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The incidence of rheumatoid arthritis in Spain: results from a nationwide primary care registry

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Objective. To estimate the incidence of early arthritis (EA) and of RA in adults (>16 yrs) in Spain.
Methods. Primary care physicians were instructed in the detection of new cases using a checklist. All cases were evaluated at EA units (EAUs) within 15 days of detection. ACR criteria for the classification of RA were assessed every 6 months thereafter.
Results. In an area covering 4 342 378 inhabitants over the age of 16 yrs, 2467 patients were referred to the EAU, of whom 1063 fulfilled EA criteria (43.1%). After 6 months, 362 patients fulfilled RA criteria. The estimated annual incidence of EA was 25/100 000 population (95% CI: 23, 26). The annual incidence of RA was 8.3 cases/100 000 (95% CI: 7.5, 9.2): 11.3/100 000 in women (95% CI: 10.0, 12.8), and 5.2/100 000 in men (95% CI: 4.3, 6.3). The incidence of RA increased with age in both sexes. At the 6 months' assessment, 187 (51.7%) of the patients with RA were RF positive. The presentation of RA was mainly polyarticular ($n = 268$; 74.0%). There were 701/1063 patients with EA who did not fulfil RA criteria by 6 months after the first rheumatologist visit. If all cases of undifferentiated arthritis ($n = 118$; 17%) became RA, the incidence would be in the range of 10 cases/100 000 population.
Conclusions. RA incidence in Spain is in the lower range of published data. The incidence of EA is about three times that of RA.

Key words: Incidence, Arthritis, Rheumatoid, Population studies, Epidemiology, Early diagnosis, Primary care, Registries, Cohort studies, Disease occurrence.

Introduction

Knowledge of the incidence of chronic diseases—especially those with devastating outcomes without proper treatment, as in the case of RA—is pivotal in the allocation of resources for disease management and prevention. The reported annual incidence rates of RA vary between 20 and 50 cases per 100 000 population in North American and Northern European countries [1–6]. The few studies conducted in Southern European countries suggest a relatively lower occurrence of the disease [7, 8].

Measuring disease incidence generally implies the establishment of disease registries, a task that requires the involvement of all partners in the care of the target disease. Most RA registries have been established in highly developed areas or nested within epidemiological cohorts with well-established limits [2, 9].

Spain provides an appropriate setting for epidemiological and collaborative studies in the field of rheumatology, as was initially shown by the EPISER study (National Survey on the Prevalence of Rheumatic Diseases in Spain) [10], a national health survey carried out in 1999–2000, as well as by many other nationwide arthritis studies, whose results have been widely published [11–13]. Data from the EPISER study show an RA prevalence rate of 0.5% (95% CI: 0.2, 0.8%) in Spain [14], which is in the lower range of European countries for which these data are available, and is close to that of other Southern European countries [15]. There is no information on the incidence of RA in Spain, and data from other Southern European countries are scarce and retrospective in nature, as shown by Alamanos in a recent systematic review of published data [15].

In November 2004, the Spanish Society of Rheumatology (SER) launched a project aimed at establishing early arthritis units (EAUs) in rheumatology clinics throughout Spain to ensure early detection and appropriate clinical intervention in patients with early arthritis (EA): the SERAP project (*Evaluación de un Modelo de Gestión de la Artritis*—Evaluation of a Model for Arthritis Care in Spain). An important first step in SERAP was to estimate the workload of the EAU; this is, to estimate the incidence of EA and RA in Spain. Knowledge of the incidence of the disease in Spain is crucial in determining the appropriate size of the EAU. It also provides important epidemiological information that is currently lacking and that may help to better comprehend the distribution of the disease worldwide.

Subjects and methods

Setting

The Spanish population of over 40 million inhabitants is universally covered by publicly financed health care, with ~10% of the population receiving care through private health insurers. A health care area consists of several primary centres and one or more reference hospitals to which complex and severe illnesses are referred. A health area manager is responsible for the organization of the primary care centres as well as the organization of the area hospitals, where most rheumatology units are located. This structural network provides an efficient system that facilitates the implementation of coordinated studies between primary and specialist care by delimiting the population catchment area.

EAUs

The SERAP project was launched in November 2004 by the SER in 36 reference hospitals with rheumatology departments. The requirements for the implementation of an EAU in any given department were to guarantee that patients with suspected EA would be seen within 15 days of the initial primary care visit, to hold a session on the use of standardized materials, and to provide formal training to the primary care physicians involved in the project. The SER provided all participating units with specific instructional materials and referral protocols.

Participating centres, and thus the EAU, were selected according to a convenience sample to ensure geographical representativeness of the country. A primary care based registry

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was established in all 36 participating EAUs. All cases registered during the first year of establishing the registry became part of a prospective EA cohort.

Primary care centres

Each participating EAU selected 5–10 primary care centres by convenience sampling, taking into account the primary care physicians' previous research experience in conjunction with the rheumatology unit or, at a minimum, with the referral centre. The number of centres selected depended on the size of the area they covered, with the aim of achieving the pre-determined minimum 2 million population catchment area needed to estimate the incidence of RA accurately. In each centre, all primary care physicians were invited to participate. Those who agreed to participate were trained using standardized materials and requested to send all patients with suspected EA to the EAU within a maximum of 15 days, according to pre-established definitions and supported by specific referral protocols and materials. Each primary care physician was in charge of a finite and delimited population area.

Case definition

Suspected EA was defined as any patient presenting for the first time within the last half year with one or more of the following symptoms: (i) more than one swollen joint; (ii) pain in MCP or MTP joints; (iii) current morning stiffness in hands for >30 min. Symptoms had to be present for longer than a month and for less than a year. These three items were included in the referral forms and checked accordingly by the primary care physician. The same items were then checked by the EAU rheumatologist. Only patients fulfilling at least one of the referral criteria in the opinion of the rheumatologist were followed in the EAU. A primary care physician could refer a patient to the EAU as many times as was considered necessary.

An incident RA case was defined as any patient over the age of 16 yrs in whom the first joint manifestations occurred no more than 6 months before the referral from primary care. The case definition included fulfilling the 1987 ACR classification criteria for RA [16] within the first 6 months of follow-up.

Case recruitment

In addition to all suspected EA cases detected by the participating primary care physicians, all of whom were sent as per protocol to the EAU, any other EA case detected in emergency rooms, at other specialist clinics or at the rheumatology clinic by any other means, were recruited by the EAU. All professionals in the area who dealt with RA patients were made aware of the project during the recruitment year. Of particular importance, patients had to live in the population area covered by the participating primary care physician in order to be counted as a case.

Data collection and ethical issues

The rheumatologists recorded sociodemographic and clinical characteristics of all patients included in the EAU who had suspected EA. The data collected included the HAQ, CRP, ESR, RF and pattern of arthritis presentation, e.g. whether it was acute or subacute, whether it affected many or few joints (oligo or polyarticular) or presented special debut patterns, such as polymyalgic or extra-articular onset. The diagnoses of all referred patients were reviewed every 6 months by the unit rheumatologist to confirm whether they fulfilled RA criteria or other disease criteria. Data were collected on paper data collection forms and then entered into a web-based application. The database underlying this application complied with the Spanish regulations for data protection and research.

Patients were required to give written informed consent to participate in the study upon arrival to the EAU. The study was performed according to the principles of the latest Helsinki recommendations, the International Guidelines for Ethical Review of Epidemiological Studies (Council for the International Organizations of Medical Sciences-CIOMS-Geneva, 1991) and the recommendations of the Spanish Society of Epidemiology. The study protocol was reviewed and approved by the Ethical Committee of the IMAS.

Statistical analysis

One year cumulative incidence rates of EA and RA with 95% CIs were estimated based on the number of new cases occurring in the population covered by the participating primary care physicians, using direct standardization. Thus, the population denominators were the total population, and the population by sex and age group, assigned to the health areas of the participating primary care physicians ($n = 4\,342\,378$). The recruitment period in each EAU was 1 yr. The follow-up time to confirm a diagnosis of RA in any patient with suspected EA was 6 months. Results are presented by EAU, age group and gender. Comparisons between RA cases and non-cases regarding baseline characteristics and clinical factors were tested by the chi-square test, Wilcoxon–Mann–Whitney's U-test or Student's *t*-test, depending on the distribution of the corresponding variable. The association between different factors present at the visit and a diagnosis of RA after 6 months was measured by odds ratios from univariate logistic models. All the analyses were performed with STATA (StataCorp. 2005, Stata Statistical Software: Release 9.2 College Station, TX, USA: StataCorp LP).

Results

At the end of the inclusion period a total of 28 EAUs were suitable for evaluation. The data from eight EAUs were not used for the estimation of RA incidence due to protocol infringements in case recruitment, absence of a reliable denominator by primary care physician, or because they had entered the study after half the recruitment period had elapsed. The population covered by the rest of the participating primary care physicians was 4 342 378 adults. During the inclusion year 2467 patients with a suspicion of EA were referred to the EAUs. Most of these referrals ($n = 2057$; 83.4%) came directly from the primary care centre, in accordance with the protocol, but additional patients presented at the EAUs via emergency rooms ($n = 83$; 3.36%) or other specialists ($n = 229$; 9.28%). A total of 1063 patients (43.1%) fulfilled one or more referral criteria according to the EAU's rheumatologists, and were thus considered as true suspected cases of EA. The estimated annual incidence of suspected EA was 24.5/100 000 population (95% CI: 23.1, 26.0). The health area had no clear effect on the rate of suspected cases ($P > 0.05$ from analysis of variance).

After 6 months of follow-up, 362 patients (37.1%) were diagnosed with RA according to the 1987 ACR criteria, 69.3% of whom were women. Thus, the annual incidence of RA in the Spanish population was 8.3 cases per 100 000 adults over the age of 16 yrs (95% CI: 7.5, 9.2). In women, the incidence was 11.3 cases/100 000 (95% CI: 10.0, 12.8), and in men, it was 5.2 cases/100 000 (95% CI: 4.3, 6.3). The incidence of RA increased with age in both sexes (Table 1).

The clinical and sociodemographic characteristics of the patients finally diagnosed with RA are shown in Table 2. Notably, within 6 months of the initial assessment, only 187 (51.7%) of the patients with RA were RF positive. The presentation of RA was mainly polyarticular ($n = 268$; 74.0%). Onset was oligoarticular in 84 patients (23.1%) and polymyalgic in 10 additional ones (2.8%). No patient classified as RA in the 6-month interval had initially presented with extra-articular manifestations of RA. There were some gender differences in

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TABLE 1. Estimates of annual RA incidence per 100 000 population over the age of 16 yrs in Spain, by age and sex

	Women		Men	
Age	New cases	IR (95% CI)	New cases	IR (95% CI)
17–20	4	3.0 (1.1, 8.1)	0	0.0 (–)
21–30	16	4.2 (2.6, 6.8)	5	1.2 (0.5, 3.0)
31–40	34	8.1 (5.8, 11.3)	14	3.2 (1.9, 5.3)
41–50	51	13.8 (10.5, 18.2)	12	3.2 (1.8, 5.6)
51–60	54	18.3 (14.0, 23.8)	20	6.9 (4.5, 10.7)
61–70	35	14.5 (10.4, 20.2)	20	9.1 (5.9, 14.1)
>70	57	15.3 (11.8, 19.8)	40	15.8 (11.6, 21.5)
Total	251	11.3 (10.0, 12.8)	111	5.2 (4.3, 6.3)

IR: Incidence rate per 100 000 population over the age of 16 yrs.

TABLE 2. Characteristics of new RA cases recruited at EAUs during the study year, by sex

	Men ($n=111$)	Women ($n=251$)
Age, mean ± S.D.	60 ± 17*	54 ± 17
RF positive, *n* (%)	52 (48)	135 (56)
HAQ score, mean + S.D.	1.3 ± 0.8	1.5 ± 0.8
Ever smoker, *n* (%)	81 (73)	68 (27)
Current smoker, *n* (%)	31 (28)***	47 (19)
RA extension—polyarticular, *n* (%)	89 (80)**	179 (71)
CRP ESR, median (IQR)	10 (3–27)	7.2 (3–21)
ESR, median (IQR)	28 (16–51)	32 (17–54.5)

*$P<0.01$; **$P<0.05$; ***$P<0.001$. IQR: interquartile range.

the presentation of RA: men were older and more frequently presented with polyarticular disease (Table 2).

There were 701/1063 patients with EA who did not fulfil RA criteria 6 months after the first visit. Diagnoses at the 6-month visit are shown in Table 3. Patients with undifferentiated arthritis may yet experience a shift in diagnosis over time and become true RA. The EA clinics identified as many as 165 patients with inflammatory and autoimmune rheumatological conditions other than RA. Table 4 shows the distribution of characteristics at the first visit for patients with RA and without RA after 6 months. Patients with RA were older on average, and scored worse on the HAQ. The clinical presentation of RA patients was more frequently polyarticular than in non-RA patients, and data on disease activity, like CRP and ESR, were significantly higher in RA than in non-RA patients. Curiously, the proportion of women was larger among non-RA patients than among those fulfilling RA criteria after 6 months of follow-up. The prevalence of smokers was no different between the two groups and belonging to a low socioeconomic level [17] was not associated with RA.

Discussion

Our study helped us to staff and equip the EAUs adequately according to the expected numbers of patients to be attended. It also provides further evidence that RA incidence is lower in Southern European than in Northern European countries.

As Wiles *et al.* [18] pointed out, estimating the incidence of RA confronts us with two major problems, both of which are clearly time dependent. The first problem is the delay between symptom onset and the medical consultation. To increase primary care physicians' awareness of arthritis and to reduce the delay in diagnosis and treatment to a minimum, we established a system that included training and commitment of primary care physicians to use a 3-item checklist to refer patients with suspected EA to an EAU. The checklist was based on previous experiences to make it as easy and sensitive as possible [19–21]. Despite many arguments that the isolated morning stiffness is not a good isolated criterion, it allowed by itself the detection of a case of RA. All referred patients were then assessed by a rheumatologist within 15 days to confirm whether the patient might truly have EA. The SERAP programme identified new RA cases within 6–18 months of symptom onset, a delay that is much shorter than previously estimated in our setting [22].

TABLE 3. Diagnoses of patients who did not fulfil RA criteria 6 months after first visit

Diagnosis	*n* (%)
OA	135 (19.3)
Undetermined	132 (18.8)
Undifferentiated arthritis	118 (16.8)
PSA	49 (6.7)
Crystal/gouty arthritis	45 (6.4)
ReA	29 (4.1)
Fibromyalgia	26 (3.7)
Carpal tunnel syndrome	22 (3.1)
SLE	20 (2.8)
Tendonitis	19 (2.7)
AS	15 (2.1)
Polymyalgia rheumatica	12 (1.7)
Arthralgia *sine* arthritis	9 (1.3)
SS	7 (0.9)
Self-limiting polyarthritis	6 (0.8)
Undifferentiated SpA	6 (0.8)
Traumatism, including stress fracture	4 (0.5)
Para-neoplastic arthritis (one lymphoma, three leukaemia)	4 (0.7)
Hyperlaxity	3 (0.4)
Sympathic reflex dystrophy	3 (0.4)
Hepatitis C virus infection	3 (0.4)
Behçet's syndrome	2 (0.3)
Hyperthyroidism	2 (0.3)
Laboratory abnormality (1 RF+, 1 B27+, 1 CPK increase)	2 (0.3)
MCTD	2 (0.3)
Palindromic rheumatism	2 (0.3)
RP	2 (0.3)
Sarcoidosis	2 (0.3)
Anti-synthetase syndrome	1 (0.1)
Coeliac disease	1 (0.1)
Chronic mononeuropathy	1 (0.1)
CREST syndrome	1 (0.1)
Dermatopolymyositis	1 (0.1)
Diabetes	1 (0.1)
Dupuytren	1 (0.1)
Eosinophilic fasciitis	1 (0.1)
Erythema nodosum	1 (0.1)
Ganglion	1 (0.1)
Jaccoud's arthropathy	1 (0.1)
Juvenile chronic arthritis	1 (0.1)
Overlap syndrome	1 (0.1)
Psychiatric disease	1 (0.1)
RS3PE	1 (0.1)
SAPHO	1 (0.1)
Scleroderma	1 (0.1)
Vasculitis	1 (0.1)
Total	701 (100)

The second problem in estimating RA incidence is that the case definition, according to the 1987 ACR criteria, depends on the time elapsed between symptom onset and assessment of RA criteria, and on how the criteria are applied [18]. The difference in the time it takes to confirm a diagnosis might be a reason why our estimate, 8 cases per 100 000, is lower than those from other Southern European countries [15]. Guillemin *et al.* [8] estimated the incidence of RA in the Lorraine district in France at around 10 cases per 100 000 [8], and Drosos, in Greece, estimated an RA incidence of 20 cases per 100 000 [7]. Both studies were retrospective searches of medical records applying the ACR 1987 criteria for RA. The French study lacks information on disease duration at diagnosis, but the Greek study shows mean disease duration, as of the incidence date, of 4.8 yrs, which is much more advanced disease than in our registry. If all EA cases in our study with undifferentiated arthritis after 6 month follow-up were to become RA cases in the next few years, the incidence might be around 11 cases per 100 000; still within the low range limit.

To ensure optimal estimate of the incidence, we made two decisions. One was to recruit cases, not only through the established clinical pathway (primary care to specialized care),

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TABLE 4. Characteristics of 1063 early arthritis patients upon entry to EAUs, by fulfilment of RA criteria after 6 months

	RA ($n=362$)	Non-RA ($n=701$)	Odds ratio (95% CI)
Women, *n* (%)	251 (69)	549 (78)	0.63 (0.47, 0.83)*
Age, mean ± S.D.	55 ± 16	49 ± 15	1.03 (1.02, 1.03)†
Socioeconomic level, *n* (%)			
High	17 (7)	12 (2)	Referent
Middle	197 (77)	468 (85)	0.30 (0.14, 0.63)*
Low	42 (16)	73 (13)	0.41 (0.18, 0.93)*
Educational level			
Less than primary	57 (16)	88 (13)	Referent
Only primary	156 (43)	231 (33)	1.04 (0.71, 1.54)
Secondary studies	113 (31)	295 (42)	0.59 (0.40, 0.88)
University	36 (10)	87 (12)	0.64 (0.38, 1.07)
Ever smoker, *n* (%)	149 (42)	281 (42)	0.98 (0.76, 1.28)
Current smoker, *n* (%)	78 (22)	173 (26)	0.80 (0.59, 1.08)
HAQ, mean ± S.D.	1.4 ± 0.8	0.8 ± 0.7	2.90 (2.40, 3.50)†
RF positive, *n* (%)	187 (53)	77 (12)	8.55 (6.23, 11.74)†
Form of disease at onset, *n* (%)			
Oligoarticular	84 (23)	296 (42)	Referent
Polyarticular	268 (74)	381 (54)	2.48 (1.86, 3.31)†
Polymyalgic	10 (3)	19 (3)	1.85 (0.83, 4.14)
Extra-articular	–	4 (1)	–
CRP (IV/ml), median (IQR)	7.7 (3–22)	3.1(1–5.8)	1.50 (1.37, 1.65)†,a
ESR (mm/h), mean ± S.D.	37 ± 25	21 ± 18	1.03 (1.03, 1.04)†
Criteria for referral according to primary care physician, *n* (%)			
More than one swollen joint	294 (81)	546 (78)	1.23 (0.89, 1.69)
Pain in MCP or MTP joints	304 (84)	597 (85)	0.91 (0.64, 1.30)
Morning stiffness	237 (65)	477 (68)	0.89 (0.68, 1.16)

*$P<0.05$; †$P<0.001$; aFrom a logistic model in which the dependent variable is the logarithm of CRP. IQR: interquartile range.

but also allowing other sources of cases. As a matter of fact, this approach was found to be decisive in nearly 10% of the suspected cases, in which patients were detected via emergency rooms or had visited rheumatologists or other specialists directly. This strategy involved making all those caring for RA patients aware of the EAU programme. We found no clear effect of the area in the estimation of suspected cases, which suggests that recruitment was homogeneous between areas. Of course, a case ascertained from other sources could only be counted if it was truly included in the catchment area. The second decision was to include in the population denominator only the population covered by the primary care physicians who had committed explicitly to the programme and had been adequately trained. Nevertheless, the area covered by SERAP is almost 10% of the Spanish population over 16 yrs of age.

It might also be argued that our numbers are slightly underestimated because ~10.5% of the population in Spain is covered by private insurance [23]; such patients, if they have RA, may not have been captured in our study, since the setting was the public health system. However, even if the estimated incidence was increased by 10% to account for patients who do not use public centres, the incidence would still be under 10 cases per 100 000.

In any case, it remains unclear why the incidence of RA is so low in Southern Europe. Studies of genes influencing RA expression and severity are scarce in Spain, and there is a wide heterogeneity among European countries, as Balsa *et al.* [24] showed in his analysis of multicase RA families. PTPN22 and the shared epitope, for instance, are more frequent in Northern than in Southern Europe [25]. Thus, genes encoding severity of RA have a lower prevalence in Spain than in other developed countries in Northern Europe, which has been suggested as an explanation for the lower prevalence and severity of RA in Southern Europe compared with Northern populations [26, 27]. The distribution of other known risk factors for RA does not seem to provide a better explanation. For instance, low educational level has been proposed as a risk factor for the development of RA [28, 29]. However, this would support a higher rather than a lower incidence in Southern Europe as compared with Scandinavian countries, where large segments of the population have a college education. Also, EA cases were considered in the risk assessment, and low educational level may be a risk factor for other diseases presenting with arthritis, like lupus [30, 31]. Moreover, Spain and most Southern European countries have a high prevalence of smoking. This would also argue against a low incidence [32–36], although our results did not show a clear difference between those who were diagnosed with RA and those who were not with regard to smoking behaviour. But this may also be due to the low prevalence of the shared epitope, whose interaction with tobacco is needed to trigger the citrullination of proteins and subsequent onset of RA [37, 38]. On the other hand, the age at onset of the RA patients who smoked was younger than the age of those who were non-smokers (50 ± 14 *vs* 58 ± 17; $P<0.001$), which would support a relationship between smoking and severity of presentation. It may also be that the Mediterranean diet or other factors related to the geographical and cultural setting might have a larger impact on aetiology than expected [39–42].

In conclusion, the incidence of RA in Spain is slightly lower than in Northern European and North American settings, but is probably within the range of what has been shown in other Southern European countries. Our results support the gene-environment aetiological hypotheses for RA that are currently advocated. Knowledge of the incidence of RA and EA has also helped us to allocate health care resources appropriately and to guarantee efficient organization of the EAUs.

Rheumatology key messages

- The incidence of RA in Spain is in the lower range of the incidences published.
- This is the first study to estimate the incidence of EA, as well as the cluster of diseases presenting as EA, in a Southern European country.

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