

EXTENDED REPORT

# Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis

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**ABSTRACT**

**Objective** Epidemiological studies of primary Sjögren's syndrome (pSS) are crucial for describing the burden of society and the public medical system and for shedding light on aetiology. Previous reports of the epidemiology of pSS show variable outcomes. We conducted a systematic review of the epidemiology of pSS to assess the prevalence rates (PRs) and incidence rates (IRs), and to investigate possible geographic variations in pSS.

**Methods** A systematic literature search of PubMed and Embase (updated to 22 October 2013) was performed to identify all published reports on the epidemiology of pSS. The incidence and prevalence rates of pSS were summarised with IRs or PRs and 95% CIs.

**Results** The literature search yielded 1880 related citations. Only 21 fulfilled the inclusion criteria. According to a random-effects model, the pooled IR for pSS was 6.92 (95% CI 4.98 to 8.86) per 100 000 person-years. The overall PR was 60.82 (95% CI 43.69 to 77.94) cases per 100 000 inhabitants with a slightly lower estimate of Baodong Qin is BDQ, Jiaqi Wang is JQW, Zaixing Yang is ZXY, Renqian Zhong is RQZ. 43.03 (25.74 to 60.31) cases per 100 000 inhabitants when only considering population-based studies. The female/male ratio in incidence data was 9.15 (95% CI 3.35 to 13.18). The female/male ratio in prevalence data was 10.72 (95% CI 7.35 to 15.62). The overall age of pSS patients was 56.16 years (95% CI 52.54 to 59.78).

**Conclusions** Incidence and prevalence rates of pSS vary widely around the world. The results help us better understand the global epidemiology of pSS. Large population-based studies combining meticulous case-finding and case-ascertainment strategies are needed.

**INTRODUCTION**

Primary Sjögren's syndrome (pSS) is a slowly progressive autoimmune disorder characterised by lymphocytic infiltration of the exocrine glands and significant loss of secretory function with oral and eye dryness.<sup>1</sup> pSS affects predominantly middle-aged women, typically in the fourth to sixth decades of life.<sup>2</sup> Since the first observation of pSS, intense research efforts have been made to understand the pathological aspects, but the aetiology is still not well understood.<sup>3-5</sup> To aid in the accurate diagnosis of pSS, several sets of diagnostic criteria have been proposed.<sup>6</sup>

Incidence and prevalence are two important indicators in the epidemiology of the disease. Incidence is a measure of the risk of developing some new pSS cases within a specified period of time, while prevalence is the proportion of a population found to have

pSS. Insight into the incidence and prevalence of pSS would be advantageous to describe the burden of the disease and to better understand its aetiology. Several studies have investigated the incidence and prevalence of pSS, but there were inconsistencies owing to different case-finding, case-ascertainment and populations under study. Until now, epidemiological studies of pSS have not been systematically summarised. In the present study, we systematically reviewed the literature regarding incidence and prevalence rates and conducted a meta-analysis to provide recommendations for future studies describing the epidemiology of pSS.

**METHODS**

**Search strategy**

We conducted a systematic literature search with a predetermined protocol according to guidelines set by Meta-analysis of Observational Studies in Epidemiology (MOOSE).<sup>7</sup> We performed a systematic review of the electronic databases including PubMed and Embase (updated October 2013). The PubMed comprehensive search strategy included the Mesh terms and keywords ("Sjögren's Syndrome"[Mesh] and ("Epidemiology"[Mesh] or epidemiol\* or "Incidence"[Mesh] or Incidenc\* or "Prevalence"[Mesh] or Prevalenc\*). The BDQ, JQW, ZXY search strategy used in EMBASE included ((exp Sjögren's Syndrome) or (Sjögren's Syndrome)) and ((exp Epidemiology) or epidemiol or (exp Incidence) or Incidenc\* or (exp Prevalence) or Prevalenc\*). The search was limited to English language, but no limitation was placed on ethnicity or human subjects. The reference lists of relevant articles were also reviewed.

**Study selection**

Population-based studies and population surveys aiming to examine an entire geographic region or using a clearly defined random or clustered sampling procedure were included. Reports consisting of surveys or audits in hospitals or clinics were excluded. Studies were eligible for inclusion if they reported incidence ratio (IR), prevalence ratio (PR) or enough data relevant to the outcomes of interest to calculate them. Studies that did not report sufficient published data or original data were excluded. This included reviews, abstracts and letters. Studies conducted in special populations were excluded. The final results were compared by two authors (QBD and WJQ) and any disagreements were resolved by consensus with the third-party authors (MY, YZX and ZRQ).

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### Data extraction

The primary variables of interest were the prevalence and incidence of pSS. The prevalence rate data included the number of patients with pSS and number of inhabitants recorded for individual years when they were reported. The incidence rate per 100 000 person-years with 95% CI was documented for the overall study period. Secondary variables extracted from the articles included country of origin, study period, age, male/female incidence rate ratio (IRR), the methods of case finding, study design and case ascertainment.

### Assessment of study quality

A population-based study is a study of the entirety from the general population in a defined region using the administrative database or hospital medical records.<sup>8</sup> And sample survey describes the process of choosing a sample of individuals from a target population often using questionnaire. Bias in sample survey is undesirable but unavoidable including non-response bias, coverage bias and selection bias. To some extent, the population-based study could avoid those bias and provide a more accurate epidemiological data of pSS. Due to the lack of standardised quality criteria for meta-analyses of epidemiology studies, evaluation of study quality was based on the method of case-finding method, the study design and the method of case ascertainment. The study quality was considered 'good' when the study design was based on population. The case-finding method included administrative databases or hospital medical records. A well-directed case ascertainment was established using internationally accepted diagnostic criteria. Study quality was classified to be 'moderate' when the study design was a population survey or the case-finding method was a questionnaire and clinical examination; the case-ascertainment method was inadequate for the diagnosis of pSS. If case finding or case ascertainment was not performed, the quality of a study would identified to be 'poor'.<sup>9</sup>

### Statistical analysis

The incidence and prevalence of pSS was summarised using IR and PR. These were defined as the number of pSS patients in a population per 100 000 person-years and per 100 000 persons, respectively. IRs and PRs adjusted for confounding factors were preferred over unadjusted values. The 95% CI for IRs and PRs were estimated under the assumption of a Poisson distribution. The female to male ratio was summarised with an Incidence Rate Ratio (IRR) and Prevalence Rate Ratio (PRR). This was defined as the IR and PR of pSS in women over the IR and PR of pSS in men. When the IRR and PRR were not reported but the number of female and male pSS patients and the total study population were included, the IRR or PRR were calculated using the assumption that ratio of women to men in the background population was 1:1.<sup>10</sup> The overall rates and 95% CI were calculated using a random effect. Heterogeneity of effects among studies was estimated using the Q test and quantified by using the  $I^2$  test.<sup>11 12</sup> Meta-regression analysis was used to identify the potential source of heterogeneity if there were sufficient number of studies. Subgroup analysis was conducted according to the method of case ascertainment, study design or case finding. Funnel plots and the Egger's test were used to determine the possibility of publication bias. Sensitivity analysis was performed to evaluate the degree that each single study affected the overall PR or IR using the one-study remove approach. All statistical analyses were done using Comprehensive meta-analysis software V2.0 (Biostat Inc, Englewood Cliffs, New Jersey, USA) (<http://www>.

meta-analysis.com). p Values less than 0.05 were considered significant.

## RESULTS

### Studies selection

A total of 1880 non-overlapping citations were identified and screened from the previously described electronic databases. A total of 1808 articles were excluded based on screening of abstracts or titles, leaving 72 articles for the full-text review and assessment for eligibility. Fifty-one of these articles were excluded after retrieving the full-text articles (figure 1), leaving 21 eligible studies for inclusion in the meta-analysis.<sup>13–33</sup> The agreement between reviewers for the eligibility of articles was 100%.

### Characteristics of included studies

All 21 studies included were published in English between 1995 and 2013. Of included studies, 15 reported incidence or prevalence rates in European populations, 2 in America<sup>30 31</sup> and 4 in Asia<sup>13 19 20 33</sup> (tables 1 and 2).

Six studies discussed the IR of pSS, all of which were population-based studies and evaluated the female/male ratio.<sup>13 14 19 31–33</sup> Studies varied in size from 53 to 3352 patients, and in catchment areas ranging from 1 358 994 to 55 866 666 person-years (table 1).

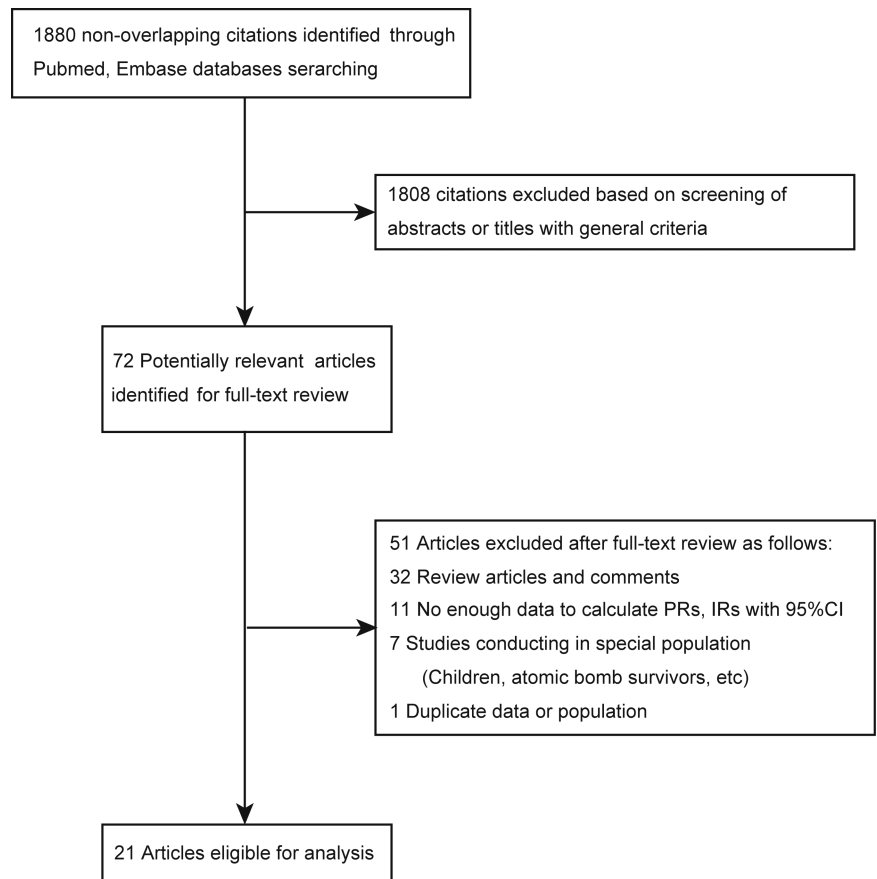
Eighteen studies assessed the prevalence rate of pSS (table 2). Various sources were used for case-finding purposes. In 11 studies, pSS was identified using questionnaires and clinical examination. Other sources included physician registries and medical record databases. The method of case ascertainment varied among these studies, including International Classification of Diseases (ICD) codes, AECG criteria (2002), EC criteria (1993, 1996) and other criteria.<sup>6 34 35</sup> Three of eleven population surveys only reported the PRs of pSS in women.<sup>21 24 26</sup>

### Incidence rate of pSS

The six studies describing IRs for pSS gave an overall IR estimate of 6.92 (95% CI 4.98 to 8.86) per 100 000 person-years at risk (figure 2). Statistically significant heterogeneity was observed between studies ( $p < 0.001$ ,  $I^2 = 98.51\%$ ). In Plesivcnik Novljan M's study, the total number of female or male patients was not reported. We analysed IRs by gender using the assumption of a 50% female background population.<sup>32</sup> In the female population, the meta-analysis indicated that the pooled IR was 12.30 (95% CI 9.07 to 15.53). The estimated IR in the male population was 1.47 (95% CI 0.81 to 2.12) (see online supplementary figure 1). The IRR for females versus males was pooled to give an overall IRR estimate of 9.29 (95% 6.61 to 13.04) (figure 3A) The IRR based on AECG (2002) classification criteria was only discussed in Alamanos Y's study, which reported an estimate of 20.1 (95% CI 12.83 to 31.49).

Of six studies reporting IR, three were from Taiwan.<sup>13 19 33</sup> The subgroup meta-analysis stratified by country showed that IR of pSS in Taiwan was 6.57 (95% CI 6.37 to 6.76) and had significant heterogeneity ( $p < 0.001$ ,  $I^2 = 99.25\%$ ). In total, 6 of 21 studies reported the age of patients with pSS at diagnosis. The meta-analysis showed the pooled age at evaluation was 56.2 years (95% CI 52.5 to 59.8 years) (see online supplementary figure 2).

Three studies from Asia gave a pooled IR of 6.57 per 100 000 person-years. Two studies from Europe reported the IRs for pSS to range from 3.9 in Slovenia up to 5.3 in Greece. The prospective population-based study from the USA between 1976 and 1992 reported an IR of 3.9.

**Figure 1** Flowchart showing article identification, inclusion and exclusion.

### Prevalence rate of pSS

The pooled PR of pSS in the total population was 60.82 (95% CI 43.69 to 77.94) cases per 100 000 inhabitants (figure 4). Seven population-based epidemiological studies reported PRs for pSS in a defined geographical area of at least 20 000 adult inhabitants. However, the number of inhabitants in eight sample surveys reporting PR was relatively small, ranging from 332–16 046. Therefore, significant heterogeneity was observed ( $p < 0.001$ ,  $I^2 = 98.95\%$ ). After stratifying by study design, the pooled PR across population-based studies was 43.03 (25.74 to 60.31) cases per 100 000 inhabitants. The pooled PR across studies consisting of sample surveys was 282.35 (135.32 to 429.38) cases per 100 000 inhabitants (see online supplementary figure 3). Population size significantly affected the evaluation of PR in patients with pSS. The prevalence rate reported in small studies was higher than that in larger studies. Metaregression suggest study design ( $p < 0.001$ ), but not sample size ( $p = 0.136$ ), may contribute to heterogeneity of pSS prevalence.

The estimated PR was 116.72 (95% CI 70.39 to 163.05) per 100 000 inhabitants in the female population and the pooled PR in the male population was 5.53 (95% CI 2.49 to 8.58) per 100 000 inhabitants (see online supplementary figure 4). The overall female/male ratio of patients used to calculate the prevalence of pSS (PRR) was 10.72 (95% CI 7.35 to 15.62) (figure 3B)

The 15 included studies were performed in Europe, Asia and South America. The 11 studies from Europe gave a pooled PR of 71.22 (95% CI 48.7 to 93.7) per 100 000 inhabitants. Studies from Asia had a lower pooled estimate of 44.85 (95% CI 3.51 to 86.2). Only one study was conducted in South America and had a relatively higher PR of 0.17%.

The number of patients in this study was only 1205 individuals.

A subgroup meta-analysis by diagnostic criteria was conducted to evaluate the different diagnostic criteria used in these studies. The pooled PR for ICD diagnoses was 38.60 (95% CI 17.21 to 59.99) per 100 000 inhabitants. The overall estimated PR for AECG (2002) was 73.57 (95% CI 37.51 to 109.63), and the pooled female/male ratio based on those studies using AECG (2002) was 16.10 (95% CI 12.10 to 21.42) (see online supplementary figure 5). The meta-analysis for EC-1993 estimated a relatively higher PR of 929.32 (95% CI 261.01 to 1597.62).

### Sensitivity analysis

The pooled IRs ranged from 5.97 (4.21 to 7.73) to 7.51 (5.35 to 9.67) per 100 000 person-years after excluding one study at a time in the sensitivity analysis. Excluding Plesivcnik Novljan M's study and evaluating only those studies that reported the total number of female and male population led to a pooled IRR of 9.15 (95% CI 3.35 to 13.18).

The overall PRs of pSS did not significantly change after one study at a time was removed (70.86 after emitting Yu's study to 51.60 after emitting Haugen's study). Four studies did not report whether they recruited secondary SS patients.<sup>17 18 22 23</sup> After excluding these four studies, the pooled PR for pSS was 68.67 per 100 000 inhabitants. The four incompletely defined studies had a PR of 42.76 per 100 000 inhabitants.

### Publication bias

There was no evidence of publication bias for the overall IR (Egger's test:  $t = 0.624$ ,  $p = 0.566$ ) or the overall PR (Egger's test:  $t = 1.566$ ,  $p = 0.145$ ). No significant publication bias was detected in the other meta-analyses.

**Table 1** Summary of studies including the incidence of primary Sjögren's syndrome

Author	Year	Country	Study period	Cases finding	Study design	Case ascertainment	Age of patients with pSS*	pSS cases (n)	Person-years	Female/male (n)	IR (95% CI)/100 000	Quality
Pillemer <i>et al</i> <sup>21</sup>	2001	USA (Minnesota)	1976–1992	Medical record search	Population based	NS	59.0±15.8	53	1 358 994	51/2	6.90 (5.01 to 8.79)	Good
Plesivcnik Novljan <i>et al</i> <sup>22</sup>	2004	Slovenia (Ljubljana)	2000–2002	Medical record search	Population based	EC-1996†	51.3±14.5	71	1 799 685	65/6†	7.22 (5.47 to 8.98)	Good
Alamanos <i>et al</i> <sup>14</sup> §	2006	Greece (north-west Greece)	1982–2003	Medical record search, personal registry physicians	Population based	AECG-2002¶	55.4±12.5	422	7 962 264	402/20	10.10 (9.11 to 11.08)	Good
Weng <i>et al</i> <sup>23</sup>	2011	China (Taiwan)	2005–2007	NHI Research Database	Population based	NS	53.5±14.2	3352	55 866 666	3040/312	11.00 (10.61 to 11.39)	Good
Yu <i>et al</i> <sup>13</sup> §	2013	China (Taiwan)	2000–2008	NHI Research Database	Population based	ICD codes System	NS	855	8 066 037	736/119	18.50 (17.16 to 19.84)	Good
See <i>et al</i> <sup>19</sup> §	2013	China (Taiwan)	2005–2009	NHI Research Database	Population based	ICD codes system	NS	583	4 953 660	501/83	20.05 (18.29 to 21.80)	Good

\*Ages shown as mean±SD.

†EC-1996 is European classification criteria for Sjögren's syndrome published in 1996.

‡Fifty per cent of the study population was assumed to be female.

§The study reported the prevalence and incidence rate of pSS. ¶AECG-2002 is a revised version of the European criteria for Sjögren's syndrome proposed by the American-European Consensus Group in 2002. NS, no stated; pSS, primary Sjögren's syndrome.

**DISCUSSION**

pSS is an autoimmune disease of unknown aetiology. The burden of this disease is substantial because of the lack of effective therapeutic options. pSS poses a significant burden to patient quality of life and the health care system.<sup>36 37</sup> At present, few population-based epidemiological studies have investigated the prevalence and incidence of pSS.<sup>38</sup> As a result, the epidemiology of this disease remains poorly defined. To better demonstrate this, we conducted the systematic review to comprehensively summarise the current literature on the epidemiology of pSS.

Six studies investigating the IR of pSS were population-based and of good quality.<sup>13 14 19 31–33</sup> The systematic review yielded a wide range of incidence rates for pSS in Europe,<sup>14 32</sup> North America<sup>31</sup> and Asia.<sup>13 19 33</sup> The studies from Asia reported a relatively higher IR than other regions, ranging from 6.0 to 11.8 per 100 000 person-years, and the pooled IR reached 6.57. Two studies from Europe reported the IRs for pSS to range from 3.9 to 5.3. A study from North America reported an IR of 3.9, which is the lowest IR of pSS found worldwide in the included study. Only two European studies and one North American study were included, which restricted us to conduct a meta-analysis to analyse the overall IR of pSS in these regions. Data regarding the incidence of pSS in Africa, Oceania and South America were lacking. The present study indicated that pSS occurred primarily in women with overall average age of 56.2 years at diagnosis. Three studies reported the IR for pSS in different age groups, all of which demonstrated that the incidence of pSS increased progressively with age in women, peaking at 55–65 years. In men, the occurrence of pSS mainly occurred in those aged 65 or older.<sup>14 31 33</sup>

In total, 7 of 18 studies regarding the prevalence of pSS fulfilled 'good' quality criteria.<sup>13 14 16–19 29</sup> The other 11 studies were designed as sample surveys in which patients with pSS were initially found through questionnaires and then diagnosed using clinical examination based on established diagnostic criteria. Due to the non-population-based nature of this study and the low response rates, the prevalence was likely largely overestimated. This is also the reason why these studies were classified as of 'moderate' study quality. Population-based studies provide a more accurate and reliable estimate of the prevalence rate of disease. The PR of 43.03 per 100 000 is likely more representative of the true prevalence of pSS. The female/male ratio in prevalence rate for pSS is 10.72, which is higher than the female/male ratio in incidence for pSS. The reason may be that all included studies of incidence were population-based, while several studies describing prevalence were not. Both the estimated PR and PRR for AECG (2002) were relatively higher than the overall PR and PRR. Different criteria have different classification items and different diagnostic efficacy, the PRs/IRs varied among different classification criteria. It is not clear why the PR or IR in female is so much higher than male population when using AECG (2002), but it remains clear that there is no difference in sex ratio among populations of different geographical areas with different ethnic backgrounds in these studies (1.04±0.09 in all studies; 1.02±0.08 in the study using AECG (2002)). So the reason may be that the AECG (2002) classification criteria could find more female pSS cases than other criteria, but the previous study has not reported this point.

Significant heterogeneity was observed across studies exploring the prevalence of pSS. Meta-regression demonstrated that study design and diagnostic criteria contributed to the significant heterogeneity by geographic region. The great heterogeneity was still present after excluding population survey studies,

**Table 2** Summary of studies including the prevalence of primary Sjogren's syndrome

Author	Year	Country	Source of cases	Study design	Case ascertainment	pSS cases (n)	Total number of population (n)	Female/male (n)	PR (95% CI)/100 000	Quality
Zhang <i>et al</i> <sup>20</sup>	1995	China (Beijing)	Questionnaire Clinical examination	Population survey	San Diego criteria*	7	2066	NS	338.82 (87.82 to 589.81)	Moderate
Dafni <i>et al</i> <sup>21</sup> †	1997	Greece (Astakos)	Questionnaire Clinical examination	Population survey	EC-1993	5	837	NS	597.37 (73.76 to 1120.98)	Moderate
Thomas, <i>et al</i> <sup>22</sup> ‡	1998	UK (Manchester)	Questionnaire Clinical examination	Population survey	EC-1993	13	343	12/1	3790.09 (1729.81 to 5850.36)	Moderate
Tomsic <i>et al</i> <sup>23</sup> ‡	1999	Slovenia (Ljubljana)	Questionnaire Clinical examination	Population survey	EC-1996	2	332	NS	602.41 (-232.47 to 1437.29)	Moderate
Bowman <i>et al</i> <sup>24</sup> ‡	2004	UK (Birmingham)	Questionnaire Clinical examination	Population survey	AECG-2002	2	846	NS	236.41 (-91.23 to 564.04)	Moderate
Trontzas <i>et al</i> <sup>25</sup>	2005	Greece	Questionnaire Clinical examination	Population survey	AECG-2002	13	8740	NS	148.74 (67.89 to 229.60)	Moderate
Kabasakal <i>et al</i> <sup>26</sup> ‡	2006	Turkey (Bornova)	Questionnaire Clinical examination	Cross-sectional population survey	EC-1993 AECG-2002	13 6	831 831	NS	722.02 (144.29 to 1299.75)	Moderate
Alamanos <i>et al</i> <sup>14</sup> §	2006	Greece (north-west Greece)	Medical record search Personal registry physicians	Population based	AECG-2002	422	488 435	402/20	86.40 (78.16 to 94.64)	Good
Haugen <i>et al</i> <sup>15</sup>	2008	Norway (Hordaland)	Questionnaire Clinical examination	Population survey	EC-1996 EC-1993¶	69 155	16 046 16 046	NS	430.01 (328.55 to 531.48)	Moderate
Birlik <i>et al</i> <sup>27</sup>	2009	Turkey (Balçova, Narlıdere)	Questionnaire Clinical examination	Population survey	AECG-2002	6	2887	6/0	207.83 (41.53 to 374.12)	Moderate
Anagnostopoulos <i>et al</i> <sup>28</sup>	2010	Greece (Prefecture)	Questionnaire Clinical examination	Cross-sectional population survey	AECG-2002	4	1705	NS	234.60 (4.70 to 464.51)	Moderate
Goransson <i>et al</i> <sup>16</sup> §	2011	Norway (Hordaland Rogaland)	Personal registry physicians/Medical record search	Population based	AECG-2002	424	852 342	396/28	49.75 (45.01 to 54.48)	Good
Eaton <i>et al</i> <sup>18</sup> ‡	2011	Denmark	Medical record linkage system	Population based	ICD-8,ICD-10	2615	5 472 032	NS	47.79 (45.96 to 49.62)	Good
Sardu <i>et al</i> <sup>17</sup> ‡	2012	Italy (Sardinia)	Medical record search	Population based	EC-1993	10	2887	9/1	30.91 (9.49 to 52.32)	Good
See <i>et al</i> <sup>19</sup>	2013	China (Taiwan)	Medical record search	Population based	ICD-9	583	1 000 000	NS	58.30 (53.57 to 63.03)	Good
Maldini C, <i>et al</i> <sup>29</sup>	2013	France (Paris)	Comprehension methods**	Population based	AECG-2002	133	1 172 482	NS	11.34 (9.42 to 13.27)	Good
Yu <i>et al</i> <sup>13</sup>	2013	China (Taiwan)	Medical record search	Population based	ICD codes system	154	963 355	136/18	15.99 (13.46 to 18.51)	Good
Valim <i>et al</i> <sup>30</sup>	2013	Brazil (Vitoria)	Questionnaire Clinical examination	Cross-sectional Population survey	AECG-2002	2	1205	NS	60.82 (43.69 to 77.94)	Moderate

\*This criteria only was used in Zhang *et al*'s study.

†The study was only conducted in female population.

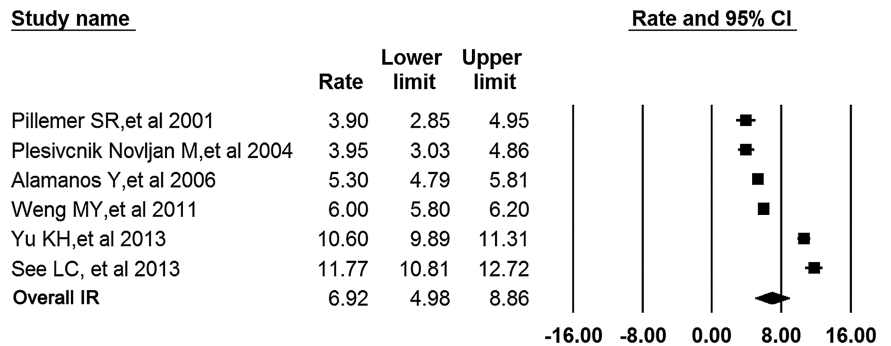
‡The study was excluded from the sensitivity analysis because it did not state the type of Sjogren's syndrome patients. §The age of pSS cases was 55.4±12.5 years, 61.6±13.2 years, respectively.

¶EC-1993 is criteria for the classification of Sjogren's syndrome proposed by the European Community.

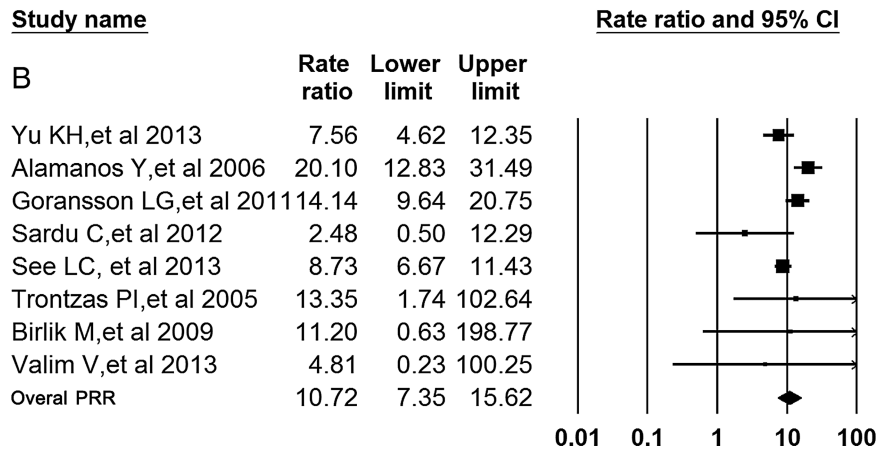
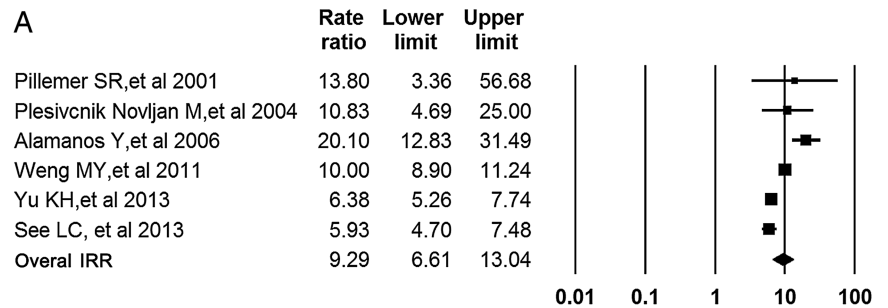
\*\*Included National Health Insurance (NHI) database, national patient support group, private laboratories and community-based physicians. IR, incidence rate; NS, no stated; PR, prevalence rate; pSS, primary Sjogren's syndrome.

Clinical and epidemiological research

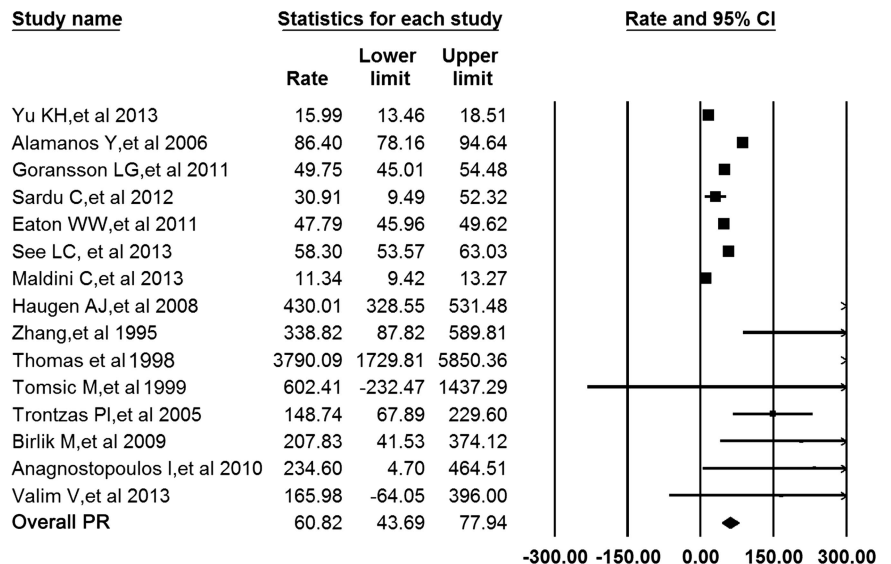
**Figure 2** Overall incidence rate estimates of primary Sjögren's syndrome per 100 000 person-years at risk (meta-analysis using the random-effects model).



**Figure 3** Rate ratios of primary Sjögren's syndrome for females versus males (a, incidence; b, prevalence; meta-analyses using the random-effects model).



**Figure 4** Pooled prevalence rate for primary Sjögren's syndrome per 100 000 inhabitants across all studies.



suggesting the consistency of heterogeneity was not entirely due to the much larger PR estimates and the smaller overall study population in these non-population-based studies. Study design (case-finding and case-ascertainment methods) was vital for assessing the incidence and prevalence rates.

Our meta-analysis had some limitations. First, the number of studies included was relatively small, especially studies of incidence. Second, due to the lack of data provided by each study for comprehensively studying the demographics and time trends of the incidence of pSS, secondary calculations were required. Third, available studies consisted of published data. Unpublished data were not identified. This suggests that publication bias cannot be absolutely excluded even though no significant publication bias was observed. It was impossible to completely exclude the influence of confounding factors inherent in these included studies, although subgroup analyses or meta-regression by gender, region, case ascertainment and study design were performed. Other confounders such as age and study period could not be excluded. Despite these limitations, this study provides a comprehensive summary of the current literature.

In conclusion, this study evaluated the epidemiology of pSS by systematically reviewing the relevant literature. The findings also highlight the need for research on the epidemiology of pSS. Such research should employ appropriate study design and include evaluation of temporal trend in the incidence and prevalence of pSS.

**Contributors** BDQ and JQW were responsible for extraction and collection of data. MY and NM analyzed the data. FLH and YL wrote the paper. ZXY and RQZ mainly designed the meta-analysis.

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**Competing interests** None.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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# Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis

Baodong Qin, Jiaqi Wang, Zaixing Yang, Min Yang, Ning Ma, Fenglou Huang and Renqian Zhong

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## Is primary Sjögren's syndrome an orphan disease? A critical appraisal of prevalence studies in Europe

A meta-analysis of epidemiological studies in primary Sjögren's syndrome (pSS) has been recently published in the *Annals of the Rheumatic Diseases* by Qin *et al.*<sup>1</sup> According to this study, the estimated prevalence of pSS worldwide is 60.82 per 100 000 inhabitants, or 1 person in 1644. Thus, the prevalence of pSS would not fit in with the definition of a rare disease. However, the extraordinary heterogeneity of the results between the different included studies is striking: the prevalence of this disease in single studies ranges from 11.34 to 3790.09 per 100 000 persons.

In Europe, a disease is considered rare when it affects less than one person per 2000: this is the definition of an orphan disease. To date, 6000 to 7000 rare diseases have been recognised, but this figure is constantly evolving with scientific knowledge (<http://www.orpha.net>). Many are genetic diseases, some are infectious or autoimmune. The recognition of a disease as rare has important implications, most importantly, for the development of new therapies. Indeed, the European Parliament and the Council adopted regulation (CE) No. 141/2000 on orphan drugs in 1999, which encourages the pharmaceutical and biotechnological industry to carry out research on and develop drugs to treat orphan diseases.

pSS is a systemic autoimmune disease, mainly characterised by sicca symptoms (eye and mouth dryness), intense fatigue, inflammatory infiltrate of exocrine glands and production of auto-antibodies. These symptoms are nonspecific and several differential diagnoses have to be excluded.<sup>2</sup> Numerous classification criteria for pSS have been proposed, but the most widely used are those issued by the American-European Study Group (AECG) in 2002.<sup>3</sup> The different criteria are not equivalent and may profoundly affect the results of epidemiological studies. For example, in a study from Turkey on adult women, the prevalence of pSS fell from 0.49% using the preliminary European criteria<sup>4</sup> to 0.30% according to the AECG criteria.<sup>5</sup> New classification criteria were proposed in 2012 and endorsed by the American College of Rheumatology,<sup>6</sup> but they are not consensual,<sup>7-10</sup> and no epidemiological study has been published to date using these criteria.

Several factors influence the quality of a prevalence study and the accuracy of its results: the case-finding method (which detects potential cases), the methodologies used to ascertain these cases (only patients who really have the disease are included) and the definition and size of the background population. Case-finding methods can be the analysis of administrative

databases or hospital medical records (which can be considered as sensitive methods) or from responses to questionnaires sent to a selected population. In questionnaire-based studies, patients with mild symptoms, who never consulted for that reason, may be newly diagnosed, artificially increasing the prevalence of the disease. Conversely, analysis of administrative databases or hospital medical records detects patients with an actual clinical diagnosis. The efficacy of case-finding is improved when several methods are used in parallel.

To assess the cases, the opinion of the patient or physician, or the administrative coding system, is not considered reliable. Instead, cases must be defined by reviewing medical charts using a validated set of criteria, such as the AECG criteria. The background population should not be specific groups of patients or hospital-based charts but, rather, should concern the whole population within a precise geographical area, using administrative data (population-based studies). The size of this population must be large enough to allow accurate estimation of the prevalence of the disease. Sample surveys, which usually use questionnaires to select part of a target population, are dampened by low response rates and selection bias. Furthermore, the prevalence of a disease may be region dependent.

Thus, to accurately estimate the prevalence of pSS in Europe, we have to focus on studies using good methodology (population-based study, effective case-finding methods, ascertainment of cases using AECG criteria, large background population) and that have been performed exclusively in European countries. Only three studies respond to these criteria: one was performed in Greece,<sup>11</sup> one in Norway<sup>12</sup> and the third in France<sup>13</sup> (table 1). When their results are combined, we estimate the prevalence of pSS in Europe to be 38.95/100 000, or one person per 2567. Of note, the methodology of Maldini's French study is the most robust as it uses five case-finding data sources and capture-recapture methods and gives the lowest prevalence figure (11.34/10 000, or one person per 8818).<sup>13</sup>

To conclude, the estimated prevalence of pSS in Europe is far lower than suggested by older sample surveys, and is probably below the 1/2000 threshold to define a rare disease. Other robust epidemiological studies are warranted to definitively confirm these preliminary results.

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**Table 1** Population-based studies evaluating the prevalence of primary Sjögren's syndrome in Europe according to the AECG criteria

Reference	Region	Case-finding methods	Cases	Reference population	Calculated prevalence (cases/100 000)
Alamanos <i>et al</i> <sup>11</sup>	Greece (North-west)	Medical record search Personal registry physicians	422	488 435	86.40
Gøransson <i>et al</i> <sup>12</sup>	Norway	Medical record search Personal registry physician	424	852 342	49.75
Maldini <i>et al</i> <sup>13</sup>	France	Capture/recapture National health insurance and National patient support and private laboratories	133	1 172 482	11.34
Overall			979	2 513 259	38.95

AECG, American-European Study Group.

## Correspondence

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# Epidemiology of Primary Sjögren's Syndrome in a French Multiracial/Multiethnic Area

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**Objective.** To describe the epidemiology of primary Sjögren's syndrome (SS) in a multiracial/multiethnic population. **Methods.** A cross-sectional study with 5 case-retrieval sources identified adults with primary SS living in the Greater Paris area (population 1,172,482 adults) in 2007. Diagnoses were verified by the American-European Consensus Group (AECG) criteria and study-specific enlarged criteria based on the presence of  $\geq 3$  of 4 AECG items among subjective oral or ocular dryness, anti-SSA/SSB positivity, and positive minor salivary gland biopsy results. Prevalence estimates were standardized to those for the world population and a 5-source capture–recapture analysis (CRA) was used. Racial/ethnic differences in primary SS features were evaluated.

**Results.** In all, 133 subjects met the AECG criteria and 203 met the enlarged criteria. The 2007 prevalence of primary SS was 1.02 cases per 10,000 adults (95% confidence interval [95% CI] 0.85–1.22) for the AECG criteria and 1.52 cases per 10,000 adults (95% CI 1.30–1.76) for the enlarged criteria. The CRA indicated completeness of case findings of  $\sim 90\%$ . Compared to subjects with European backgrounds, those with non-European backgrounds had 2.1–2.3 times higher primary SS prevalence and were younger ( $P < 0.0001$ ) and were more likely to have polyclonal hypergammaglobulinemia ( $P < 0.0001$ ) and anti-SSA/SSB antibodies ( $P = 0.0005$  and  $P < 0.0001$  for the AECG and enlarged criteria, respectively).

**Conclusion.** The figure of 1.02–1.52 cases per 10,000 adults we found and estimates from the few other population-based census surveys support that the prevalence of diagnosed primary SS is between 1 and 9 cases per 10,000 people (0.01–0.9%) in the general population. Non-European race/ethnicity may be associated with increased primary SS risk and a distinct disease profile.

## INTRODUCTION

Primary Sjögren's syndrome (SS) is a chronic autoimmune connective tissue disorder that manifests as oral and ocular dryness and parotid gland enlargement due to lympho-

cytic infiltration of exocrine glands and extraglandular involvement, including joint symptoms, skin symptoms, neurologic symptoms, and/or other symptoms. The most prominent laboratory features of primary SS are the production of antinuclear antibodies, particularly anti-SSA and anti-SSB antibodies, which are found in  $\sim 50$ – $70\%$  of cases, and features of B lymphocyte activation with fre-

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## Significance & Innovations

- This population-based census study estimated the prevalence of primary Sjögren's syndrome (SS) at 1–1.5 cases per 10,000 subjects.
- People of non-European racial/ethnic background were at increased risk of primary SS and had a distinct clinical profile.
- To a large extent, the prominent between-study variations in published primary SS frequency estimates seemed to account for methodologic differences.

quent polyclonal hypergammaglobulinemia. The prognosis of primary SS, which predominantly affects middle-aged women (1,2), is generally good, although the risk of developing B cell non-Hodgkin's lymphomas is 16- to 18-fold higher than in the general population (3,4). Primary SS has been distinguished from secondary SS, which occurs in the context of an underlying rheumatic disease (1).

Primary SS epidemiology remains poorly investigated. The few published frequency estimates for the general population showed annual incidence rates of 0.11–0.53 cases per 10,000 people (5–8) and markedly discrepant prevalence figures ranging from 2–330 cases per 10,000 people (5,9–15). Whether these numbers reflect genuine between-population variability or methodologic differences in study design is unclear. In addition, the impact of race/ethnicity on primary SS is largely unknown because there are virtually no frequency data outside of European countries or from multiracial/multiethnic populations (16). Accrual of solid epidemiologic data is essential to understand the clinical characteristics and etiopathogenesis of primary SS, to determine the needs for drug development and for public health purposes. We conducted a survey in a French multiracial/multiethnic population to assess primary SS prevalence and search for possible racial/ethnic differences in the burden or presentation of primary SS.

## PATIENTS AND METHODS

**Surveyed population and study period.** This cross-sectional study was carried out in Seine-Saint-Denis County, a northeastern suburb of the highly urbanized Greater Paris area in France. This area has previously been used for epidemiologic studies of other systemic autoimmune or inflammatory diseases with methods similar to those used in the present survey (17–19). The study period was the entire calendar year of 2007 and the survey took place between April 2008 and March 2011.

According to the 2007 census, 1,502,342 people (with 1,172,482 adults aged  $\geq 15$  years) lived in the study area. Using information on nationality at birth and on place of birth, we estimated that the adult population comprised 790,578 adults (67.4%) of European origin and 381,904

adults (32.6%) of non-European origin. The European population comprised 707,076 adults (89.4%) with a French background and 83,502 adults (10.6%) with a non-French background. The residents with a non-European origin included people with backgrounds from Northern Africa (essentially Morocco, Algeria, and Tunisia;  $n = 161,270$  [42%]), sub-Saharan Africa ( $n = 93,746$  [24.5%]), Asia ( $n = 74,366$  [19.5%]), the Caribbean and other overseas French counties and territories ( $n = 37,516$  [9.8%]), US ( $n = 14,921$  [3.9%]), and Oceania ( $n = 82$  [0.02%]). All 2007 census survey data were purchased from the Institut National des Statistiques et des Etudes Economiques).

The study was approved by the Comité Consultatif sur le Traitement de l'information en Matière de Recherche dans le Domaine de la Santé and the Commission Nationale de l'Informatique et des Libertés.

**Case ascertainment.** Cases of primary SS in adults living in the study area were sought by use of the following 5 case-retrieval sources.

**Hospitals.** Nine departments of internal medicine and rheumatology from all 6 teaching or public hospitals in or near the study area were approached for study participation. Additionally, we involved 1 department of pulmonology in a teaching hospital in the study area and 2 departments of internal medicine and rheumatology in teaching hospitals located in the Greater Paris area because of their particular interest in primary SS.

The department heads and, when appropriate, additional medical staff members were contacted by e-mail or telephone to ask for their willingness to participate in the study. If they agreed, they were asked to provide information on the cases of primary SS seen in their respective facilities. Unless the departments had an existing list of such cases, the physicians at the individual sites were prompted to also search the computerized hospital discharge system, which includes comprehensive information on medical conditions for hospitalized patients covering several years up to the time of the inquiry. Data for potential primary SS cases were provided as a list of patients with full identification information, including the surname, first name, date of birth, sex, and postal code of residency.

**Community-based physicians.** All community-based general practitioners, ophthalmologists, and rheumatologists working in the study area were contacted by postal mail to identify cases with primary SS. The mailed material included a letter with general information, a 2-page questionnaire, and a return-addressed paid envelope. The recipients were asked to return the questionnaire, which asked for anonymous information (initials of the first and last name, sex, month and year of birth, and postal code of residency) on known primary SS cases and, if applicable, the hospital physician's name and the hospital name for the corresponding case. The recipients were requested to return the questionnaires even if they knew of no case. A reminder mailing was sent to nonresponders 3 months after the initial mailing.

**Private laboratories.** Throughout France, all autoantibody tests for private practices are performed by 2 central

**Table 1. Criteria used for classification of primary SS cases by the AECG classification criteria described by Vitali et al (22)\***

Classification items	Classification criteria	
	AECG	Enlarged AECG
Subjective symptoms		
Oral dryness	Item 1	Item 1
Ocular dryness	Item 2	Item 2
Objective signs		
Oral signs	Item 3	
Ocular signs	Item 4	
Immunologic/histologic criteria		
Positive anti-SSA/SSB antibodies	Item 5	Item 3
Positive minor salivary gland biopsy	Item 6	Item 4
No exclusion criteria†	Item 7	Item 5
AECG criteria fulfilled	≥4 of 6 items (among items 1–6 and including items 5 or 6) or ≥3 of 4 items (among items 3, 4, 5, and 6)	
Enlarged AECG criteria fulfilled	Item 7 required	≥3 of 4 items (among items 1–4) Item 5 required

\* The study-specific enlarged American–European Consensus Group (AECG) criteria were defined to allow for primary Sjögren's syndrome (SS) classification of subjects with no available information on objective oral or ocular dryness (see Patients and Methods for further details).  
† The exclusion criteria included those defined by Vitali et al (22) and secondary SS (i.e., association with another well-defined major connective tissue disease).

laboratories. These 2 laboratories generated a list of all subjects living in the study area who had tested positive for anti-SSA and/or anti-SSB antibodies in 2007–2008. The data provided included anonymized patient data (initials, month and year of birth, sex, and postal code of residency) and the name and, when available, address of the physician who had ordered the test and the date of sampling.

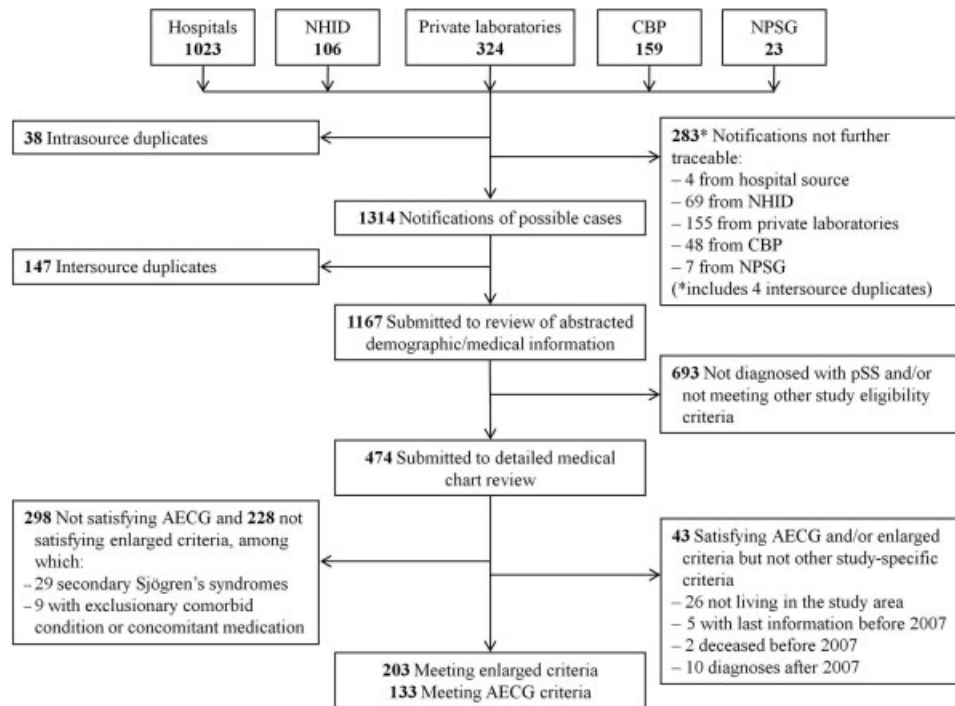
**National patient support group.** The Association Française du Gougerot-Sjögren et des Syndromes secs (20) is a patient support group for primary SS and other sicca syndromes in France. The board of directors of the association agreed to participate in the study and approached all registered members who had a postal address indicating that they lived in the study area. The members who gave written consent were contacted to provide information about their medical followup and to identify the hospital physician who had diagnosed primary SS.

**National health insurance database.** The statutory French health insurance system covers health care–related expenses for chronic or costly illnesses upon an application by a physician. The régime général is the most common statutory insurance plan and covers 86% of French citizens (21). This database was screened by members of the health insurance agency of the study area to identify residents whose medical expenses for primary SS (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision code 35.0) were covered during 2007. All identified patients were contacted by members of the health insurance agency by postal mail to request their consent to participate in the study; nonresponders were sent a reminder mailing. The patients who gave their written consent to participate were then directly contacted by the investigators to give information about their medical followup and, particularly, to identify the treating hospital physician.

**Inclusion criteria and case definitions.** All treating physicians were approached and asked for access to patient medical files; for the few cases not followed up in a hospital, information was retrieved with the help of the community-based treating physician. Duplicate cases were identified by matching the first and last name initials, sex, month and year of birth, and postal code of residency for records. Nontraceable cases corresponded to a notification for which no specific person could be identified (even after additional contact with the notifying hospital or community-based physician or search of computerized hospital databases), the lack of any examinable medical chart, or a refusal or nonresponse to participate in the study.

All medical files were studied by the same investigator (CM). Information was collected by use of a 60-item, study-specific instrument for demographic, clinical, and laboratory data and the time of the last visit. Ethnic origin was defined on the basis of parental and grandparental country of birth.

Recorded case diagnoses were verified against the American–European Consensus Group (AECG) criteria (22). Cases fulfilling the criteria for rheumatoid arthritis (23), systemic lupus erythematosus (24), or systemic sclerosis (25,26) were considered secondary SS and were excluded. During the study, we became aware of the limited availability of test results for objective ocular or oral dryness status. To avoid eliminating patients with true primary SS for whom the AECG criteria could not be verified for these features, we defined enlarged AECG criteria based on the presence of ≥3 of 4 remaining AECG items, including mandatorily positive anti-SSA/SSB serology and/or positive minor salivary gland biopsy results (Table 1). To be considered a prevalent case, subjects had to be adults with primary SS by the AECG criteria or



**Figure 1.** Flow of identification of cases of primary Sjögren's syndrome (pSS). NHID = National Health Insurance database; CBP = community-based physicians; NPSG = national patient support group; AECG = American–European Consensus Group.

enlarged criteria and reside in the study area at some point during 2007.

**Statistics and capture–recapture analysis.** The 2007 prevalence estimate was obtained by dividing the number of prevalent cases of primary SS by the adult population of the study area. All estimates were standardized for age and sex to the world population by direct standardization (27). The estimates were calculated for primary SS defined by the AECG criteria and enlarged criteria. In addition, stratified estimates were computed according to sex and according to racial/ethnic origin categorized into European and non-European origin. The 95% confidence intervals (95% CIs) were calculated on the basis of a hypothesis of Poisson distribution. We compared European or non-European racial/ethnic origin for demographic characteristics and manifestations recorded for at least 10% of primary SS cases overall (plus non-Hodgkin's lymphoma) by chi-square test, Fisher's exact test, and Student's *t*-test.

Five-source capture–recapture analyses were performed to estimate the completeness of case finding. Log-linear modeling was used to assess the number of cases missed by any source and to assess potential source dependencies. We built 26 models, including the independent model and all single first-, second-, and third-order interactions between the 5 sources. We tested 45 additional models, including the remaining possible combinations of multiple first-order interaction terms. The model that best fitted the data was based on Akaike's information criterion (AIC); good fit of a given model to the data was indicated by a low AIC value. To assess the possibility of heterogeneous case capture across sources, we described

preselected characteristics of the subjects identified in each source. The capture–recapture analyses involved the Rcapture package (28) in R statistical software.

## RESULTS

**Responses to surveys and total case notifications.** All contacted hospital departments participated in the study. In all, 466 (34.8%) of 1,339 treating physicians (1,209 general physicians, 93 ophthalmologists, and 37 rheumatologists) returned the survey. We received 1,635 notifications of possible cases of primary SS. Among them, 283 notifications (corresponding to 279 subjects) could not be traced, mostly involving subjects identified through the private laboratories as having positive anti-SSA/SSB antibodies. There were an additional 38 intrasource and 147 intersource duplicates, and 693 case notifications were immediately discarded after a review of demographic and medical data indicated that they did not meet eligibility criteria. We finally selected 474 subjects for medical chart review (Figure 1).

**Case reviews.** We included 133 cases meeting the AECG criteria and 203 meeting the enlarged AECG criteria; except for 1 case, all cases meeting the AECG criteria also met the enlarged criteria (Figure 1). The main characteristics of the identified cases are shown in Table 2. Information on the racial/ethnic background was available for all subjects meeting the AECG criteria and for 201 subjects (99.0%) meeting the enlarged criteria. The cases meeting the AECG criteria included 67 subjects of non-European

Table 2. Main demographic and disease characteristics of adults with primary Sjögren's syndrome living in Seine-Saint-Denis County, France in 2007\*

	AECG criteria, all		AFCG criteria, by racial/ethnic background		P	Enlarged AECG criteria, all		Enlarged AECG criteria, by racial/ethnic background		P	
	criteria, all	Europeans	Non-Europeans	Europeans		Non-Europeans	Europeans	Non-Europeans	Europeans		Non-Europeans
Total	133 (100)	66 (49.6)	67 (50.4)	203 (100)	105 (52.2)	96 (47.8)	1.0			1.0	
Age at assessment, mean ± SD years	57.1 ± 15.1	64.7 ± 12.1	49.7 ± 14.0	58.4 ± 15.1	64.11 ± 13.4	52.1 ± 14.5	< 0.0001			< 0.0001	
Women	126 (94.7)	62 (93.9)	64 (95.5)	190 (93.6)	99 (94.3)	89 (92.7)	0.72			0.65	
Constitutional symptoms	58 (43.6)	28 (42.4)	30 (44.8)	84/201 (41.8)	39/104 (37.5)	43/95 (45.3)	0.78			0.27	
Asthenia	50 (37.6)	25 (37.9)	25 (37.3)	75/201 (37.3)	36/104 (34.6)	37/95 (38.9)	0.95			0.53	
Xerostomia	128 (96.2)	66 (100)	62 (92.5)	196 (96.6)	104 (99)	90 (93.8)	0.06			0.06	
Xerophthalmia	127 (95.5)	64 (97)	63 (94)	194 (95.6)	102 (97.1)	90 (93.8)	0.68			0.32	
Parotid gland enlargement	38 (28.6)	20 (30.3)	18 (26.9)	41 (20.2)	21 (20)	19 (19.8)	0.66			0.97	
Arthralgia/arthritis	95 (71.4)	43 (65.2)	52 (77.6)	146/202 (72.3)	69 (65.7)	77/95 (81.1)	0.11			0.02	
Cutaneous involvement	23 (17.3)	11 (16.7)	12 (17.9)	32/202 (15.8)	16 (15.2)	15/95 (15.8)	0.85			0.91	
Purpura	13 (9.8)	7 (10.6)	6 (9)	17/202 (8.4)	10 (9.5)	7/95 (7.4)	0.75			0.59	
Pulmonary involvement	21 (15.8)	10 (15.2)	11 (16.4)	33 (16.3)	16 (15.2)	17 (17.7)	0.84			0.64	
Neurologic involvement	17 (12.8)	9 (13.6)	8 (11.9)	20/202 (9.9)	10 (9.5)	10/95 (10.5)	0.77			0.81	
Raynaud's phenomenon	36 (27.1)	18 (27.3)	18 (26.9)	50/202 (24.8)	26 (24.8)	23/95 (24.2)	0.96			0.93	
Non-Hodgkin's lymphoma	5 (3.8)	3 (4.5)	2 (3)	7 (3.4)	4 (3.8)	3 (3.1)	0.68			1.00	
Objective oral dryness	20/28 (71.4)	15/20 (75.0)	5/8 (62.5)	20/27 (74.1)	15/20 (75.0)	5/7 (71.4)	0.65			1.00	
Objective ocular dryness	97/104 (93.3)	48/52 (92.3)	49/52 (94.2)	97/126 (77.0)	49/67 (73.1)	48/59 (81.4)	1.0			0.25	
Hematologic involvement†	48 (36.1)	25 (37.9)	23 (34.3)	65/202 (32.2)	34 (32.4)	30/95 (31.6)	0.67			0.90	
Leukopenia (<4,000/mm <sup>3</sup> )	30 (22.6)	12 (18.2)	18 (26.9)	38/202 (18.8)	14 (13.3)	24/96 (25.3)	0.23			0.03	
Lymphopenia (<1,500/mm <sup>3</sup> )	38 (28.6)	24 (36.4)	14 (20.9)	52/202 (25.7)	32 (30.5)	19/95 (20.0)	0.048			0.09	
Polyclonal hypergammaglobulinemia (≥16 g/liter)	70/129 (54.3)	22/63 (34.9)	48/66 (72.7)	84/192 (43.8)	27/99 (27.3)	56/91 (61.5)	< 0.0001			< 0.0001	
Cryoglobulinemia	22/91 (24.2)	13/47 (27.7)	9/44 (20.5)	23/128 (18.0)	15/69 (21.7)	8/57 (14.0)	0.42			0.27	
Rheumatoid factor	58/117 (49.6)	24/56 (42.9)	34/61 (55.7)	68/170 (40.0)	28/86 (32.6)	39/82 (47.6)	0.16			0.047	
Antinuclear antibodies	103 (77.4)	46 (69.7)	57 (85.1)	139/201 (69.2)	67/104 (64.4)	71/95 (74.7)	0.03			0.12	
Anti-SSA and/or anti-SSB antibodies	100 (75.2)	41 (62.1)	59 (88.1)	127/200 (63.5)	52/103 (50.5)	74/95 (77.9)	< 0.001			< 0.0001	
Positive minor salivary gland biopsy	111/126 (88.1)	58/65 (89.2)	53/61 (86.9)	160/186 (86.0)	87/98 (88.8)	72/86 (83.7)	0.68			0.32	
AECG criteria satisfied	133 (100)	66 (100)	67 (100)	132 (65.0)	66 (62.9)	66 (68.8)	1.0			0.38	

\* Values are the number (percentage) or the number/total (percentage) unless indicated otherwise. AECG = American-European Consensus Group.

† Includes autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, leukopenia, and/or lymphopenia.



**Table 3. Age- and sex-standardized prevalence estimates (per 10,000 adults aged ≥15 years) for primary Sjögren's syndrome in Seine-Saint-Denis County in 2007\***

Population	Population size	AECG criteria		Enlarged AECG criteria	
		No. of cases	Prevalence (95% CI)	No. of cases	Prevalence (95% CI)
Total	1,172,482	133	1.02 (0.85–1.22)	203	1.52 (1.30–1.76)
By racial/ethnic origin					
Non-European	381,904	67	1.64 (1.27–2.11)	96†	2.31 (1.85–2.84)
European	791,578	66	0.71 (0.54–0.92)	105†	1.10 (0.88–1.36)
By sex					
Women	606,026	126	1.90 (1.57–2.28)	190	2.79 (2.38–3.24)
Men	566,365	7	0.11 (0.04–0.23)	13	0.19 (0.10–0.35)

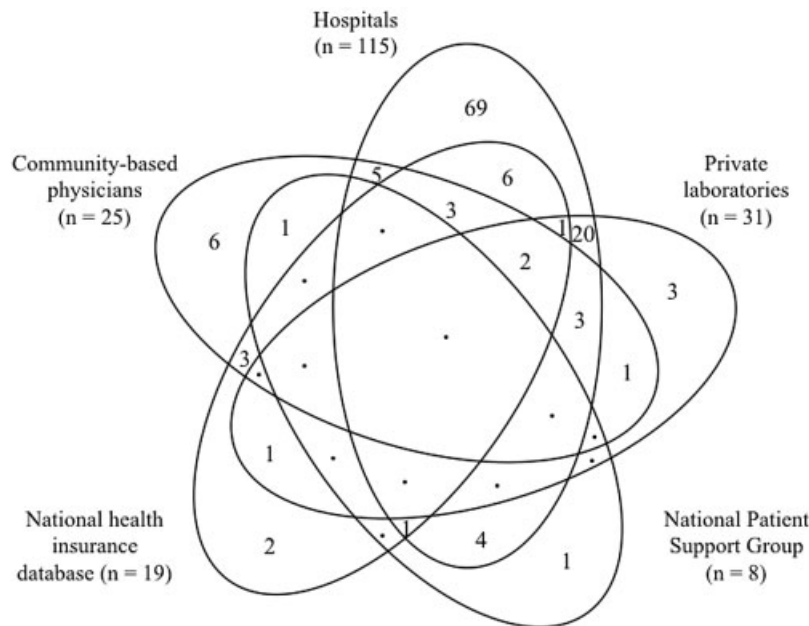
\* AECG = American–European Consensus Group; 95% CI = 95% confidence interval.  
 † Information on racial/ethnic origin was available for 201 cases.

ancestry (50.4%) and the cases meeting the enlarged AECG criteria included 96 subjects of non-European ancestry (47.8%). For non-European cases, the breakdown by continent/region of origin was as follows: for Northern Africa, n = 35 (52.2%) and n = 56 (58.3%) for the AECG criteria and enlarged AECG criteria, respectively; for sub-Saharan Africa, n = 9 (13.4%) and n = 12 (12.5%) for the AECG criteria and enlarged AECG criteria, respectively; and for other areas (mainly Asia and French overseas countries and territories), n = 23 (34.3%) and n = 28 (29.2%) for the AECG criteria and enlarged AECG criteria, respectively.

The main primary SS characteristics stratified by European or non-European racial/ethnic background are shown in Table 2. Regardless of the classification criteria used, cases with non-European background were significantly younger and more likely to show polyclonal hypergammaglobulinemia and anti-SSA/SSB antibody positivity.

**Prevalence estimates.** The computed overall primary SS prevalence for 2007 was 1.02 cases per 10,000 adults (95% CI 0.85–1.22) according to the AECG criteria and 1.52 cases per 10,000 adults (95% CI 1.30–1.76) according to the enlarged criteria. The prevalence was 2.1- and 2.3-fold higher for residents with a non-European background than those with a European background, depending on the AECG criteria used (Table 3).

**Capture–recapture analyses.** The distribution of primary SS cases (defined by the AECG criteria) across the 31 possible 5-source combinations is shown in Figure 2. No case was identified by all 5 sources, whereas 2 (1.5%), 9 (6.8%), and 41 (30.8%) cases were identified by 4, 3, and 2 sources, respectively. For cases defined by the enlarged AECG criteria, these numbers were 0, 2 (1.0%), 12 (5.9%), and 54 (26.6%) for 5, 4, 3, and 2 sources, respectively. The



**Figure 2.** Venn diagram of the distribution of identified primary Sjögren's syndrome (SS) cases among the 5 sources of case ascertainment. Data are for the 133 identified cases of primary SS defined by American–European Consensus Group criteria.

hospital source contributed the most cases by identifying 115 cases (86.5%) fulfilling the AECG criteria and 172 cases (84.7%) fulfilling the enlarged criteria.

Among the 71 log-linear regression models tested, the model that included the 2 interaction terms between the “community-based physicians” and “hospital” sources and between “community-based physicians” and “National Health Insurance database” sources was the best-fit model in both analyses (see Supplementary Tables 1 and 2, available in the online version of this article at <http://onlinelibrary.wiley.com/doi/10.1002/acr.22115/abstract>). Accordingly, the number of missed definite cases calculated by capture–recapture analyses was 14.9 and 30.7 for the AECG criteria and AECG enlarged criteria, respectively, yielding a total number of 147.9 (95% CI 133.4–162.4) and 233.7 (95% CI 210.4–257.0) definite cases for the AECG criteria and AECG enlarged criteria, respectively. Thus, the completeness of case finding was estimated at 89.9% for the AECG criteria and 86.9% for the AECG enlarged criteria. We found no between-source heterogeneity for the following 6 case characteristics: mean age at assessment and percentages of cases with non-European background, anti-SSA/SSB positivity, polyclonal hypergammaglobulinemia, positive minor salivary gland biopsy, and fulfillment of AECG criteria (data not shown).

## DISCUSSION

This study describes the epidemiology of primary SS in a population of the Greater Paris, France area, with an estimated 33% of residents originating from the African continent and other non-European countries. Using the AECG criteria and the study-specific enlarged AECG criteria, we estimated the primary SS prevalence in 2007 at 1.02 cases and 1.52 cases per 10,000 adults, respectively. The prevalence was 2.1- to 2.3-fold higher in residents with a non-European background than those with a European background, depending on the AECG criteria used. Analyses of ethnicity/race-specific primary SS features showed that polyclonal hypergammaglobulinemia, anti-SSA/SSB antibody positivity, and younger age were more frequent among subjects with a non-European background than those with a European background.

The primary SS population frequency data raise questions about the causes underlying the substantial variability in primary SS prevalence estimates. Evidence is growing that study design is an important inconsistency factor, with sampling surveys generating 10- to 20-fold higher estimates than census surveys (Table 4). Census surveys such as ours follow the principle of counting diagnosed cases within entire populations, whereas multistage sampling surveys actively screen for the disease under study in small, randomly selected parts of populations. Sampling surveys thereby allow for the identification of previously unrecognized cases, and the substantially higher frequencies they reveal could indicate that a large proportion of prevalent primary SS remains undiagnosed. Indeed, from such sampling surveys, none of the 10 (9) and 16 (15) identified cases were previously known to have

primary SS. Sampling studies face limitations, including skewed sample selection, sampling error, and preferential recruitment of patients with health issues (responder bias), which may result in biased or imprecise estimates, whereas census surveys are jeopardized by the problem of undercounting known cases.

The findings of prevalence studies may also be susceptible to the evolving criteria for classification of primary SS (29), and the newly introduced preliminary American College of Rheumatology primary SS classification criteria (30) highlight ongoing efforts to refine primary SS classification systems. However, our data suggest that classification criteria might have a comparatively modest impact, and the estimate based on our more inclusive enlarged AECG criteria caused only a slight (1.5-fold) increase in prevalence compared with the established AECG criteria. This effect size is in agreement with the estimated 48% sensitivity of AECG criteria as compared with clinical definitions (31) and with findings from studies that also used several sets of primary SS classification criteria with the same study population (9,15) (Table 4). The discrepancies in primary SS classification may also result from the more or less stringent differentiation of primary SS from secondary SS and exclusion of cases in which sicca syndrome may result from other causes.

Our study provides the first evidence of racial/ethnic influences on primary SS risk and phenotype, with a significant 2-fold higher primary SS prevalence among subjects with a non-European background versus those with a European background. The variations in disease frequency between immigrant and host populations are generally interpreted as supportive of genetic determinants in disease risk, although they may also reflect a role of race/ethnicity-specific socioeconomic or lifestyle factors. Candidate gene association studies provide support for a genetic underpinning in primary SS, notably with links to HLA class II alleles and polymorphisms in the STAT-4 and interferon regulatory factor 5 genes (32–34), but no inferences can yet be made regarding whether these risk loci are differentially distributed across racial/ethnic subpopulations. No environmental factor has been firmly linked to primary SS, and the reasons underlying the prominent primary SS predilection for women are unexplained.

The increased frequency of polyclonal hypergammaglobulinemia and positive anti-SSA and/or anti-SSB antibodies in non-European cases also suggests an impact of race/ethnicity on the clinical-immunologic profile of primary SS. Both characteristics define a primary SS subset with common systemic disease manifestations and a young age at disease onset (35). An increased severity in disease presentation among people of non-European descent was described for scleroderma and systemic lupus erythematosus (16), and the identification of specific associations for anti-SSA and/or anti-SSB antibody-positive primary SS with HLA-DRB1\*15 and HLA-DRB1\*03 (36) polymorphisms could suggest that the clinical-immunologic shape of primary SS is genetically driven. Alternatively, there may be a tendency toward non-Europeans being diagnosed with primary SS only if presenting with more severe disease; although possible, this seems unlikely.

**Table 4. Main characteristics and results of population-based prevalence and incidence surveys for primary SS reported from previous publications and the present survey by sample survey or census survey study design \***

Author, year (ref.)	Publication year	Country	Population size	Classification criteriat	Prevalence		Annual incidence	
					No. of primary SS cases	Rate (per 10,000 people)	No. of primary SS cases	Rate (per 10,000 people)
<b>Census surveys</b>								
Miyasaka, 1995 (11)	1995	Japan	~120,000,000	Japanese	~17,000	2		
Pillemer et al, 2001 (6)	2001	US	108,145	Physician diagnosis			53	0.39
Plesivcnik Novljan et al, 2004 (7)	2004	Slovenia	599,895	European			71	0.39
Alamanos et al, 2006 (5)	2006	Greece	~500,000	AECG	NS	8.6	422	0.53
Goransson et al, 2011 (10)	2011	Norway	852,342	AECG	424	5		
Yu et al, 2013 (8)	2013	China (Taiwan)	1,000,000	Physician diagnosis	154	1.6	855	0.106
Present study	2014	France	1,172,482	AECG	133	1.0‡		
				Enlarged AECG	204	1.5‡		
<b>Sample surveys</b>								
Zhang et al, 1995 (15)	1995	China	2,066	Modified San Diego	7	33§		
				Copenhagen	16	77		
Thomas et al, 1998 (12)	1998	UK	341	Study-specific	13	180/330¶		
Tomsic et al, 1999 (13)	1999	Slovenia	332	European	2	60		
Birlik et al, 2009 (9)	2008	Turkey	2,835	AECG	6	21#		
				European	10	35#		
Trontzas and Andrianakos, 2005 (14)	2005	Greece	8,740	AECG	13	15**		

\* Studies that reported population-based estimates for women only (41–44), for narrow age strata (41,45–49), or for primary SS combined with secondary Sjögren's syndrome (50,51) are not included in this Table. SS = Sjögren's syndrome; AECG = American-European Consensus Group; NS = not stated.  
 † References for classification criteria are as follows: modified San Diego (35), Copenhagen (36), European (52), AECG (22), and Japanese (53).  
 ‡ Estimate for background population age ≥15 years.  
 § Estimate for background population age >16 years.  
 ¶ Crude and covariate-adjusted estimations. Estimate for background population age 18–75 years.  
 # Estimate for background population age ≥20 years.  
 \*\* Estimate for background population age ≥19 years.

The strengths of this study include the large background population and extensive case identification through disparate sources of information. The low private practitioner response rate (35%) may raise concerns regarding incomplete notification from this source, although the capture–recapture analyses supported that our case finding was fairly exhaustive, with an 87–90% estimate of completeness. In addition, the study allowed for gaining insight into a capture–recapture analysis relying on >3 sources, which has rarely been used in other research settings (37–39). The highly stable estimates of missed cases obtained in the regression models suggest decreased vulnerability of capture–recapture estimates to between-source dependencies with increasing numbers of sources involved. Because of almost 6,900 potential combinations of between-source interactions (40), the use of 5 sources implies a theoretical shortcoming in that investigating all between-source dependencies is impractical. Because of the consistency of capture–recapture estimates we observed for the 71 investigated models, any other combination of interactions generating substantially different results was unlikely.

The main study limitation is that 283 case notifications could not be traced; however, under the worst-case assumption that all of these subjects had true primary SS, the total estimate would not have increased by >2–3-fold and thereby would still fall in the range of estimates reported from former census surveys. The fact that a few other case notifications were lost to medical followup before the prevalence study period highlights the possibility that primary SS cases with uneventful courses may be difficult to capture despite extensive searching through a variety of sources of medical information. That said, the similarities in main characteristics of the cases identified in our survey and those of another population-based study (5) do not suggest that our study specifically depicted only part of the primary SS spectrum.

In summary, the collective results from our study and previously published census surveys support that the prevalence of diagnosed primary SS is between 1 and 9 cases per 10,000 people in the general population (0.01–0.09%). These figures need to be separated from those derived from sampling surveys that potentially rely on a majority of cases that may never manifest symptoms and therefore less accurately reflect the clinical burden of primary SS. More data, especially from non-European locations, are warranted to further describe the geoepidemiologic aspects of primary SS.

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## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Mahr had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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**Acquisition of data.** Maldini, Seror, Fain, Dhote, De Bandt, Delassus, Falgarone, Guillevin, Le Guern, Lhote, Meyer, Ramanoelina, Sacré, Uzunhan, Leroux, Mariette, Mahr.

**Analysis and interpretation of data.** Maldini, Seror, Amoura, Mariette, Mahr.

## ROLE OF THE STUDY SPONSOR

Roche Pharmaceuticals had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Roche Pharmaceuticals.

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## Response to: 'Is primary Sjögren's syndrome an orphan disease? A critical appraisal of prevalence studies in Europe' by Cornec and Chiche

We thank Divi Cornec and Laurent Chiche<sup>1</sup> for their valuable comments on our article.<sup>2</sup> We think that the majority of remarks they made were reasonable and helpful for a deep understanding of the prevalence of primary Sjögren's syndrome (pSS). Due to the great differences between a population-based study and sample survey, it is obvious that a high heterogeneity ( $p < 0.001$  for Q statistic,  $I^2 = 98.95\%$ ) could be observed across these articles when conducting a meta-analysis. According to the definition of a rare disease, the total prevalence rate from our study did show that pSS is not a rare disease (one case in 1644). But the prevalence rate was one case per 2304 persons when only considering a population-based study, suggesting pSS is a rare disease.

Among the included studies in our paper, pSS patients from sample survey were mainly found through the questionnaire. In this process, several biases including non-response bias, coverage bias and selection bias, and so on influence the accurate prevalence rate of pSS in a defined region or a target population. However, a population-based study is often used from the administrative database or hospital medical records. Then, the population-based study could avoid these biases and provide a more accurate prevalence rate of pSS. When conducting the systematic review and meta-analysis, it is impossible to completely exclude the effect of these biases on the results. This is also a limitation of this study which was present in our article.<sup>2</sup> Then, we analysed the differences in prevalence rate through a subgroup analysis, and the results also demonstrated that prevalence rate was greatly different between those two types of studies (43.03 cases per 100 000 inhabitants vs 282.35 cases per 100 000 inhabitants). The results from subgroup analysis

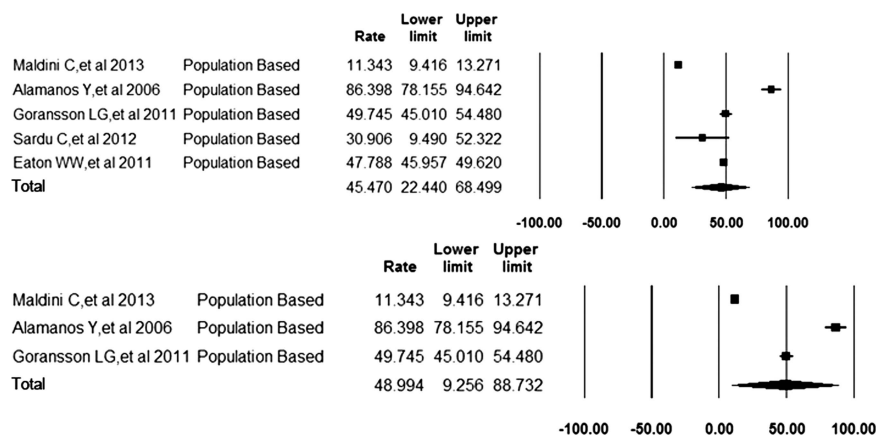
showed that pSS is a rare disease (population-based study), but also not a rare disease (sample survey). Of course, the results from the population-based study may be more accurate and reliable. Except for the study design, the sample sizes also vary greatly among these included studies. But the results from meta-regression show that study design contributes to the high heterogeneity rather than sample sizes.

In all, 50% of included studies concerning the prevalence rate of pSS were based on the AECG 2002 diagnostic criteria. AECG 2002 criteria is the most widely accepted classification criteria currently, which was published by the American-European Consensus Group in 2002.<sup>3</sup> The pooled prevalence rate originated from studies using AECG 2002 was 73.57 per 100 000 inhabitants, but most studies were designed as sample survey. The studies using ICD diagnoses gave a relatively low estimated prevalence rate of 38.60, but most studies using ICD code were designed as a population-based study. Therefore, we think the study design may be a main reason for these differences.

There are 11 studies from Europe, which gave a pooled prevalence rate of 71.22 cases per 100 000 inhabitants (one case per 1404 persons). Based on these data, pSS may be not a rare disease in Europe. The pooled prevalence rate from European population-based studies was 45.47 cases per 100 000 in figure 1A. When only including studies that were designed as population-based studies and using AECG 2002, the meta-analysis also gave a pooled prevalence rate of 48.99 cases per 100 000 in figure 1B. All these results suggest that pSS is a rare disease. Due to the high accuracy of the population-based study, the concept that pSS is a rare disease in Europe could be acceptable, to some extent.

Of note, the case-finding method, case-ascertainment method and study design are important indexes to evaluate the quality of an epidemiological study. The population-based study using definition diagnostic criteria has a better quality than others. This type of epidemiological study could provide accurate data, therefore, and needs to be conducted in different regions to assess whether pSS is a rare disease.

**Figure 1** Pooled prevalence rate for primary Sjögren's syndrome per 100 000 inhabitants across European studies. (A) All European population-based study; (B) All European population-based study using American-European Consensus Group 2002.



## Correspondence response

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