Prevalence of rheumatoid arthritis in France – 2001

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**Running title:** Prevalence of rheumatoid arthritis in France – 2001
Background: Prevalence estimates of rheumatoid arthritis (RA) vary across Europe. Recent estimates in southern European countries showed lower prevalence rates than in northern countries.

Objectives: To estimate the prevalence rate of RA in France in a multiregional representative sample in the year 2001.

Methods: A two-stage random sample was constituted in 7 areas (20 counties) from the national telephone directory of households and by the next birthday method in each household. Patient interviewers, member of self-help groups, were trained to administer telephone surveys using a validated questionnaire for case detection of inflammatory rheumatisms, and conducted the survey under quality control. All detected cases with suspicion of RA were confirmed by their rheumatologist or by clinical examination. Prevalence estimates after probability sampling correction were standardized on age and sex (national census 1999).

Results: An average response rate of 64.7% (two stages combined) led to a total of 9,395 respondents. Standardized prevalence rates were 0.31% [0.18 – 0.48] for RA, 0.51% in females and 0.09% in males, with higher age-specific rate in the 65-74 years age-band. A geographical analysis of county clustering evidenced a significant gradient of heterogeneity across the country.

Conclusion: This national multiregional cooperative study demonstrates the interest of working in association with patients of self-help groups. It evidences similar prevalence rates to that of spondylarthropathies estimated concomitantly during the survey. It provides a reliable basis for definition of population targets for health care delivery and drug treatments.

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INTRODUCTION
The prevalence of chronic disease provides indication about the burden of a disease useful to health professionals and policy makers for health care planning. Variations of rheumatoid arthritis (RA) prevalence have been observed both in time and geographical distribution. The hypothesis of a decline of rheumatoid arthritis occurrence has been raised in countries where epidemiological studies have been conducted in previous decades, particularly in UK, and USA (1). The geographical distribution of prevalence estimates across Europe is uneven according to estimates in the past decades, varying from 0.8 to 1% in former northern countries estimates to 0.3 to 0.5% in recent southern countries estimates. Recently, a study, using an original survey method of community case detection by telephone interview conducted by patient interviewer followed by case confirmation, was conducted in Brittany, west France. It showed a 0.5% prevalence rate (2). Since then, the method was formalized, extensively tested in a nationwide survey, and its validity has been documented (3). Preliminary reports indicated that France might be in an intermediate situation within the European north-south gradient. With 60 millions inhabitants over 95 counties, a mix of ethnicities of various origin, and variance in environment and lifestyle across the country, this may lead to some heterogeneity of RA between regional areas.

The objective was first, to estimate the point prevalence of RA in France, and second, to investigate whether there was regional differences within the country.

MATERIAL AND METHOD
A nationwide multistage sample survey was conducted in 20 counties distributed among various regions and piloted in 7 investigating centres (figure 1). The survey was conducted using a validated method of telephone survey by patient interviewer (3) recruited in self-help groups and trained by professional poll staff.

Area for conducting the survey were selected on the basis of a widespread coverage of the population distribution over the country, in 20 counties grouped around 7 investigating centers. Area of high urban concentration with high rate of migratory movements like Paris were excluded from the survey.

The first stage of sampling was a random selection of numbers on the public telephone list to be dialed. Enterprise and business numbers as well as elderly institutions were excluded prior to dial, and second home when identified on phone contact to avoid redundancy.

The second stage of sampling was a random selection of adults in the household, using the next birthday method (4). Adults with age equal or over 18 in the household were listed with the answering person. Then the person with birthday date closest to the interview date was selected and invited to answer. No particular exclusion criteria were applied.

The process of case ascertainment comprised of case detection and case confirmation stages. Case detection was conducted by patient interviewers using the validated detection questionnaire (3) including 33 questions among which main items were ‘have you or have you had pain in your neck, your back or your buttocks ?’, ‘are you at present experiencing, or have you in the past experienced, pains in your joints ?’ and ‘what was the diagnosis ?’. According to this interview, any suspected arthritis patient was further called by a physician rheumatologists who screened for diagnosis with a standardised form of signs and symptoms. If the diagnosis of RA could not be eliminated, the patient’s rheumatologist physician was contacted to confirm diagnosis. Patients without rheumatologist physician were invited to the investigation centre where they undergo complete rheumatologic examination, laboratory examination and x-rays to ascertain or reject the diagnosis.
The sample size of the study was calculated on the basis of an expected low prevalence rate in some regions with as low as 0.3% to be estimated with a 20% refusal rate. Accordingly, using a Poisson distribution assumption, a number of 4000 persons contacted on the phone would provide a 95% confidence interval of 0.14 to 0.54% around 0.3% estimate.

Estimates calculation procedure accounted for the two-stage sampling procedure, i.e. the proportion of the sample in each county population and the size of the household in each county sample. Standardized estimates were calculated based on age and sex distribution as per national census data 1999 (National Census, INSEE http://insee.fr/). The 95% confidence interval were calculated using an approximation by a gamma distribution of the weighted sum of independent random Poisson variables, which provides a conservative confidence interval estimate whenever the standard population is not proportional with the study population (5). Statistical analysis was run using Sudaan® software (SAS).

RESULTS
Among the 15219 selected anonymous telephone numbers, 3.6% revealed to be business or second home. An average 64.7% of households accepted to participate in the survey and answered according to the next birthday method. Non-response rate differed significantly between counties (30.1 to 44.9%; p<0.001). A total of 9395 persons participated in the survey in Bretagne-Ouest (n=1695), Bretagne-Est (n=1750), Nord-Picardie (n=1105), Midi-Pyrénées (n=1264), Provence-Côte d’Azur (n=751), Lorraine (n=2024), Rhônes-Alpes (n=806). They were interviewed by a total of 110 patient interviewers recruited and trained in the 7 centres. Survey supervision and case confirmation was performed by 23 rheumatologists.
Table 1: Survey population and sample age and sex distribution

<table>
<thead>
<tr>
<th>Age class</th>
<th>Sample n (%)</th>
<th>Survey population n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>18-24</td>
<td>330 (9.3)</td>
<td>447 (7.7)</td>
</tr>
<tr>
<td>25-34</td>
<td>684 (19.2)</td>
<td>960 (16.4)</td>
</tr>
<tr>
<td>35-44</td>
<td>749 (21.1)</td>
<td>1 051 (18.0)</td>
</tr>
<tr>
<td>45-54</td>
<td>641 (18.0)</td>
<td>935 (16.0)</td>
</tr>
<tr>
<td>55-64</td>
<td>409 (11.5)</td>
<td>829 (14.2)</td>
</tr>
<tr>
<td>65-74</td>
<td>488 (13.7)</td>
<td>897 (15.4)</td>
</tr>
<tr>
<td>75-84</td>
<td>213 (6.0)</td>
<td>560 (9.6)</td>
</tr>
<tr>
<td>85+</td>
<td>40 (1.1)</td>
<td>162 (2.8)</td>
</tr>
<tr>
<td>Total</td>
<td>3 554 (100)</td>
<td>5 841 (100)</td>
</tr>
</tbody>
</table>
Among the 9395 persons, 36 cases were suspected of any clinical presentation of RA at the case detection stage, of which 32 were confirmed to present RA, based on clinical diagnosis at the confirmation stage, while 4 RA diagnosis were rejected at this stage. None refused to participate in the confirmation stage. Among confirmed RA cases, 2 were previously undiagnosed and confirmed by the investigating centre where they were further offered treatment. Six patients had no rheumatologist-made diagnosis and were confirmed after an outpatient visit at the investigating center. These 32 RA cases had a mean age of 61.3 (11.0) years [29.9 to 78.9], were 27 females and 5 males, with a median 12.7 years of disease duration. The overall estimate of age and sex standardised prevalence rate was 0.31 % [0.18 – 0.48]. It increased with age up to 75 years and showed a sharp decrease at older age (Table 2). With 0.51 % [0.27 – 0.82] in females and 0.09 % [0.02 – 0.20] in males, the female to male ratio was 5.66.

Table 2: Prevalence of RA according to age distribution

<table>
<thead>
<tr>
<th>Age class</th>
<th>Rate (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-24 years</td>
<td>0.00</td>
<td>.</td>
</tr>
<tr>
<td>25-34 years</td>
<td>0.13</td>
<td>0.003 - 0.47</td>
</tr>
<tr>
<td>35-44 years</td>
<td>0.11</td>
<td>0.003 - 0.39</td>
</tr>
<tr>
<td>45-54 years</td>
<td>0.67</td>
<td>0.18 - 1.46</td>
</tr>
<tr>
<td>55-64 years</td>
<td>0.44</td>
<td>0.14 - 0.89</td>
</tr>
<tr>
<td>65-74 years</td>
<td>0.79</td>
<td>0.36 - 1.39</td>
</tr>
<tr>
<td>75-84 years</td>
<td>0.10</td>
<td>0.002 - 0.36</td>
</tr>
<tr>
<td>85+ years</td>
<td>0.00</td>
<td>.</td>
</tr>
</tbody>
</table>
Estimates of standardized prevalence rates by region, ranged from 0.16 to 0.62 %, evidencing a significant gradient of heterogeneity across the country, with lower prevalence in north-west and higher prevalence in south-east area (p=0.012).

DISCUSSION
This prevalence study is a contribution to highlight the burden of RA, as called for in the frame of the Bone and Joint Decade (6). According to current estimates, one can infer from our results that some 130 000 adults within the range of 95 000 to 210 000 persons are suffering RA in France. This is a precious indication both for policy makers, professionals and patients groups.

This is the first nationwide estimate in France, showing a low observed standardized prevalence rate of 0.31 % overall conducted in a representative sample over the country. Interestingly, these results are comparable to recent estimates published in southern Europe like Spain (7), Italy (8), and Greece (9).

This estimate is obtained at relatively low cost, using a methodology that is reproducible and can be replicated in the future to assess for trends. It comes in lines with recent French estimate of a low prevalence (2) conducted with smaller sample size and wider 95% confidence interval. It is also congruent with previous estimate of a low incidence rate in France (10). A shorter disease duration, possibly related to treatment, or lesser severity in more recent cohorts of incident cases could not be an explanation since biologics were not yet introduced on the French market at the study time, and lesser severity would only influence on health care resources use, which was not considered for cases identification. It is consistent with a European north-south slightly decreasing gradient with northern estimates consistently about 0.5 % (11-13). Given the sensitivity (0.95) performances of the detection questionnaire used (3), and that specificity error has been controlled for at the confirmation stage, one could extrapolate that the true prevalence in the French population might be up to 0.326 %.

Assuming an average life expectancy of 35 years at age of 50, a mean age of incident cases of 50, a reduction of about 10 years of life duration due to RA in the estimates of 90’s (14), one could roughly extrapolated a prevalence rate to be around 0.3 % at the time. Therefore, it does not allow to conclude for any change of the disease occurrence over this period.

The survey method applied has proved cost saving, by obtaining the collaboration of patient interviewer on a voluntary basis. Heterogeneity in interviewer conduct of phone survey was controlled for by initial standard training by professional poll staff company, and continuous monitoring of their interview technique along the survey. Post-hoc quality control was performed to check for percentage of household non response according to interviewers. It is well suited for countries were telephone coverage is sufficient. In France, households telephone coverage was above 97 % in 2001 (France-Telecom personal communication).

The method allows for replication of the study in other countries, and allows for reasonably valid comparison with countries where population-based RA registry are available (UK, Norway) when such population-based registry are not available. A similar survey conducted in one of this registry area would give more insight into the validity of the method used. Such a study has been conducted in the area of the ARC Manchester registry, using a physician-administered questionnaire (15). The generalisation of the method in combination with decennial population census would also improve the comparability of the data and improve knowledge about this disease.

The survey has some limitations. Many people now have only mobile phone, particularly in young people. This was the beginning of an exploding phenomenon at the time of the survey. However, the presence of a fixed phone in the household kept being the rule.
People in institutions were not reached by the survey, which probably biases the estimates in elderly, since disabled people have more chance to be institutionalised than non disabled. This likely is one of the explanation of the low prevalence rate observed over the age of 75. The excess mortality in RA (14) also contributes to this low rate. A measurement bias could be evoked as a reason for such a prevalence rate to be an underestimate. However the procedure of clinical diagnosis and taxonomy are now well standardised. In a companion paper (16) reporting on estimate of spondylarthropathy conducted in the same survey, similar figures of this diseases category was found, surprisingly higher than expected. One explanation could be that there is a long tradition in France of making a difference in clinical practice between RA and peripheral forms of spondylarthropathies, thus leading to a better recognition of the latter and a lower prevalence estimate of the former. Some people may have ignored the diagnosis of their condition. However, the fact that the survey was able to identify and diagnose 3 out of 34 RA cases is reassuring of the capacity of the questionnaire to clearly identify true cases. Moreover the sensitivity and specificity supported the need to implement the confirmation process mandatory. This cross-sectional prevalence study includes all possible active cases and could reasonably have counted patients in remission, since the questionnaire addressed both current and past manifestations of the disease, as well as diagnosis labelled in the past. Therefore, it can be considered a cumulative prevalence (1), which has more utility to assess geographical differences, while point prevalence of currently active disease may be more useful to plan health care provision, considering only those patients in current need of care. The statistical power of this investigation was set to allow regional comparison based on a 0.14-0.54 confidence interval estimate. Our findings show a significant trend at the county level (17). The difference observed may be related to small number of cases observed and sampling variations, although significant heterogeneity has been recently reported within Finland (18). While a prevalence study provides an estimate of the disease frequency, specific study designs are required to investigate the role of factors on the disease development like smoking habits, oral contraceptive, diet, climate or ethnicity, so as to avoid ecological fallacy, i.e. any apparent correlation of some overall level of population exposure with disease occurrence rate across counties in France, or across countries in Europe.

What this study does not tell is detailed information about the severity distribution of the disease, which is needed to identify the profile of severe patient deserving more aggressive therapy like recent biologic agents. Given the low prevalence rates, population studies do not fit such questions, although it increases the chance to include mild disease patients. Other study designs are required. But it indicates that there is no variation across the country, which is a rationale to distribute resources equally across the country for health care of RA.
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Figure 1: Process of sampling (random selection of telephone numbers and random selection of adults in the households) and case ascertainment (case detection and case confirmation stages)

**First step**
Random selection of households telephone numbers (n=15,219)

**Second step**
Exclusion of second home and place of work
Random selection of adults in households by next birthday method (n=9,395)
Case detection by patient interviewers using a validated questionnaire (detection 1)

**Third step**
Suspected RA patients were called by rheumatologists (detection 2) (n=36)

**Fourth step**
Patient’s rheumatologist physician contacted (confirmation 1) (n=30)
Patients without rheumatologist physician were invited to the investigation centre (confirmation 2) (n=6)

Rheumatoid arthritis confirmed (n=32)
REFERENCES


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