

Rheumatoid Arthritis and Spondyloarthropathies: Geographical Variations in Prevalence in France

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ABSTRACT. *Objective.* To determine geographical variation in the prevalence of rheumatoid arthritis (RA) and spondyloarthropathies (SpA) in France.

Methods. The survey sample was drawn from 7 areas of France. Households were randomly selected using the national telephone directory, and an individual within each household was randomly chosen by the next-birthday method. All cases of suspected RA and SpA were confirmed by the patient's rheumatologist or by clinical examination. Standardized estimates of prevalence were compared between regions and groups of regions.

Results. In total 15,219 anonymous telephone numbers were selected. An average response rate of 64% led to a total of 9395 respondents included in the study. The highest regional rates of RA were observed in the south (range 0.59–0.66%), and the lowest in the north (range 0.14–0.24%), with a national rate of 0.31% (95% CI 0.18–0.48%). Regional heterogeneity was observed for SpA, with the highest rates in Bretagne (0.47%) and the Sud-Est (0.53%) and a national rate of 0.30% (95% CI 0.17–0.46%).

Conclusion. This study is the largest of its kind conducted in France. It shows inter-regional variations, mainly in RA, with a higher prevalence in the south of the country. The many potential reasons for the heterogeneity observed, including genetic and environmental factors, warrant further research. (First Release Nov 15 2006; J Rheumatol 2007;34:117–22)

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The prevalence of rheumatoid arthritis (RA) and spondyloarthropathies (SpA) is poorly documented in France, although a few regional studies have reported differences¹⁻³. More broadly based surveys generally indicate that rates of RA are higher in northern European countries (0.5–0.8%) than in the south (0.3–0.5%)³⁻⁸, but there are exceptions; for example, one group puts the figure in Greece at 0.67%⁹. The prevalence of SpA is even less well documented. As in other southern European countries, marked genetic heterogeneity is

seen in France due to the major migrations that have occurred throughout its history, as confirmed by genetic analysis of HLA in RA¹⁰. A recent national study reported standardized prevalences of 0.30% for RA and 0.31% for SpA^{11,12}. Those figures are close to several southern European rates for RA and do not reflect the country's intermediate geographical location.

There exist a few studies in Europe and none in France about geographical variations^{13,14}. Such epidemiological data

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could improve etiological knowledge and lead to derivation of specific denominators that would be useful for health economic studies.

We surveyed regional variations in the prevalence of RA and SpA in France.

MATERIALS AND METHODS

A nationwide survey sample was drawn in 2001 from 20 counties representative of the geographical breadth of France. Figure 1 outlines the methods used. The survey was managed by 7 university research centers and has been reported in detail^{11,12}. It was conducted using a validated telephone method using a complex 2-stage sampling procedure³ and carried out by trained patient interviewers recruited from self-help groups. The questionnaire was suitable for use by patient interviewers: some questions covered the relevant signs and symptoms and requested a self-report diagnosis, and others were based on the respective criteria for RA (American College of Rheumatology 1987¹⁵) and SpA (European Spondylarthropathy Study Group 1991¹⁶).

The sample size required was calculated on the assumption that the prevalence in some regions would be as low as 0.3%, and that the refusal rate would be roughly 20%. Assuming a Poisson distribution, it was calculated that telephone contact with 4000 people would provide a 95% confidence interval of 0.14–0.54% around a 0.3% estimate.

Our analysis focuses on regional variation. Standardized estimates were calculated on the basis of age and sex distribution data in the 1999 French national census (National Census, INSEE; available from: <http://insee.fr/>); 95% confidence intervals for regional estimates were calculated using an approximation based on a gamma distribution of the weighted sum of independent random Poisson variables¹⁷, which provides a conservative confidence interval estimate whenever the study population is not proportional to the standard population.

Confidence intervals were used to compare regions and groups of regions (formal statistical testing conventional in this context was not performed due to the complex 2-stage sampling method).

Regions were grouped by geographical location (Figure 2), as follows: (1) Na/Sa: Nord, Lorraine, Bretagne, Dauphiné/Midi-Pyrénées, Sud-Est. (2) Nb/Sb: Nord, Lorraine, Bretagne/Midi-Pyrénées, Sud-Est, Dauphiné. (3)

Wa/Ea: Nord, Bretagne, Midi-Pyrénées/Lorraine, Dauphiné, Sud-Est. (4) Wb/Eb: Bretagne, Midi-Pyrénées/Nord, Lorraine, Dauphiné, Sud-Est. (5) NW/NEa/Sa: Nord, Bretagne/Lorraine, Dauphiné/Midi-Pyrénées, Sud-Est. (6) N-Eb/SW: Nord, Lorraine, Dauphiné/Bretagne, Midi-Pyrénées, Sud-Est.

Six comparisons were made: North vs South (groups 1 and 2: Na, Nb vs Sa, Sb); East vs West (3 and 4: Wa, Wb vs Ea, Eb); North-West vs North-East vs South (5); and North-East vs South-West (6).

The Dauphiné and Nord regions being at the geographical limit, 2 different situations were considered for comparison of groups of regions “1 and 2” and “3 and 4.”

Statistical analysis was performed using SAS-Callable Sudaan® software and SAS® software.

RESULTS

A total of 110 patient interviewers were recruited from 7 centers (mean of 16 per center). Twenty-three rheumatologists were involved in confirming diagnoses and overseeing the study. In total, 15,219 anonymous telephone numbers were selected; 3.6% were a business or second home. A total of 9395 people participated in the survey, 3444 in Bretagne, 1105 in Nord, 1265 in Midi-Pyrénées, 751 in Sud-Est, 2024 in Lorraine, and 806 in Rhone Alpes. The mean response rate among households was 64%, ranging from 55.1% to 69.9% in different areas (55.1% in Sud-Est, 58% in Midi-Pyrénées, between 68% and 69.9% in other regions).

Among the cases of definite RA, 2 were previously undiagnosed and confirmed by the investigating center. Six patients did not have a diagnosis made by rheumatologist and were confirmed after an outpatient visit to an investigating center. Among the cases of SpA, diagnosis was not made by a rheumatologist in 5 patients and was confirmed after outpatient visit to the investigating center.

Geographical variation in RA. In total, 32 cases of RA were

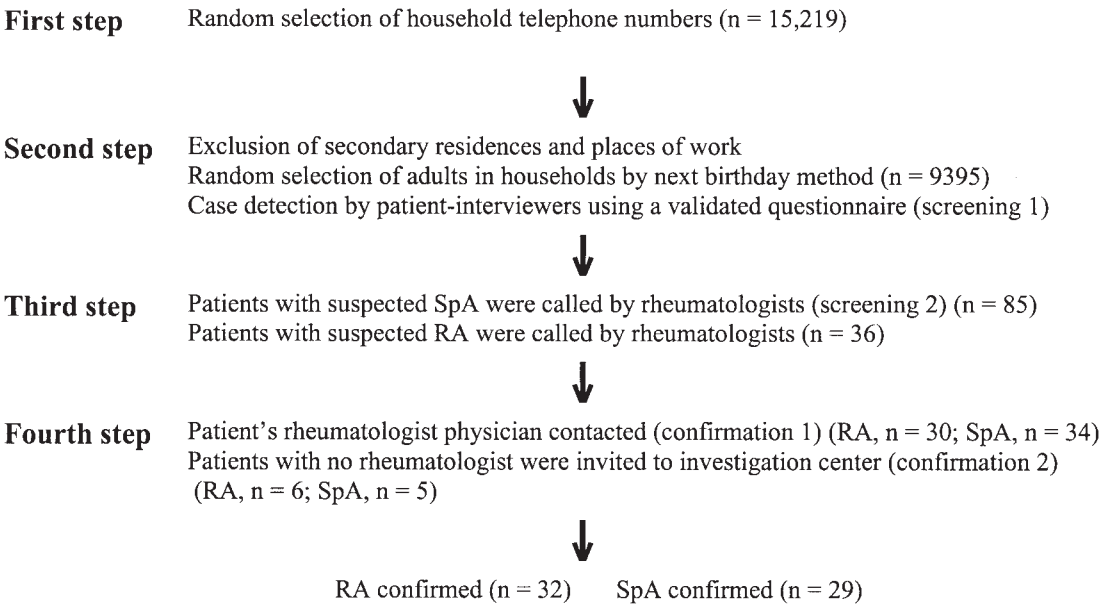


Figure 1. The sampling process (random selection of telephone numbers and random selection of one adult from each household) and case ascertainment (case detection and case confirmation).

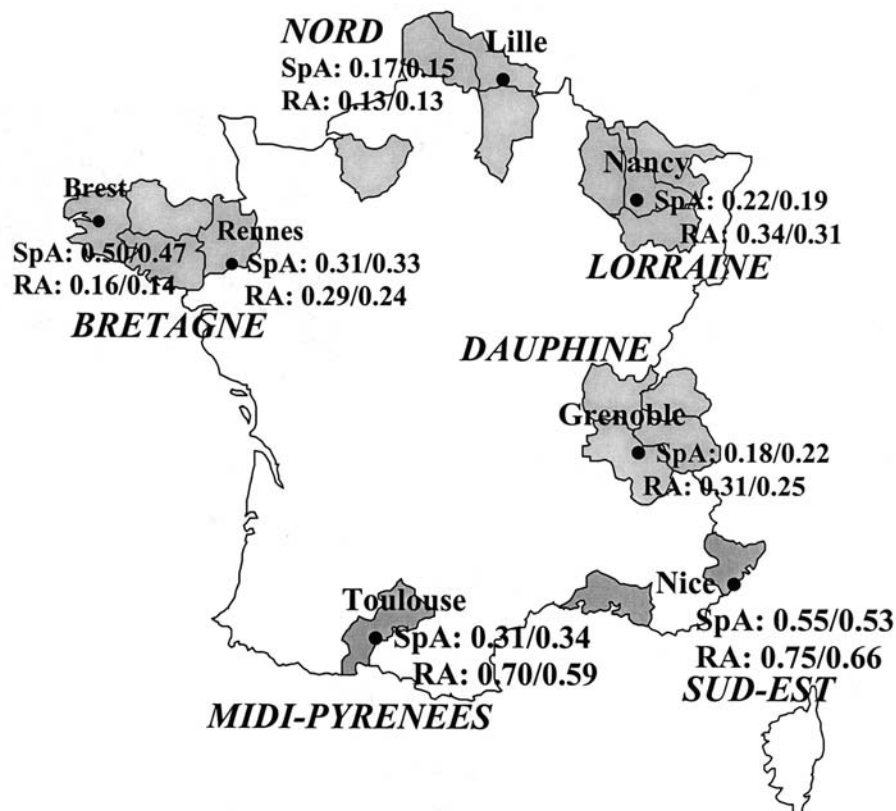


Figure 2. Regions studied and estimates of prevalence (crude/standard percentages) in each.

detected and confirmed. Twenty-seven patients were female and 5 male, with a mean age of 61.3 years (range 29.9–78.9 yrs). The standardized prevalence was 0.31% (95% CI 0.18–0.48%) overall, 0.51% (95% CI 0.27–0.82%) among women and 0.09% (95% CI 0.02–0.20%) among men: a 5.66-fold difference.

Prevalence was highest in the southern regions: Sud-Est (Nice; 0.66%) and Midi-Pyrénées (Toulouse; 0.59%). The lowest rates were observed in the north: Lorraine (Nancy; 0.31%), Dauphiné (Grenoble; 0.25%), Nord (Lille; 0.13%), and Bretagne (Brest; 0.14%) (Figure 2).

A comparison between southern regions (Sa: Sud-Est and Midi-Pyrénées) and northern regions (Na: Bretagne, Lorraine, Dauphiné, and Nord) failed to detect a significant difference. The prevalence was 0.63% (0.24–1.20%) in the south, and 0.21% (0.11–0.35%) in the north (Figure 3).

A comparison between 3 geographical areas, NW (Brest, Lille, Rennes), NEa (Dauphiné, Lorraine), and Sa (Midi-Pyrénées, Sud-Est), showed the prevalence of RA to be highest in the south (0.63%), lowest in the northwest (0.16%), and intermediate in NEa (0.28%) (Table 1).

Geographical variation in SpA. A total of 29 cases of SpA (11 men and 18 women) were detected. Mean age of patients was 47 years (range 21–78 yrs). Fourteen cases involved ankylosing spondylitis, 12 psoriatic arthritis, and 4 undifferentiated

SpA. The standardized prevalence of SpA was estimated at 0.30%, slightly higher in men than in women.

The highest prevalence was observed in Bretagne (Brest area; 0.47%) and the Sud-Est region (0.53%). Rates in other regions varied between 0.15% (Nord) and 0.34% (Midi-Pyrénées) (Figure 2). No significant difference was observed between the north [0.24% (0.13–0.37%)] and south [0.49% (0.13–1.07%)] (Figure 3 and Table 1).

DISCUSSION

Our study shows heterogeneity in the prevalence of RA. The overall prevalence was 0.31%. With higher rates in southern [0.63% (range 0.24–1.20%)] than in northern regions [0.21% (range 0.11–0.35%)], the prevalence we observed went in the reverse direction compared to the trend observed in Europe as a whole.

Some heterogeneity in the estimated prevalence of SpA was also observed between regions, with higher rates in Sud-Est (0.53%) and Brest (0.47%), but without a structured geographical trend. The overall standardized prevalence was 0.30%.

The prevalence of RA in France is similar to the 0.33% observed in Italy⁶ and in a study from the northwest of Greece⁵, and lower than in several northern European countries^{18–20} where estimates are about 0.5%. Low prevalence is

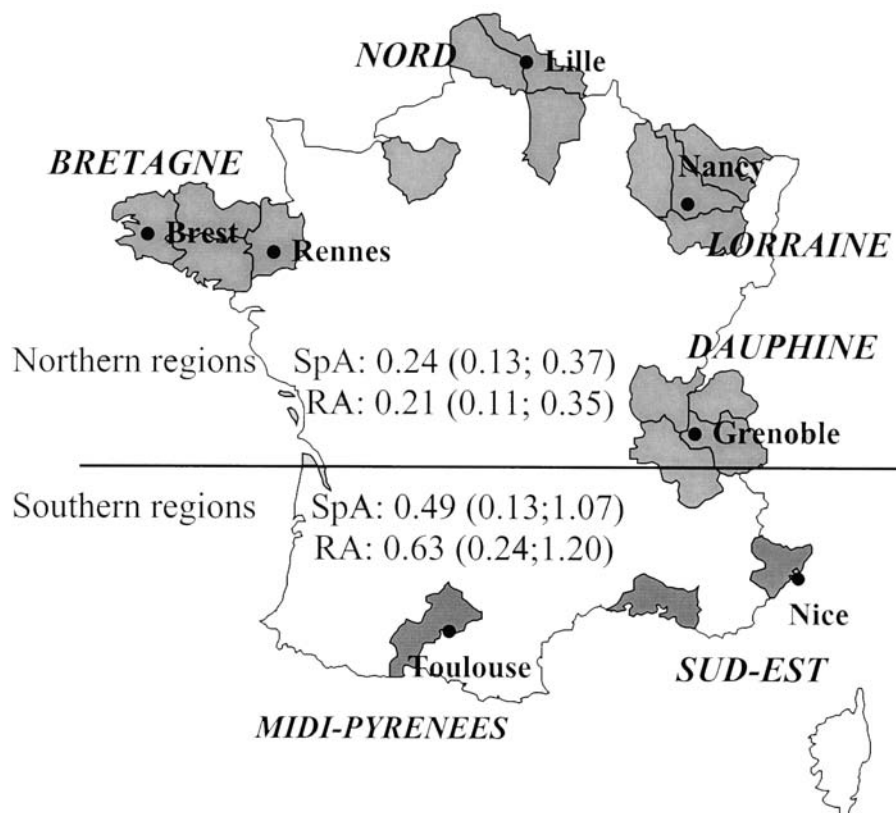


Figure 3. Regions studied to compare north with south France, and estimates of prevalence.

Table 1. RA and SpA prevalence rates in three areas of France.

Region	RA, % (95% CI)	SpA, % (95% CI)
Brest, Rennes, Lille (NW)	0.16 (0.06–0.31)	0.25 (0.12–0.43)
Nancy, Grenoble (NEa)	0.28 (0.11–0.55)	0.20 (0.06–0.43)
Toulouse, Nice (Sa)	0.63 (0.24–1.20)	0.49 (0.13–1.07)
p*	0.02	NS

* Comparison between regions.

not a consistent observation in southern Europe — our results in the south of France are close to those reported by Spanish (0.5%), Greek (0.68%), and Italian investigators (0.46%)^{7-9,21}. Discrepancies in findings may relate to methodological differences or perhaps to different time periods. Here, some interregional variations were observed, with higher rates in the South than in the North (Figure 2). The heterogeneity is striking.

Interregional variations have also been reported elsewhere, including Russia²², Taiwan²³, Scotland¹⁴, England²⁴, and Finland¹³. Genetic factors linked to important migrations can have an influence. Genetic heterogeneity in France is well known. Studies of the association of the shared epitope with RA give different results: HLA-DRB1*0401 is increased in western France²⁵, whereas the predominant allele in the south¹⁰ and the east²⁶ is DRB1*0101. The southern French

population is related genetically to southwestern Europeans who are geographically close, with a high frequency of HLA-DRB1²⁷.

The risk of developing RA is at most 50% determined by genes, and environmental factors may also contribute to the heterogeneity seen in RA, as in other disorders (principally coronary diseases in France²⁸) that have risk factors in common with RA, including smoking, hypercholesterolemia, and obesity. Smoking appears to be a major environmental factor in the context of HLA-DR shared-epitope genes²⁹. Improvement of hygiene seems likely to begin the pathological process of RA³⁰. Diet also plays a role, but no specific food has proved to be deleterious or protective³¹.

In our study, higher prevalence rates were found in some highly urbanized regions, e.g., Sud-Est and Midi-Pyrénées (with an urbanization rate between 80% and 100%), but not in the Nord region, which is the most urbanized (88.3%)³², so a direct link for this factor is difficult to prove.

Whatever the reasons, we observed that RA prevalence rates from the south of France (Sud-Est and Midi-Pyrénées) were not different from those of Spain⁷ and Italy⁸, which are geographically close.

Several mechanisms may account for this discrepancy. First, the number of cases identified in each area may not be large enough to exclude random variation. Participation rates

are inversely linked to RA prevalence rates, perhaps because patients with RA are often in search of help, discussions, and information, and may respond more readily to telephone survey studies.

Considered together, the ranges of prevalence of SpA show some variations in Europe, with some geographical differences and some correlations with the prevalence of HLA-B27. In France the global prevalence is 0.30%, in keeping with data obtained in the United States³³, China³⁴, and Scotland¹⁴, and in a population of northwest Greece³⁵. It is lower than in general population studies from Greece³⁶ and Japan³⁷.

In our study, ankylosing spondylitis and psoriatic arthritis are the most common patterns of SpA, with similar numbers of cases detected, which were close to results from Italy⁸.

The prevalence of SpA is not as heterogeneous as that of RA, and variability is observed between regions. This may be explained, at least in part, by genetic factors linked to the HLA-B27 haplotype³⁸. The population of Bretagne (Brittany) has the highest prevalence of SpA in France, and the highest proportion of the HLA-B27 haplotype (gene frequency 0.047, phenotypic frequency 0.092). In other regions values are very close (with gene frequencies of 0.034–0.037 and phenotypic frequencies of 0.066–0.072)³⁸. Other countries in which 3-fold to 6-fold interregional differences have been reported include Japan³⁷ and Taiwan²³. HLA-B27 is responsible for 30% of the SpA genetic determinism³⁹. Other genes of the major histocompatibility complex and environmental influences such as infectious processes probably play a major role in the variability that cannot be attributed to major histocompatibility complex genetic factors. In our study, the highest prevalences occurred in coastal regions.

Potential selection biases in this investigation are discussed elsewhere. They include failure to survey institutionalized people, and exclusion of those with mobile telephones^{11,12}. France-Telecom estimated that in 2001, 97% of main residences had fixed telephones. The study design also carries some risk of ascertainment bias due to respondents failing to communicate their diagnosis. However, efforts were made to inform the general population beforehand, and details of the study were announced in local newspapers before it began. The advantages of this type of telephone survey have been documented⁴⁰.

Our report completes an earlier national survey and documents interregional variations in RA in France. Prevalence differs between the north and the south, and is highest in the south of France. The many potential reasons for the heterogeneity we observed, including genetic and environmental factors, warrant further research.

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