding the last (biological) domain. Each domain is divided into 3-4 levels according to the degree of activity and scored as 0 (no activity), 1 (low activity), 2 (moderate activity) or 3 (high activity) [19]. Disease activity states (DAS) were calculated as: no activity (global score = 0), low activity (global score 1-4), moderate activity (global score 5-13) and high activity (global score ≥ 14) [20].

Statistical analysis

Descriptive data are presented as mean and standard deviation (SD) for continuous variables and numbers and percentages (%) for categorical variables. The Chi-square test was used to study systemic features at diagnosis according to gender, age at diagnosis, geolocation and ethnic group. The t-test was used to compare the mean ESSDAI and clinESSDAI scores. A new variable "activity subsets" was created with the following categories: no activity (ESSDAI score = 0), no high activity in any ESSDAI domain and high activity in ≥ 1 ESSDAI domain. To study the geographical determinants, countries were separated into two groups (north *vs.* south) according to previous studies [14]. Data visualization techniques were used to summarize information. Pyramid and clustered bar charts were used to compare systemic activity according to gender and age at diagnosis. Polar area charts were constructed to represent the association between disease activity and ethnicity. Combined box and jitter plots were used to compare ESSDAI scores between countries and continents according to the north vs. south classification. A choropleth map was used to visualize variations in disease activity between countries. To handle missing data due to non-evaluated features, "available case analysis" was assumed for the comparisons according to age at diagnosis and ethnic group. All significance tests were two-tailed and values of $p < 0.05$ were considered significant. The raw p-values are reported unadjusted for any multiple testing. All analyses were conducted using the R V.3.5.0 for Windows statistical software package (https://www.R-project.org/).

RESULTS

The baseline characteristics of the final cohort are summarized in **Supplementary Table 1**, and included 9,352 (93.5%) women with a mean age at diagnosis of primary SjS of 53 (SD 14.1) years. The frequencies of fulfilment of the 2002 classification criteria items were 92.4% for dry eye (item I), 93.7% for dry mouth (item II), 83% for abnormal ocular tests (item III), 81.6% for positive minor salivary gland biopsy (item IV), 78% for abnormal oral diagnostic tests (item V) and 75.8% for positive anti-Ro/La antibodies (item VI). The frequency of other immunological markers at diagnosis was: positive ANA in 79.1% of patients, positive RF in 47.9, low C3 levels in 13.4%, low C4 levels in 14.6% and positive serum cryoglobulins in 7% of patients. There are xx (xx%) patients that retrospectively did not fulfil the 2016 criteria since they have La autoantibodies in the absence of Ro autoantibodies.

The mean total ESSDAI score at diagnosis of the entire cohort was 6.1 (SD 7.5); 81.8% of patients had systemic activity (global ESSDAI score ≥ 1) at diagnosis (see **Supplementary Table 1**). The domains with the highest frequency of active patients included the biological (51%), articular (37.7%), haematological (22.4%), glandular (21.4%) and pulmonary (10.4%) domains. The distribution of the degree of activity (no activity, low, moderate and high) in the entire cohort for each domain is summarized in **Supplementary Table 2**.

Males with primary SjS had higher mean ESSDAI (8.1 vs. 6.0, $p<0.001$) and clinESSDAI (8.4 vs. 6.1, $p<0.001$) scores, and a higher frequency of high DAS (22.5% vs. 11.7%, $p<0.001$) compared with females (**Table 1**). The organ-specific ESSDAI domains that showed significantly-increased activity in males compared with females included the lymphadenopathy ($p<0.001$), glandular ($p<0.001$), pulmonary ($p=0.001$), peripheral

nervous system (PNS) (p<0.001) and CNS (p<0.001) domains (**Table 1** and **Supplementary Figure 1**).

With respect to the age at disease diagnosis, the highest global scores were homogeneously reported in patients diagnosed at <35 years, although the organ-by-organ analysis showed a differentiated predominance in each age group (**Table 1**). Although the frequency of active patients in most domains was highest in patients diagnosed at <35 years (constitutional, lymphadenopathy, glandular, cutaneous, renal, haematological and biological), the frequency of other domains (pulmonary and PNS) was higher in patients diagnosed at > 65 years (see **Supplementary Figure 2**).

Information on ethnicity was recorded in 9,610 (96%) patients: 7,394 (76.9%) were classified as White, 1,335 (13.9 %) as Asian, 554 (5.8%) as Hispanic, 138 (1.4%) as Black/African American (BAA) and 189 (2%) as other ethnicities (see **Supplementary Table 1**). **Table 2** shows systemic activity at diagnosis according to the main ethnic subsets: the highest global scores were reported in BAA, followed by White, Asian and Hispanic patients (6.7, 6.5, 5.4 and 4.8, respectively; p<0.001). The distribution of systemic activity across the different organ-specific domains varied widely between ethnicities: BAA patients had the highest frequencies of activity in the lymphadenopathy, articular, neurological and biological domains, White patients in the glandular, cutaneous and muscular domains, Asian patients in the pulmonary, renal and haematological domai5ns, and Hispanic patients in the constitutional domain (**Table 2** and **Figure 1**).

Table 3 shows the differences in baseline systemic activity between the northern and southern countries of the three continents with the highest number of cases (Europe, America and Asia). Global scores (ESSDAI, clinESSDAI, DAS) were higher in the southern

countries of each continent (**Table 3, Figure 2**). The distribution of the organ-by-organ degree of activity (low, moderate and high) also showed a differentiated pattern between northern and southern cohorts (see **Supplementary Figure 3**). Moreover, a broad worldwide geographical variation in the frequency of patients with moderate systemic activity (global ESSDAI score of ≥ 5) at diagnosis was reported following a north-south gradient (see **Supplementary Figure 4**).

DISCUSSION

Primary SjS has traditionally been considered a disease characterized primarily by dryness, fatigue and pain [21]. In 2010, the development of the ESSDAI by the EULAR-SS Task Force Group [5] provided a helpful, objective instrument for the homogeneous measurement of systemic disease [6–8]. However, very little information is available on how personal determinants may influence the systemic presentation of SjS. This study reports, for the first time, the significant influence of geoepidemiological determinants (age, gender, ethnicity and geolocation) in the systemic phenotype presented by primary SjS patients at diagnosis.

Gender plays a key role in driving the systemic baseline phenotype of primary SjS. Although infrequently affected by the disease (< 7% in our cohort), males present a severe systemic phenotype [22], and several studies have reported that male SjS is associated with poor outcomes (neoplasia and death) [22–24]. Our results show that that male gender was associated with higher global (ESSDAI, clinESSDAI and DAS) and organ-specific (lymphadenopathy, glandular, pulmonary, PNS and CNS domains) systemic scores compared with females; a recent study by Ramirez-Sepulveda et al. [25] also reported a higher frequency of adenopathic and pulmonary involvement. Because greater systemic activity is associated with poor outcomes, a potential delay in the diagnosis, due to the infrequency of the diagnosis of SjS in men, might explain the severe pattern of systemic expression. Genetic determinants could also play a role [26].

The age at diagnosis is also a key determinant of the expression of systemic disease in primary SjS. Studies in small series of patients have suggested a key role for the age at diagnosis in the disease phenotype [4]: the diagnosis of SjS at young ages is often

associated with a higher frequency of immunologic markers which, in turn, are associated with an enhanced risk of systemic involvement [14]. Our results show the highest systemic scores were reported for patients diagnosed at <35 years. However, age also modulated how the increase in activity in each organ. Although a younger diagnosis was associated with an enhanced risk of presenting activity at diagnosis in most domains (constitutional, lymphadenopathy, glandular, cutaneous, renal, haematological and biological), patients diagnosed at older ages had an enhanced risk of presenting activity in the pulmonary and PNS domains. Very recent studies in small series of patients have reported similar results in some organs, linking a younger age at diagnosis with lymphadenopathy [27] and an older age with pulmonary involvement [25,28]. The reasons why the systemic disease phenotype varies so widely according to the age at diagnosis is not clear, but our results may help physicians increase or decrease clinical suspicion of a specific SjS-related organ involvement by considering the patient's age.

Ethnicity is a key influencer of the clinical phenotype and outcomes of other autoimmune-related diseases [29–31]. Very recent studies have analysed the potential role of ethnicity in SjS phenotypic expression. Ethnicity has a strong influence on the age at diagnosis [14,32,33] and the phenotypic expression of sicca symptomatology, with an enhanced frequency in White patients, and a decreased frequency in BAA and Asian patients [14,34,35]. Underreporting of sicca symptoms has been suggested to be related to differentiated patient perceptions, understanding and socio-economic status in Asian cohorts [36]. Our results confirm that the systemic phenotype of SjS at diagnosis is also strongly driven by ethnicity, with enhanced systemic activity detected in BAA patients compared with the other ethnicities; in terms of global systemic

activity, BAA patients were followed by White patients, with Asian and Hispanic patients having the lowest rates. In addition, organ-by-organ systemic involvement follows a clearly-differentiated pattern between ethnicities; no studies have compared the systemic phenotype between ethnicities, while only studies in Asian cohorts have reported an enhanced risk of pulmonary and renal involvement [36], as shown by our results. Recent studies have reported a differing genetic susceptibility to SJS, driven by ethnicity [37,38].

Several studies have reported a north-south autoimmune gradient in the prevalence and incidence of some organ-specific autoimmune diseases [30,39–41] In primary SjS, we recently reported, for the first time, significant geoepidemiological variations in the prevalence of dryness, the frequency of abnormal diagnostic tests and the positivity of the main immunological markers. In this study, we report a consistent north-south gradient of systemic activity at diagnosis, with enhanced systemic activity in patients from the southern countries of the continents for which more data is available. Other personal determinants, closely linked to the local or personal environment, may also be involved, as reported in other autoimmune diseases [30]. Although most environmental risk factors have been identified in observational studies, evidence for a key etiopathogenic role of lifestyle and environmental factors is growing rapidly [42–44]. Recent studies in SjS have reported the potential role of seasonality [45], soil metals [46], air pollution [47] or silicone breast implants [48,49]. In addition, differentiated biogeographical patterns in the microbiota [50], which has recently been linked with systemic activity in primary SjS [51,52], could also influence the differentiated geographical phenotypic expression. Our results also suggest a worldwide geographical gradient in systemic activity in primary SjS. Because ongoing

trials in primary SjS are using a moderate activity ESSDAI (score ≥ 5) as one of the key inclusion criteria, our findings may be of value when future RCTs are designed, with the country or countries hosting the trial being a key variable to be taken into account (in our cohort, the percentage of this subset of active patients ranged from 14% to 79% according to country, see **Supplementary Figure 4**).

The study has some limitations. Retrospective studies are designed to analyse pre-existing data obtained from medical records, and this may result in recall bias. The retrospective use of the ESSDAI score (which was published in 2010) also means that some laboratory parameters were not available at diagnosis in all patients; however, this missing information affected < 5% of the total cohort with respect to the biological domain and < 1% for the haematological domain. In addition, very large descriptive studies may detect some differences which, although statistically significant, may not be clinically relevant, with further studies being necessary to confirm their relevance in more homogeneous populations. Therefore, the predominant presence of European patients (due to the origin of the project in the EULAR SS Group) could limit the generalization of the results in non-European populations due to the small size of some ethnic subpopulations, such as BAA patients. In addition, the physician assessment and the referral patterns from each centre (in some countries the patients included will all be patients within a catchment area, while others represent tertiary referral centres) may influence how systemic disease is scored.

In summary, the great variability in the presentation of systemic SjS was strongly linked in our study with personal determinants such as age, gender, ethnicity and place of residence. Both the type of organ affected and the severity of the involvement are modulated by these geoepidemiological factors, which should be considered as critical

when a personalized follow-up is planned for a patient newly-diagnosed with SjS, and should also be taken into account when analysing the results of therapeutic studies or when designing randomized controlled trials.

CONFLICT OF INTEREST

None declared.

FUNDING

This work was supported by Grants Fondo de Investigaciones Sanitarias [INT15/00085 to MRC] and Hospital Clinic Barcelona [Ajut per a la Recerca Josep Font to PBZ].

ACKNOWLEDGMENTS

The authors wish to thank David Buss for his editorial assistance. Members of the EULAR-SS Task Force Big Data Consortium:

a) Members of the EULAR-SS Task Force

P. Brito-Zerón, C. Morcillo (Autoimmune Diseases Unit, Department of Medicine, Hospital CIMA- Sanitas, Barcelona, Spain); P. Brito-Zerón, A. Flores-Chávez, M. Ramos-Casals (Sjögren Syndrome Research Group (AGAUR), Laboratory of Autoimmune Diseases Josep Font, IDIBAPS-CELLEX, Department of Autoimmune Diseases, ICMiD, University of Barcelona, Hospital Clínic, Barcelona, Spain); N. Acar-Denizli (Department of Statistics, Faculty of Science and Letters, Mimar Sinan Fine Arts University, Istanbul, Turkey); F. Ng (Institute of Cellular Medicine, Newcastle University, Newcastle Upon Tyne, UK); M. Zeher†, Ildike-Fanny Horvath (Division of Clinical Immunology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary); A. Rasmussen, K. Sivils, H. Scofield (Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, USA); R. Seror, X. Mariette (Center for Immunology of Viral Infections and Autoimmune Diseases, Assistance Publique – Hôpitaux de Paris, Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre, Université Paris Sud, INSERM, Paris, France Paris, France); T. Mandl, P. Olsson (Department of Rheumatology, Malmö University Hospital, Lund University, Lund, Sweden); X. Li, B. Xu (Department of Rheumatology and Immunology, Anhui Provincial Hospital, China); C. Baldini, S. Bombardieri (Rheumatology Unit, University of Pisa, Pisa, Italy); J.E. Gottenberg (Department of Rheumatology, Strasbourg University Hospital, Université de Strasbourg, CNRS, Strasbourg, France); D. Danda, P. Sandhya

(Department of Clinical Immunology & Rheumatology, Christian Medical College & Hospital, Vellore, India); L. Quartuccio, L. Corazza, S De Vita (Clinic of Rheumatology, Department of Medical and Biological Sciences, University Hospital "Santa Maria della Misericordia", Udine, Italy); R. Priori, A. Minniti (Department of Internal Medicine and Medical Specialties, Rheumatology Clinic, Sapienza University of Rome, Italy); G. Hernandez-Molina, J. Sánchez-Guerrero (Immunology and Rheumatology Department, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. México City, Mexico); A.A. Kruize, E. van der Heijden (Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, The Netherlands); V. Valim (Department of Medicine, Federal University of Espírito Santo, Vitória, Brazil); M. Kvarnstrom, M. Wahren-Herlenius (Department of Medicine, Solna, Division of Experimental Rheumatology, Karolinska Institutet, and Karolinska University Hospital, Stockholm); D. Sene (Service de Médecine Interne 2, Hôpital Lariboisière, Université Paris VII, Assistance Publique-Hôpitaux de Paris, 2, Paris, France); R. Gerli, E. Bartoloni (Rheumatology Unit, Department of Medicine, University of Perugia, Italy); S. Praprotnik (Department of Rheumatology, University Medical Centre, Ljubljana, Slovenia); D. Isenberg (Centre for Rheumatology, Division of Medicine , University College London , UK); R. Solans (Department of Internal Medicine, Hospital Vall d'Hebron, Barcelona, Spain); M. Rischmueller, S. Downie-Doyle (Department of Rheumatology, The Queen Elizabeth Hospital, University of Adelaide, South Australia, Australia); S-K. Kwok, S-H. Park (Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea); G. Nordmark (Rheumatology, Department of Medical Sciences, Uppsala University, Uppsala, Sweden); Y. Suzuki, M. Kawano (Division of Rheumatology , Kanazawa University Hospital , Kanazawa , Ishikawa , Japan); R. Giacomelli, F. Carubbi (Clinical Unit of Rheumatology, University of l'Aquila, School of Medicine, L'Aquila, Italy); V. Devauchelle-Pensec, A. Saraux (Rheumatology Department, Brest University Hospital, Brest, France); M. Bombardieri, E. Astorri (Centre for Experimental Medicine and Rheumatology, Queen Mary University of London, UK); B. Hofauer, A. Knopf (Otorhinolaryngology / Head and Neck Surgery, Technical University Munich, Munich, Germany); H. Bootsma, A. Vissink (Department of Rheumatology & Clinical Immunology, University of Groningen, University Medical Center Groningen, the Netherlands); D. Hammenfors, J.G. Brun (Department of Rheumatology, Haukeland University Hospital, Bergen, Norway); G. Fraile (Department of Internal Medicine, Hospital Ramón y Cajal, Madrid, Spain); S. E. Carsons (Division of Rheumatology, Allergy and Immunology Winthrop-University Hospital, Stony Brook University School of Medicine, Mineola, NY, USA); T. A. Gheita, (Rheumatology Department, Kasr Al Ainy School of Medicine, Cairo University, Egypt); E.M. Abd El-Latif (Ophthalmology Department, Faculty of Medicine, Alexandria University, Egypt); H.M. Khalil (Ophthalmology Department, Faculty of Medicine, Beni Suef University, Egypt); J. Morel (Department of Rheumatology, Teaching hospital and University of Montpellier, Montpellier, France); C. Vollenveider (German Hospital, Buenos Aires, Argentina); F. Atzeni (IRCCS Galeazzi Orthopedic Institute, Milan and

Rheumatology Unit, University of Messina, Messina, Italy); S. Retamozo (Instituto De Investigaciones En Ciencias De La Salud (INICSA), Universidad Nacional de Córdoba (UNC), Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET) - Córdoba - Argentina. Instituto Universitario de Ciencias Biomédicas de Córdoba (IUCBC), Córdoba- Argentina); V. Moça Trevisano (Federal University of São Paulo, Sao Paulo, Brazil); B. Armagan, L. Kilic, U. Kalyoncu (Department of Internal Medicine, Hacettepe University, Faculty of Medicine, Ankara, Turkey); H. Nakamura, T. Shimizu, A. Takatani (Department of Immunology and Rheumatology, Division of Advanced Preventive Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan); T. Nakamura, Y. Takagi (Department of Radiology and Cancer Biology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan); A. Sebastian, P. Wiland (Department of Rheumatology and Internal Medicine, Wroclaw Medical Hospital, Wroclaw, Poland); S.G. Pasoto (Rheumatology Division, Hospital das Clinicas, Faculdade de Medicina da Universidade de Sao Paulo (HCFMUSP), Sao Paulo, Brazil); B. Kostov, A. Sisó-Almirall (Primary Healthcare Transversal Research Group, IDIBAPS, Centre d'Assistència Primària ABS Les Corts, CAPSBE, Barcelona, Spain).

b) Members of the French ASSESS Cohort

J. Sibilia (Rheumatology Centre National de Référence des Maladies Auto-Immunes Rares, Institut National de la Santé et de la Recherche Médicale UMRS_1109, Fédération de Médecine Translationnelle de Strasbourg, Strasbourg University Hospital, Université de Strasbourg, Strasbourg, France); C. Miceli-Richard, G. Nocturne (Rheumatology, Bicetre Hospital, Institut National de la Santé et de la Recherche Médicale U-1012, Université Paris Sud, Assistance Publique des Hôpitaux de Paris, Paris, France); J. Benessiano (Centre de Ressources Biologiques, Bichat Hospital, Assistance Publique des Hôpitaux de Paris, Paris, France); P. Dieude (Rheumatology, Bichat Hospital, Assistance Publique des Hôpitaux de Paris, Paris, France); J-J. Dubost (Rheumatology, Clermont-Ferrand Hospital, Clermont-Ferrand, France); A-L. Fauchais (Internal Medicine, Limoges Hospital, Limoges, France); V. Goeb (Rheumatology, Amiens University Hospital, Amiens, France); E. Hachulla (Pierre Yves Hatron, Internal Medicine, Lille University Hospital, Lille, France); C. Larroche (Internal Medicine, Avicenne Hospital, Assistance Publique des Hôpitaux de Paris, Bobigny, France); V. Le Guern, X. Puéchal (Internal Medicine, Cochin Hospital, Assistance Publique des Hôpitaux de Paris, Paris, France); J. Morel (Rheumatology, Montpellier University Hospital, Montpellier, France); A. Perdriger (Rheumatology, Rennes University Hospital, Rennes, France); S. Rist, Rheumatology, Orléans Hospital, Orléans, France; O. Vittecoq (Rheumatology, Rouen University Hospital, Rouen, France); P. Ravaud (Centre of Clinical Epidemiology, Hotel Dieu Hospital, Assistance Publique des Hôpitaux de Paris, Institut National de la Santé et de la Recherche Médicale U378, University of Paris Descartes, Faculty of Medicine, Paris, France).

c) Members of the Spanish GEAS Cohort (SS Study Group, Autoimmune Diseases Study Group GEAS, Spanish

Society of Internal Medicine SEMI):

B. Díaz-López (Department of Internal Medicine, Hospital Universitario Central de Asturias, Oviedo), A. Casanovas, (Department of Internal Medicine, Hospital Parc Taulí, Sabadell), L. Pallarés (Department of Internal Medicine, Hospital Son Espases, Palma de Mallorca), M. López-Dupla (Department of Internal Medicine, Hospital Joan XXIII, Tarragona), R. Pérez-Alvarez (Department of Internal Medicine, Hospital do Meixoeiro, Vigo), M. Ripoll (Department of Internal Medicine, Hospital Infanta Sofía, Madrid), B. Pinilla (Department of Internal Medicine, Hospital Gregorio Marañón, Madrid), M. Akasbi (Department of Internal Medicine, Hospital Infanta Leonor, Madrid), B. Maure (Department of Internal Medicine, Complejo Hospitalario Universitario, Vigo), E. Fonseca (Department of Internal Medicine, Hospital de Cabueñes, Gijón), J. Canora (Department of Internal Medicine, Hospital Universitario de Fuenlabrada, Madrid), G de la Red (Department of Internal Medicine, Hospital Espíritu Santo, Barcelona), A.J. Chamorro (Department of Internal Medicine, Complejo Hospitalario de Ourense, Ourense), I. Jiménez-Heredia (Department of Internal Medicine, Hospital de Manises, Valencia, Spain), P. Fanlo (Complejo Universitario de Navarra), P. Guisado-Vasco (Hospital Quirón, Madrid), M. Zamora (Hospital Virgen de las Nieves, Granada).

d) Members of the UK Primary Sjogren's syndrome registry:

Frances Hall (Addenbrooke's Hospital, Cambridge); Elalaine C Bacabac, Helen Frankland, Robert Moots (Aintree University Hospitals); Kuntal Chadravarty, Shamin Lamabadusuriya (Barking, Havering and Redbridge NHS Trust); Michele Bombardieri, Constantino Pitzalis, Nurhan Sutcliffe, Celia Breston (Bart and the London NHS Trust); Nagui Gendi, Karen Culfear (Basildon Hospital); Claire Riddell (Belfast Health and Social Care Trust); John Hamburger, Andrea Richards (Birmingham Dental Hospital); Saaeha Rauz (Birmingham & Midland Eye Centre); Sue Brailsford, Joanne Dasgin (Birmingham University Hospital); Joanne Logan, Diarmuid Mulherin (Cannock Chase Hospital); Jacqueline Andrews, Paul Emery, Alison McManus, Colin Pease, David Pickles (Chapel Allerton Hospital, Leeds); Alison Booth, Marian Regan (Derbyshire Royal Infirmary); Jon King, Amanda Holt (Derriford Hospital, Plymouth); Theodoros Dimitroulas, Lucy Kadiki, Daljit Kaur, George Kitas (Dudley Group of Hospitals NHS Foundation Trust); Abdul Khan, Tracey Cosier (East Kent University Hospitals); Panthakalam, Kelly Mintrim (East Sussex Healthcare NHS); Mark Lloyd, Lisa Moore (Frimley Park Hospital); Esther Gordon, Cathy Lawson (Harrogate District Foundation Trust Hospital); Monica Gupta, John Hunter, Lesley Stirton (Gartnavel General Hospital, Glasgow); Gill Ortiz, Elizabeth Price; Suzannah Pelger (Great Western Hospital); Claire Gorman, Balinder Hans (Homerton Hospital); Gavin Clunie, Suzanne Lane, Ginny Rose, Sue Cuckow (Ipswich Hospital NHS Trust); Michael Batley, Ruby Einosas (Maidstone Hospital); Susan Knight, Deborah Symmons, Beverley Jones (Macclesfield District General Hospital & Arthritis Research UK Epidemiology Unit, Manchester); Andrew Carr, Suzanne Edgar, Francisco Figuereido, Heather Foggo, Dennis Lendrem, Iain Macleod, Sheryl Mitchell, Christine Downie, Jessica Tarn, James Locke, Shereen Al-Ali,

Sarah Legg, Kamran Mirza, Ben Hargreaves, Laura Hetherington (Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University); Adrian Jones, Peter Lanyon, Alice Muir (Nottingham University Hospital); Paula White, Steven Young-Min (Portsmouth Hospitals NHS Trust); Susan Pugmire, Saravanan Vadivelu (Queen Elizabeth's Hospital, Gateshead); Annie Cooper, Marianne Watkins (Royal Hampshire County Hospital); Anne Field, Stephen Kaye, Devesh Mewar, Patricia Medcalf, Pamela Tomlinson, Debbie Whiteside (Royal Liverpool University Hospital); Neil McHugh, John Pauling, Julie James, Andrea Dowden (Royal National Hospital for Rheumatic Diseases); Mohammed Akil, Jayne McDermott, Olivia Godia (Royal Sheffield Hospital); David Coady, Elizabeth Kidd, Lynne Palmer (Royal Sunderland Hospital); Charles Li (Royal Surrey Hospital); Sarah Bartrum, Dee Mead (Salisbury District Hospital); Bhaskar Dasgupta, Victoria Katsande, Pamela Long, Olivia Godia (Southend University Hospital); Erin Vermaak, Janet Turner (Staffordshire Stoke-on-Trent Partnership); Usha Chandra, Kirsten MacKay (Torbay Hospital); Stefano Fedele, Ada Ferenkeh-Koroma, Ian Giles, David Isenberg, Helena MaConnell, Nyarko Ahwireng, Stephen Porter (University College Hospital & Eastman Dental Institute); Paul Allcoat, John McLaren (Whyteman's Brae Hospital, Kirkcaldy).

REFERENCES

1 Brito-Zerón P, Baldini C, Bootsma H, *et al.* Sjögren syndrome. *Nat Rev Dis Prim* 2016;**2**:16047. doi:10.1038/nrdp.2016.47

2 Mariette X, Criswell LA. Primary Sjogren's Syndrome. *N Engl J Med* 2018;**378**:931–9. doi:10.1056/NEJMcp1702514

3 Ramos-Casals M, Brito-Zerón P, Sisó-Almirall A, *et al.* Primary Sjogren syndrome. *BMJ* 2012;**344**:e3821.http://www.ncbi.nlm.nih.gov/pubmed/22700787 (accessed 14 Dec 2015).

4 Brito-Zeron P, Retamozo S, Ramos-Casals M. Phenotyping Sjogren's syndrome: towards a personalised management of the disease. *Clin Exp Rheumatol* 2018;**36 Suppl 1**:198–209.

5 Seror R, Ravaud P, Bowman SJ, *et al.* EULAR Sjogren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjogren's syndrome. *Ann Rheum Dis* 2010;**69**:1103–9. doi:10.1136/ard.2009.110619

6 Brito-Zeron P, Kostov B, Solans R, *et al.* Systemic activity and mortality in primary Sjogren syndrome: predicting survival using the EULAR-SS Disease Activity Index (ESSDAI) in 1045 patients. *Ann Rheum Dis* 2016;**75**:348–55. doi:10.1136/annrheumdis-2014-206418

7 Baldini C, Pepe P, Quartuccio L, *et al.* Primary Sjogren's syndrome as a multi-organ disease: impact of the serological profile on the clinical presentation of the disease in a large cohort of Italian patients. *Rheumatology (Oxford)* 2014;**53**:839–44. doi:10.1093/rheumatology/ket427

8 Gottenberg JE, Seror R, Miceli-Richard C, *et al.* Serum Levels of Beta2-

Microglobulin and Free Light Chains of Immunoglobulins Are Associated with Systemic Disease Activity in Primary Sjögren's Syndrome. Data at Enrollment in the Prospective ASSESS Cohort. *PLoS One* 2013;**8**:1–6. doi:10.1371/journal.pone.0059868

9 Dumusc A, Ng W-F, James K, *et al.* Comparison of ESSDAI and ClinESSDAI in potential optimisation of trial outcomes in primary Sjogren's syndrome: examination of data from the UK Primary Sjogren's Syndrome Registry. *Swiss Med Wkly* 2018;**148**:w14588. doi:10.4414/smw.2018.14588

10 Flores-Chavez A, Kostov B, Solans R, *et al.* Severe, life-threatening phenotype of primary Sjogren's syndrome: clinical characterisation and outcomes in 1580 patients (GEAS-SS Registry). *Clin Exp Rheumatol* 2018;**36 Suppl 1**:121–9.

11 Papageorgiou A, Ziogas DC, Mavragani CP, *et al.* Predicting the outcome of Sjogren's syndrome-associated non-hodgkin's lymphoma patients. *PLoS One* 2015;**10**:e0116189. doi:10.1371/journal.pone.0116189

12 Retamozo S, Gheitasi H, Quartuccio L, *et al.* Cryoglobulinaemic vasculitis at diagnosis predicts mortality in primary Sjögren syndrome: Analysis of 515 patients. *Rheumatol (United Kingdom)* 2016;**55**:1443–51. doi:10.1093/rheumatology/kew194

13 Ramos-Casals M, Brito-Zerón P, Solans R, *et al.* Systemic involvement in primary Sjögren's syndrome evaluated by the EULAR-SS disease activity index: Analysis of 921 spanish patients (GEAS-SS registry). *Rheumatol (United Kingdom)* 2014;**53**:321–31. doi:10.1093/rheumatology/ket349

14 Brito-Zeron P, Acar-Denizli N, Zeher M, *et al.* Influence of geolocation and ethnicity on the phenotypic expression of primary Sjogren's syndrome at

diagnosis in 8310 patients: a cross-sectional study from the Big Data Sjogren Project Consortium. *Ann Rheum Dis* 2017;**76**:1042–50. doi:10.1136/annrheumdis-2016-209952

15 Gibert K, Sánchez-Marré M, Joaquin I. A survey on pre-processing techniques: relevant issues in the context of environmental data mining. *AI Commun Eur J Artif Intell* 2016;**29**:627–63.http://hdl.handle.net/2117/123530

16 Vitali C, Bombardieri S, Jonsson R, *et al.* Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002;**61**:554–8. doi:10.1136/ard.61.6.554

17 Vitali C, Bombardieri S, Moutsopoulos HM, *et al.* Preliminary criteria for the classification of Sjögren's syndrome. Results of a prospective concerted action supported by the European Community. *Arthritis Rheum* 1993;**36**:340–7. doi:10.1002/art.1780360309

18 Seror R, Meiners P, Baron G, *et al.* Development of the ClinESSDAI: A clinical score without biological domain. A tool for biological studies. *Ann Rheum Dis* 2016;**75**:1945–50. doi:10.1136/annrheumdis-2015-208504

19 Seror R, Bowman SJ, Brito-Zeron P, *et al.* EULAR Sjögren's syndrome disease activity index (ESSDAI): A user guide. *RMD Open* 2015;**1**. doi:10.1136/rmdopen-2014-000022

20 Seror R, Bootsma H, Saraux A, *et al.* Defining disease activity states and clinically meaningful improvement in primary Sjogren's syndrome with EULAR primary Sjogren's syndrome disease activity (ESSDAI) and patient-reported indexes (ESSPRI). *Ann Rheum Dis* 2016;**75**:382–9. doi:10.1136/annrheumdis-2014-

206008

21 Ng W-F, Bowman SJ. Primary Sjogren's syndrome: too dry and too tired. *Rheumatology (Oxford)* 2010;**49**:844–53. doi:10.1093/rheumatology/keq009

22 Brandt JE, Priori R, Valesini G, *et al.* Sex differences in Sjogren's syndrome: a comprehensive review of immune mechanisms. *Biol Sex Differ* 2015;**6**:19. doi:10.1186/s13293-015-0037-7

23 Vasaitis L, Nordmark G, Theander E, *et al.* Comparison of patients with and without pre-existing lymphoma at diagnosis of primary Sjogren's syndrome. *Scand J Rheumatol* 2018;:1–6. doi:10.1080/03009742.2018.1523456

24 Brito-Zerón P, Kostov B, Fraile G, *et al.* Characterization and risk estimate of cancer in patients with primary Sjögren syndrome. *J Hematol Oncol* 2017;**10**:90. doi:10.1186/s13045-017-0464-5

25 Ramirez Sepulveda JI, Kvarnstrom M, Eriksson P, *et al.* Long-term follow-up in primary Sjogren's syndrome reveals differences in clinical presentation between female and male patients. *Biol Sex Differ* 2017;**8**:25. doi:10.1186/s13293-017-0146-6

26 Linden M, Ramirez Sepulveda JI, James T, *et al.* Sex influences eQTL effects of SLE and Sjogren's syndrome-associated genetic polymorphisms. *Biol Sex Differ* 2017;**8**:34. doi:10.1186/s13293-017-0153-7

27 Baldini C, Ferro F, Luciano N, *et al.* Artificial neural networks help to identify disease subsets and to predict lymphoma in primary Sjogren's syndrome. *Clin Exp Rheumatol* 2018;**36 Suppl 1**:137–44.

28 Kakugawa T, Sakamoto N, Ishimoto H, *et al.* Lymphocytic focus score is positively related to airway and interstitial lung diseases in primary Sjogren's syndrome.

Respir Med 2018;**137**:95–102. doi:10.1016/j.rmed.2018.02.023

29 Uribe AG, McGwin GJ, Reveille JD, *et al.* What have we learned from a 10-year experience with the LUMINA (Lupus in Minorities; Nature vs. nurture) cohort? Where are we heading? *Autoimmun Rev* 2004;**3**:321–9. doi:10.1016/j.autrev.2003.11.005

30 Shapira Y, Agmon-Levin N, Shoenfeld Y. Geoepidemiology of autoimmune rheumatic diseases. *Nat Rev Rheumatol* 2010;**6**:468–76. doi:10.1038/nrrheum.2010.86

31 Sreih AG, Mandhadi R, Aldaghlawi F, *et al.* ANCA-associated vasculitis in Hispanic Americans: an unrecognized severity. *Clin Rheumatol* 2015;**34**:943–8. doi:10.1007/s10067-014-2617-z

32 Maldini C, Seror R, Fain O, *et al.* Epidemiology of primary Sjögren's syndrome in a French Multi-Racial/Ethnic area. *Arthritis Care Res (Hoboken)* Published Online First: 2013. doi:10.1002/acr.22115

33 Izmirly PM, Buyon JP, Wan I, *et al.* The Incidence and Prevalence of Adult Primary Sjogren's Syndrome in New York County. *Arthritis Care Res (Hoboken)* Published Online First: July 2018. doi:10.1002/acr.23707

34 Billings M, Dye BA, Iafolla T, *et al.* Significance and Implications of Patient-reported Xerostomia in Sjogren's Syndrome: Findings From the National Institutes of Health Cohort. *EBioMedicine* 2016;**12**:270–9. doi:10.1016/j.ebiom.2016.09.005

35 Zhao Y, Li Y, Wang L, *et al.* Primary Sjogren syndrome in Han Chinese: clinical and immunological characteristics of 483 patients. *Medicine (Baltimore)* 2015;**94**:e667. doi:10.1097/MD.0000000000000667

36 Sandhya P, Danda D. Primary Sjogren's syndrome in Asia: Yin and Yang? Int. J. Rheum. Dis. 2017;**20**:1309–12. doi:10.1111/1756-185X.13201

37 Zhao J, Ma J, Deng Y, *et al.* A missense variant in NCF1 is associated with susceptibility to multiple autoimmune diseases. *Nat Genet* 2017;**49**:433–7. doi:10.1038/ng.3782

38 Taylor KE, Wong Q, Levine DM, *et al.* Genome-Wide Association Analysis Reveals Genetic Heterogeneity of Sjogren's Syndrome According to Ancestry. *Arthritis Rheumatol (Hoboken, NJ)* 2017;**69**:1294–305. doi:10.1002/art.40040

39 Shapira Y, Agmon-Levin N, Shoenfeld Y. Defining and analyzing geoepidemiology and human autoimmunity. *J Autoimmun* 2010;**34**:J168-77. doi:10.1016/j.jaut.2009.11.018

40 Grant WB, Mascitelli L. Evidence that the north-south gradient of multiple sclerosis may not have disappeared. J. Neurol. Sci. 2012;**315**:178–9. doi:10.1016/j.jns.2012.01.002

41 Logan I, Bowlus CL. The geoepidemiology of autoimmune intestinal diseases. *Autoimmun Rev* 2010;**9**:A372-8. doi:10.1016/j.autrev.2009.11.008

42 Manzel A, Muller DN, Hafler DA, *et al.* Role of 'Western diet' in inflammatory autoimmune diseases. *Curr Allergy Asthma Rep* 2014;**14**:404. doi:10.1007/s11882-013-0404-6

43 Sharif K, Amital H, Shoenfeld Y. The role of dietary sodium in autoimmune diseases: The salty truth. *Autoimmun Rev* 2018;**17**:1069–73. doi:10.1016/j.autrev.2018.05.007

44 Farhat SCL, Silva CA, Orione MAM, *et al.* Air pollution in autoimmune rheumatic diseases: a review. *Autoimmun Rev* 2011;**11**:14–21.

doi:10.1016/j.autrev.2011.06.008

45 van Setten G, Labetoulle M, Baudouin C, *et al.* Evidence of seasonality and effects of psychrometry in dry eye disease. *Acta Ophthalmol* 2016;**94**:499–506. doi:10.1111/aos.12985

46 Lian I-B, Wen I-R, Su C-C. Incidence of sicca syndrome is 3.6 fold higher in areas with farm soils high in chromium and nickel. *J Formos Med Assoc* 2018;**117**:685–90. doi:10.1016/j.jfma.2018.04.008

47 Bernatsky S, Smargiassi A, Barnabe C, *et al.* Fine particulate air pollution and systemic autoimmune rheumatic disease in two Canadian provinces. *Environ Res* 2016;**146**:85–91. doi:10.1016/j.envres.2015.12.021

48 Watad A, Rosenberg V, Tiosano S, *et al.* Silicone breast implants and the risk of autoimmune/rheumatic disorders: a real-world analysis. *Int J Epidemiol* 2018;**47**:1846–54. doi:10.1093/ije/dyy217

49 Coroneos CJ, Selber JC, Offodile AC 2nd, *et al.* US FDA Breast Implant Postapproval Studies: Long-term Outcomes in 99,993 Patients. *Ann Surg* Published Online First: September 2018. doi:10.1097/SLA.0000000000002990

50 Proctor DM, Fukuyama JA, Loomer PM, *et al.* A spatial gradient of bacterial diversity in the human oral cavity shaped by salivary flow. *Nat Commun* 2018;**9**:681. doi:10.1038/s41467-018-02900-1

51 de Paiva CS, Jones DB, Stern ME, *et al.* Altered Mucosal Microbiome Diversity and Disease Severity in Sjogren Syndrome. *Sci Rep* 2016;**6**:23561. doi:10.1038/srep23561

52 Mandl T, Marsal J, Olsson P, *et al.* Severe intestinal dysbiosis is prevalent in primary Sjogren's syndrome and is associated with systemic disease activity. *Arthritis Res Ther* 2017;**19**:237. doi:10.1186/s13075-017-1446-2

FIGURE LEGENDS

Figure 1. 1A. Radar chart for the percentage of active patients for each ESSDAI domain in the four main FDA categories of ethnicity. 1B. Distribution of DAS-ESSDAI in each ethnicity.

Figure 2. Box plots for the mean global ESSDAI scores in patients from northern vs southern countries in Europe (latitude > or <50N), America (equator ><) and Asia (latitude > or <30N).

Supplementary Figure 1. Bar charts of the percentage of active patients for each ESSDAI domain in males and females;* statistically-significant differences.

Supplementary Figure 2. Cluster bar charts of the percentage of active patients for each ESSDAI domain in the three age categories at diagnosis ordered according to the age-related increased/decreased frequency; the articular domain is not represented (does not follow the pattern).

Supplementary Figure 3. Distribution of the organ-by-organ degree of activity (low, moderate and high) between northern and southern cohorts. The countries were separated into two groups by latitude (north vs south) in Europe (latitude > or <50N), America (equator ><) and Asia (latitude > or <30N).

Supplementary Figure 4. Percentage of patients with at least moderate DAS (mean ESSDAI score ≥5) in each country.

Table 1. Influence of epidemiological features on systemic activity at the time of diagnosis of primary SjS

Variables	Gender (n=10007)				Age at diagnosis (n=10004)				
	n	Female (n=9352)	Male (n=655)	*P*	n	<35 (n=1110)	35-65 (n=6848)	>65 (n=2046)	*P*
ESSDAI	9599	6.0 ± 7.4	8.1 ± 9.3	<0.001	9596	6.7 ± 6.8	6.2 ± 7.7	5.6 ± 7.2	0.001
ClinESSDAI	9839	6.1 ± 8.0	8.4 ± 10.1	<0.001	9836	6.5 ± 7.3	6.4 ± 8.4	5.8 ± 7.9	0.031
DAS	9599			<0.001	9596				<0.001
Low		5122 (57.1)	294 (47.2)			527 (49.3)	3700 (56.5)	1186 (60.1)	
Moderate		2801 (31.2)	189 (30.3)			396 (37.0)	2022 (30.8)	572 (29.0)	
High		1053 (11.7)	140 (22.5)			147 (13.7)	831 (12.7)	215 (10.9)	
Activity subsets	9599			<0.001	9596				<0.001
No activity (ESSDAI = 0)		1653 (18.4)	95 (15.2)			131 (12.2)	1162 (17.7)	453 (23.0)	
No high activity in any domain		6682 (74.5)	446 (71.6)			848 (79.3)	4908 (74.9)	1371 (69.5)	
High activity in at least 1 domain		641 (7.1)	82 (13.2)			91 (8.5)	483 (7.4)	149 (7.5)	
ESSDAI domains									
Constitutional	10007	878 (9.4)	72 (11.0)	0.199	10004	127 (11.4)	682 (10.0)	141 (6.9)	<0.001
Lymphadenopathy	10007	780 (8.3)	83 (12.7)	<0.001	10004	156 (14.1)	595 (8.7)	112 (5.5)	<0.001
Glandular	10007	1969 (21.1)	177 (27.0)	<0.001	10004	292 (26.3)	1536 (22.4)	318 (15.5)	<0.001
Articular	10007	3541 (37.9)	231 (35.3)	0.199	10004	400 (36.0)	2721 (39.7)	650 (31.8)	<0.001
Cutaneous	10007	883 (9.4)	57 (8.7)	0.577	10004	137 (12.3)	634 (9.3)	169 (8.3)	0.001
Pulmonary	10007	950 (10.2)	93 (14.2)	0.001	10004	63 (5.7)	708 (10.3)	272 (13.3)	<0.001
Renal	10007	414 (4.4)	28 (4.3)	0.932	10004	73 (6.6)	299 (4.4)	70 (3.4)	<0.001
Muscular	10007	210 (2.2)	22 (3.4)	0.090	10004	15 (1.4)	169 (2.5)	48 (2.3)	0.072
PNS	10007	524 (5.6)	76 (11.6)	<0.001	10004	38 (3.4)	414 (6.0)	148 (7.2)	<0.001
CNS	10007	164 (1.8)	25 (3.8)	<0.001	10004	22 (2.0)	129 (1.9)	38 (1.9)	0.969
Haematological	9839	2061 (22.4)	146 (22.9)	0.815	9836	286 (26.1)	1487 (22.1)	434 (21.7)	0.008
Biological	9678	4608 (50.9)	323 (51.0)	1.000	9675	728 (67.5)	3316 (50.2)	887 (44.6)	<0.001

Values are represented as mean ± standard deviation for continuous variables and numbers (percentages) for categorical variables.

Table 2. Influence of ethnicity on systemic activity at the time of diagnosis of primary SjS

Variables	n	Ethnicity* (n=9421)				*P*
		White (n=7394)	Asian (n=1335)	Hispanic (n=554)	BAA (n=138)	
ESSDAI	9031	6.5 ± 8.0	5.4 ± 6.2	4.8 ± 5.6	6.7 ± 7.6	<0.001
ClinESSDAI	9259	6.7 ± 8.7	5.3 ± 6.8	5.1 ± 6.2	6.7 ± 8.1	<0.001
DAS	9031					<0.001
Low		3885 (55.1)	758 (58.0)	334 (61.7)	60 (45.1)	
Moderate		2211 (31.4)	415 (31.7)	164 (30.3)	54 (40.6)	
High		953 (13.5)	135 (10.3)	43 (8.0)	19 (14.3)	
Activity subsets	9031					0.035
No activity (ESSDAI = 0)		1242 (17.6)	264 (20.2)	123 (22.7)	22 (16.6)	
No high activity in any domain		5249 (74.5)	952 (72.8)	378 (69.9)	99 (74.4)	
High activity in at least 1 domain		558 (7.9)	92 (7.0)	40 (7.4)	12 (9.0)	
ESSDAI domains						
Constitutional	9421	733 (9.9)	126 (9.4)	59 (10.6)	9 (6.5)	0.492
Lymphadenopathy	9421	710 (9.6)	68 (5.1)	44 (7.9)	14 (10.1)	<0.001
Glandular	9421	1784 (24.1)	146 (10.9)	85 (15.3)	32 (23.2)	<0.001
Articular	9421	3036 (41.1)	318 (23.8)	219 (39.5)	57 (41.3)	<0.001
Cutaneous	9421	749 (10.1)	108 (8.1)	45 (8.1)	13 (9.4)	0.069
Pulmonary	9421	786 (10.6)	144 (10.8)	30 (5.4)	14 (10.1)	0.001
Renal	9421	279 (3.8)	136 (10.2)	12 (2.2)	2 (1.4)	<0.001
Muscular	9421	196 (2.7)	15 (1.1)	7 (1.3)	2 (1.4)	0.002
PNS	9421	469 (6.3)	47 (3.5)	27 (4.9)	18 (13.0)	<0.001
CNS	9421	156 (2.1)	14 (1.0)	6 (1.1)	5 (3.6)	0.012
Haematological	9259	1612 (22.2)	350 (26.4)	89 (16.1)	31 (23.3)	<0.001
Biological	9105	3551 (49.9)	759 (57.8)	232 (42.9)	80 (58.8)	<0.001

Values are represented as mean ± standard deviation for continuous variables and numbers (percentages) for categorical variables.

* Excluded other ethnicities

Table 3. Systemic activity at the time of diagnosis of primary SjS in each continent

Variables	America (n=1301)				Europe (n=7289)				Asia (n=1185)			
	n	North (n=862)	South (n=439)	*P*	n	North (n=1857)	South (n=5432)	*P*	n	North (n=475)	South (n=710)	*P*
ESSDAI	1290	3.5 ± 4.6	5.2 ± 5.9	<0.001	6951	4.2 ± 5.0	7.4 ± 8.6	<0.001	1174	4.0 ± 5.4	6.4 ± 6.5	<0.001
ClinESSDAI	1301	3.4 ± 5.2	5.6 ± 6.5	<0.001	7152	4.2 ± 5.5	7.6 ± 9.4	<0.001	1185	3.7 ± 5.9	6.4 ± 7.2	<0.001
DAS	1290			<0.001	6951			<0.001	1174			<0.001
Low		638 (75.0)	259 (59.0)			1137 (66.6)	2611 (49.8)			337 (71.0)	344 (49.2)	
Moderate		178 (20.9)	140 (31.9)			477 (27.9)	1759 (33.5)			105 (22.1)	265 (37.9)	
High		35 (4.1)	40 (9.1)			93 (5.5)	874 (16.7)			33 (6.9)	90 (12.9)	
Activity subsets	1290			<0.001	6951			<0.001	1174			<0.001
No activity (ESSDAI = 0)		185 (21.7)	100 (22.8)			453 (26.5)	747 (14.2)			140 (29.5)	104 (14.9)	
No high activity in any domain		637 (74.9)	300 (68.3)			1205 (70.6)	3980 (75.9)			316 (66.5)	532 (76.1)	
High activity in at least 1 domain		29 (3.4)	39 (8.9)			49 (2.9)	517 (9.9)			19 (4.0)	63 (9.0)	
ESSDAI domains												
Constitutional	1301	33 (3.8)	38 (8.7)	<0.001	7289	213 (11.5)	515 (9.5)	0.015	1185	37 (7.8)	76 (10.7)	0.116
Lymphadenopathy	1301	70 (8.1)	18 (4.1)	0.009	7289	105 (5.7)	573 (10.5)	<0.001	1185	20 (4.2)	44 (6.2)	0.176
Glandular	1301	172 (20.0)	66 (15.0)	0.036	7289	280 (15.1)	1419 (26.1)	<0.001	1185	29 (6.1)	78 (11.0)	0.006
Articular	1301	220 (25.5)	172 (39.2)	<0.001	7289	517 (27.8)	2476 (45.6)	<0.001	1185	97 (20.4)	171 (24.1)	0.160
Cutaneous	1301	32 (3.7)	36 (8.2)	0.001	7289	143 (7.7)	599 (11.0)	<0.001	1185	23 (4.8)	73 (10.3)	0.001
Pulmonary	1301	42 (4.9)	56 (12.8)	<0.001	7289	127 (6.8)	659 (12.1)	<0.001	1185	51 (10.7)	79 (11.1)	0.908
Renal	1301	13 (1.5)	11 (2.5)	0.295	7289	35 (1.9)	247 (4.5)	<0.001	1185	11 (2.3)	118 (16.6)	<0.001
Muscular	1301	4 (0.5)	4 (0.9)	0.548	7289	22 (1.2)	187 (3.4)	<0.001	1185	4 (0.8)	9 (1.3)	0.686
PNS	1301	20 (2.3)	21 (4.8)	0.025	7289	85 (4.6)	413 (7.6)	<0.001	1185	18 (3.8)	26 (3.7)	1.000
CNS	1301	3 (0.3)	16 (3.6)	<0.001	7289	15 (0.8)	143 (2.6)	<0.001	1185	5 (1.1)	7 (1.0)	1.000
Haematological	1301	111 (12.9)	55 (12.5)	0.928	7152	262 (15.2)	1425 (26.3)	<0.001	1185	92 (19.4)	220 (31.0)	<0.001
Biological	1290	446 (52.4)	153 (34.9)	<0.001	7006	835 (47.5)	2725 (51.9)	0.001	1174	235 (49.5)	432 (61.8)	<0.001

Values are represented as mean ± standard deviation for continuous variables and numbers (percentages) for categorical variables.
The countries were separated into two groups by latitude (north vs south) in Europe (latitude > or <50N), America (equator ><) and Asia (latitude > or <30N).