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Original article

Epidemiological profile and north–south gradient driving baseline systemic involvement of primary Sjögren's syndrome

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CLINICAL SCIENCE

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Abstract

Objective. To characterize the systemic phenotype of primary Sjögren's syndrome at diagnosis by analysing the EULAR-SS disease activity index (ESSDAI) scores.

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

Results. The cohort included 10 007 patients (9352 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 $\geq$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, 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 Black/African American patients showing the highest frequencies in the lymphadenopathy, articular, peripheral nervous system, 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, clinical ESSDAI (clinESSDAI) and disease activity states was higher in patients from southern countries ($P < 0.001$).

Conclusion. The systemic phenotype of primary Sjögren's syndrome 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.

Key words: primary Sjögren's syndrome, gender, ethnicity, geoepidemiology, phenotype

Rheumatology key messages

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

Introduction

Primary Sjögren's syndrome (SS) is a systemic autoimmune disease that mainly affects middle-aged women, with a frequency ranging between 0.01% and 0.72% [1]. Etiopathogenically, SS targets the exocrine glands, which are infiltrated by lymphocytes (focal sialadenitis) [2]. Over 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 SS. 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

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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 SS-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 SS 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 SS by measuring the ESSDAI scores at diagnosis in a large international, multi-ethnic cohort of patients.

Methods

Patients

The Sjögren Big Data Consortium is an international, multicentre registry designed in 2014 to take a 'high-definition' picture of the main features of primary SS using worldwide data-sharing cooperative merging of pre-existing clinical SS databases from leading centres in clinical research in SS 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 visualization 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 SS as a primary disease were chronic HCV/HIV infection, previous lymphoproliferative processes and associated systemic autoimmune diseases. Diagnostic tests for SS (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, RF, 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 clinical ESSDAI domains at diagnosis. 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 Food and Drug Administration (FDA) definitions [14]. Geolocation variables were the continent, country and city, with an additional north–south sub-classification (see 'Statistical analysis' section). Systemic involvement at diagnosis was retrospectively classified and scored according to the ESSDAI [5], which evaluates 12 domains or organ systems, and the clinical ESSDAI (clinESSDAI) [18], which evaluates the same domains but excluding the last (biological) domain. Each domain is divided into three to four 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 S.D. for continuous variables and number and percentage for categorical variables. The χ^2 test was used to study systemic features at diagnosis according to gender, age at diagnosis, geolocation and ethnic group. Student's *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

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reported unadjusted for any multiple testing. All analyses were conducted using the R V.3.5.0 for Windows statistical software package (R Foundation for Statistical Computing, Vienna, Austria).

Results

The baseline characteristics of the final cohort are summarized in Supplementary Table S1, available at *Rheumatology* online, and included 9352 (93.5%) women with a mean age at diagnosis of primary SS of 53 (S.D. 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 were 242 (2.4%) patients that retrospectively did not fulfil the 2016 criteria since they had La autoantibodies in the absence of Ro autoantibodies.

The mean total ESSDAI score at diagnosis of the entire cohort was 6.1 (S.D. 7.5); 81.8% of patients had systemic activity (global ESSDAI score $\geq$1) at diagnosis (see Supplementary Table S1, available at *Rheumatology* online). 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 S2, available at *Rheumatology* online.

Males with primary SS 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 Fig. S1, available at *Rheumatology* online).

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 Fig. S2, available at *Rheumatology* online).

Information on ethnicity was recorded in 9610 (96%) patients: 7394 (76.9%) were classified as White, 1335 (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 S1, available at *Rheumatology* online). 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 domains and Hispanic patients in the constitutional domain (Table 2 and Fig. 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 and Fig. 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 Fig. S3, available at *Rheumatology* online). Moreover, a broad worldwide geographical variation in the frequency of patients with moderate systemic activity (global ESSDAI score of $\geq$5) at diagnosis was reported following a north–south gradient (see Supplementary Fig. S4, available at *Rheumatology* online).

Discussion

Primary SS 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 SS. 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 SS patients at diagnosis.

Gender plays a key role in driving the systemic baseline phenotype of primary SS. Although infrequently affected by the disease (<7% in our cohort), males present a severe systemic phenotype [22], and several studies have reported that male SS is associated with poor outcomes (neoplasia and death) [22–24]. Our results show 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]

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Table 1 Influence of epidemiological features on systemic activity at time of primary SS diagnosis

Variable	Gender ($n = 10\,007$)				Age at diagnosis ($n = 10\,004$)				
	n	Female ($n = 9352$)	Male ($n = 655$)	*P*-value	*n*	<35 ($n = 1110$)	35–65 ($n = 6848$)	>65 ($n = 2046$)	*P*-value
ESSDAI, mean (S.D.)	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, mean (S.D.)	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, *n* (%)	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 subset, *n* (%)	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 one domain		641 (7.1)	82 (13.2)			91 (8.5)	483 (7.4)	149 (7.5)	
ESSDAI domain, *n* (%)									
Constitutional	10 007	878 (9.4)	72 (11.0)	0.199	10 004	127 (11.4)	682 (10.0)	141 (6.9)	<0.001
Lymphadenopathy	10 007	780 (8.3)	83 (12.7)	<0.001	10 004	156 (14.1)	595 (8.7)	112 (5.5)	<0.001
Glandular	10 007	1969 (21.1)	177 (27.0)	<0.001	10 004	292 (26.3)	1536 (22.4)	318 (15.5)	<0.001
Articular	10 007	3541 (37.9)	231 (35.3)	0.199	10 004	400 (36.0)	2721 (39.7)	650 (31.8)	<0.001
Cutaneous	10 007	883 (9.4)	57 (8.7)	0.577	10 004	137 (12.3)	634 (9.3)	169 (8.3)	0.001
Pulmonary	10 007	950 (10.2)	93 (14.2)	0.001	10 004	63 (5.7)	708 (10.3)	272 (13.3)	<0.001
Renal	10 007	414 (4.4)	28 (4.3)	0.932	10 004	73 (6.6)	299 (4.4)	70 (3.4)	<0.001
Muscular	10 007	210 (2.2)	22 (3.4)	0.090	10 004	15 (1.4)	169 (2.5)	48 (2.3)	0.072
PNS	10 007	524 (5.6)	76 (11.6)	<0.001	10 004	38 (3.4)	414 (6.0)	148 (7.2)	<0.001
CNS	10 007	164 (1.8)	25 (3.8)	<0.001	10 004	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

ClinESSDAI: clinical EULAR-SS disease activity index; DAS: disease activity states; ESSDAI: EULAR-SS disease activity index; PNS: peripheral nervous system; SS: Sjögren's syndrome.

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 SS 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 SS. Studies in small series of patients have suggested a key role for the age at diagnosis in the disease phenotype [4]: the diagnosis of SS at young ages is often associated with a higher frequency of immunological 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 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 SS-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 SS 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 SS 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,

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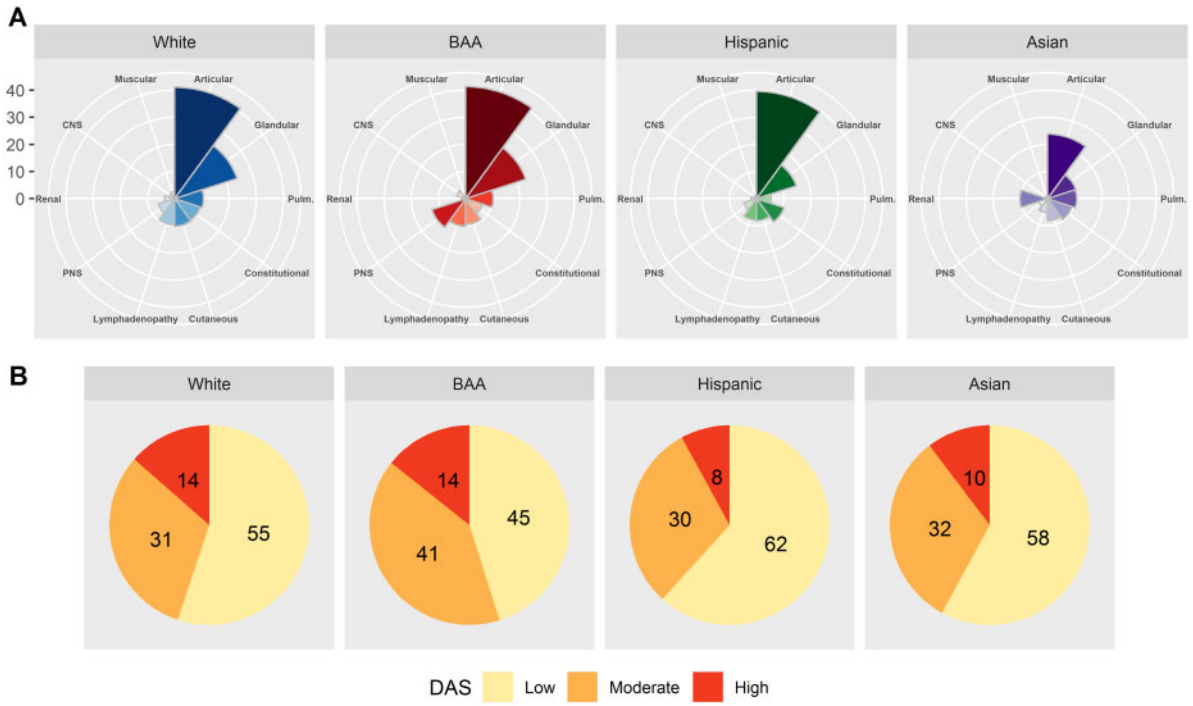
FIG. 1 Disease activity by the four main FDA categories of ethnicity



(**A**) Radar chart for the percentage of active patients for each ESSDAI domain in the four main FDA categories of ethnicity. (**B**) Distribution of DAS-ESSDAI in each ethnicity. BAA: Black/African American; DAS: disease activity states; ESSDAI: EULAR-SS disease activity index; FDA: Food and Drug Administration; PNS: peripheral nervous system.

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 Sjögren's syndrome, 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 SS, 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 are 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 SS 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 SS [51, 52], could also influence the differentiated geographical phenotypic expression. Our results also suggest a worldwide geographical gradient in systemic activity in primary SS. Because ongoing trials in primary SS are using a moderate activity ESSDAI (score $\geq$5) as one of the key inclusion criteria, our findings may be of value when future randomized controlled trials 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 Fig. S4, available at *Rheumatology* online).

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 that, 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-

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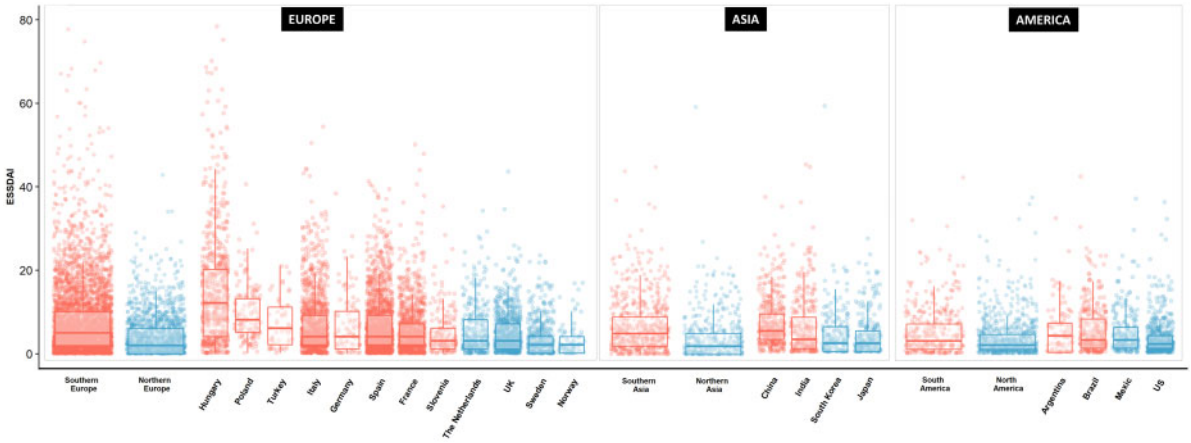
Table 2 Influence of ethnicity on systemic activity at the time of diagnosis of primary SS

Variable		Ethnicity[a] ($n = 9421$)				
	n	White ($n = 7394$)	Asian ($n = 1335$)	Hispanic ($n = 554$)	BAA ($n = 138$)	*P*-value
ESSDAI, mean (S.D.)	9031	6.5 (8.0)	5.4 (6.2)	4.8 (5.6)	6.7 (7.6)	<0.001
ClinESSDAI, mean (S.D.)	9259	6.7 (8.7)	5.3 (6.8)	5.1 (6.2)	6.7 (8.1)	<0.001
DAS, *n* (%)	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 subset, *n* (%)	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 one domain		558 (7.9)	92 (7.0)	40 (7.4)	12 (9.0)	
ESSDAI domain, *n* (%)						
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

[a]Excluded other ethnicities. BAA: Black/African American; clinESSDAI: clinical EULAR-SS disease activity index; DAS: disease activity states; ESSDAI: EULAR-SS disease activity index; PNS: peripheral nervous system; SS: Sjögren's syndrome.

Fig. 2 Box plots for the mean global ESSDAI scores in Europe, America and Asia



The countries were separated into two groups by latitude (north *vs* south) in Europe (latitude greater than or less than 50° N), America (above or below the equator) and Asia (latitude greater than or less than 30°N). ESSDAI: EULAR-SS disease activity index.

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.

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

Variable	America ($n = 1301$)				Europe ($n = 7289$)				Asia ($n = 1185$)			
	n	North ($n = 862$)	South ($n = 439$)	*P*-value	*n*	North ($n = 1857$)	South ($n = 5432$)	*P*-value	*n*	North ($n = 475$)	South ($n = 710$)	*P*-value
ESSDAI, mean (S.D.)	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, mean (S.D.)	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, *n* (%)	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 subset, *n* (%)	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 one domain		29 (3.4)	39 (8.9)			49 (2.9)	517 (9.9)			19 (4.0)	63 (9.0)	
ESSDAI domain, *n* (%)												
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

The countries were separated into two groups by latitude (north *vs* south) in Europe (latitude greater than or less than 50° N), America (above or below the equator) and Asia (latitude greater than or less than 30°N). ClinESSDAI: clinical EULAR-SS disease activity index; DAS: disease activity states; ESSDAI: EULAR-SS disease activity index; PNS: peripheral nervous system; SS: Sjögren's syndrome.

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In summary, the great variability in the presentation of systemic SS 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 SS, and should also be taken into account when analysing the results of therapeutic studies or when designing randomized controlled trials.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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