# The Oslo experience with arthritis registries

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**ABSTRACT**

*The Oslo experience with early rheumatoid arthritis (RA) is based on studies performed within the setting of a register of RA patients and of the longitudinal follow-up of patients with early RA. This article discusses some relevant issues for research on early arthritis: whether the current RA classification criteria are appropriate, the shift in incidence toward elderly patients, and the heterogeneity of the disease. Our data clearly show that 3 of the items of the classification criteria are infrequently fulfilled early in the disease and that RA most frequently starts after the age of 60. Our data also suggest that disease onset may be defined either as symptom onset or as when the classification criteria are fulfilled. The choice between these 2 options does not seem to influence the longitudinal results.*

## Background for arthritis research in Oslo

A wide spectrum of areas serves as targets for epidemiological research in patients with arthritides, e.g. criteria, occurrence, etiological factors, mortality, and morbidity. During the last 10 or 15 years, several major epidemiological advances in rheumatoid arthritis (RA) have been achieved, including revised classification criteria for RA (1), core sets for assessment of disease activity (2-4), response criteria for the assessment of drug efficacy (5, 6), and agreement on a core set of measures for longitudinal observational studies (7). Another important advance is the evidence for the importance of early intervention with disease-modifying therapies in RA (8-15).

From studies on reactive arthritis in the late 1980s and early 1990s (16), we knew that the county of Oslo could serve as a reliable setting for epidemiological studies in rheumatology. One challenge in establishing true early arthritis clinics is to continuously collect data during routine care when patients are seen for the first time – or to have a clinical research facility attached to the clinical unit with the capacity to perform immediate on-demand data collection. We succeeded in this approach in an earlier study focusing on patients being referred with early arthritides where reactive arthritis was the suspected diagnosis, but we have not been able to do this with regard to the entire spectrum of arthritides.

The Oslo approach has been to establish a register of all patients with RA diagnosed according to the American College of Rheumatology (ACR) criteria and to perform follow-up studies of selected cohorts of patients (17-19). RA was selected as the focus of our research because the setting of Oslo provided opportunities for establishing a register of RA patients that could be assumed to be representative of the entire underlying patient population. Furthermore, the setting would provide longitudinal follow-up of the patients. The objective of this report is to present some data and experiences from the Oslo RA register (ORAR) and the European Research on Incapacitating Disease and Social Support (EURIDISS) study that are relevant to an increased understanding of early diagnosis and therapy in RA.

## Materials and methods

*The ORAR*

The work on ORAR started in 1992 and the register was established per January 1st, 1994. Inclusion criteria were a diagnosis of RA (1) and a residential address in Oslo (17). Patients with juvenile arthritides, i.e., disease onset before the age of 16, were excluded. On January 1, 1994 Oslo had 477,781 inhabitants, of whom 356,486 were between 20 and 79 years of age. Rheumatology service in Oslo was provided by two hospitals: the Department of Rheumatology at Diakonhjemmet Hospital had responsibility for the care of rheumatic patients from the entire city of Oslo, with short waiting lists and

good access to specialized care. The major responsibility of Oslo Sanitetsforening Rheumatism Hospital was as a referral center for the whole country, especially focusing on childhood arthritis and complicated surgery for rheumatic diseases. To ensure the complete registration of patients with RA with a residential address in Oslo, we identified all patients who had been treated in Diakonhjemmet Hospital and Oslo Sanitetsforening Rheumatism Hospital. In 1994 no full-time rheumatologists in private practice were working in Oslo (17).

Enrollment in the register was based on an ascertainment of the RA diagnosis by reviewing the hospital charts. Disease onset was recorded as the date when at least 4 out of 7 classification criteria of RA (1) were fulfilled. By January 1, 1994, 1552 RA patients were included in the register. Of these 1552, 1333 were between the ages of 20 and 79 (17). The register has been updated annually by enrolling new patients with RA who were referred to the Department of Rheumatology at Diakonhjemmet Hospital. Approximately 1,625 living patients are currently enrolled.

We assumed that almost all patients with RA in Oslo had been treated in either Diakonhjemmet or Oslo Sanitetsforening Rheumatism Hospitals, i.e., that the register should be representative of the underlying patient population in the county of Oslo. This assumption was tested in a population survey (20). A 4-page questionnaire was mailed to 10,000 randomly selected individuals between the ages 20 and 79. Of 5886 respondents, 158 patients (2.7%) reported having RA diagnosed by a physician (n = 107) and/or according to their own opinion (n = 142). RA was confirmed in 35 of these 158 individuals (20). All patients with self-reported RA were checked against the ORAR. Thirty of the 35 patients with confirmed RA were identified in the register, and the remaining 5 patients were diagnosed after a clinical, laboratory, and x-ray examination. Thus, 5 of the 35 RA patients identified from a population survey of 10,000 random subjects between ages 20 and 79 were not enrolled in the register. From this result, we have assumed that the completeness of the register is about 30/35, i.e., 85% (17).

Non-respondents in surveys are another source of potential left censorship. In some of the studies from the ORAR non-respondents were older, but generally there have been no major differences between non-respondents and respondents when data have been collected.

Several waves of data for patients in the ORAR have been collected since 1994. Surveys were mailed to the entire patient population in 1994, 1996 and 2001. The response rates in these mail surveys were 60-70%. The first comprehensive clinical examination of patients born in 1926 or later, i.e., not older than 70 years, was performed in 1996-1997 with a subsequent 2-year follow-up (21, 22). The clinical measurements were obtained by research nurses with specific training under the supervision of rheumatologists. It seems that the rate of respondents has been decreasing over the last years. There is also a tendency toward a lower non-respondent rate in the younger age group than that seen at the time of the first assessments. Other researchers in Norway performing large-scale patient surveys have also observed this trend (A. Finset, personal communication). The reason may be that patients, as well as the population in general, are approached by marketing surveys with increasing frequency. Another possible explanation could be that the patients have fewer health complaints and are thus less motivated to participate in research.

*The EURIDISS study*

This study was part of an international collaborative research effort, with coordinating centers in Nancy, France and Groningen, The Netherlands. The Norwegian patient sample comprised 238 individuals with a short disease duration of RA. Inclusion criteria were age 20 to 70 years, disease duration of 4 years or less, and a diagnosis of RA according to the ACR classification criteria, confirmed at baseline examination by a rheumatologist (23). Of the 326 consecutive patients invited, 268 (82%) were willing to participate. Thirty of these 268 patients were excluded (for example, 21 did not meet the ACR criteria). At baseline the mean age was 51.9 (SD 13.0, range 22-70) years and mean disease duration was 2.2 (SD 1.27) years. Baseline assessments (n = 238) were succeeded by follow-up at 1 year (n = 227), 2 years (n = 216) and 5 years (n = 182). Non-participants were not followed up at a later stage. The numbers of patients who completed data collection at each time point were: 1992 (baseline): 238; 1993: 227; 1994: 216; and 1997: 182 (24).

The 182 patients (76.5% of the enrolled patients) who completed the follow-up at 5 years had the following baseline characteristics: mean disease duration 2.2 years, mean age 50.8 years, 74% females, 69% IgM rheumatoid factor (RF)-positive by enzyme linked immunosorbent assay (ELISA). The mean (SD) age of the completers was lower than that of the non-completers at baseline, i.e. 50.8 (12.9) versus 55.7 (12.6) years, whereas other demographic characteristics were similar (24).

The data collection at each time point was comprehensive, covering the recommended end points for longitudinal observational studies (7).

**Selected results**

*When does RA most frequently start?*

The ORAR has been used to estimate the incidence and prevalence of RA in the county of Oslo. The calculation of prevalence was based on the number of RA patients identified in the register as the numerator, with the population number in the denominator, corrected for the assumed incompleteness of the register. We found the prevalence to be 0.4-0.5% in the 20 to 79 age group, a remarkably similar value to what was found in the population survey (17).

Cohorts of RA patients in the ORAR with disease onset in 1988-1993 were used to compute the annual incidence of RA. A very similar number of RA patients was identified each year, and the average incidence was found to be 25 per 100,000 in the 20-79 age group (18). We further confirmed findings from the Norfolk Arthritis Register indicating that the incidence increases

**Table I.** Two-year progression of the modified total Sharp score in patient subgroups with different disease duration at baseline.

| | All patients (n = 183) | 0-1 year (n = 35) | 1-2 years (n = 40) | 2-3 years (n = 46) | 3-4 years (n = 62) | P-value * |
|---|---|---|---|---|---|---|
| Mean increase in the modified Sharp score (SD) | 6.3 (9.6) | 5.7 (8.2) | 7.5 (11.0) | 5.4 (9.5) | 6.7 (9.5) | 0.74 |

*ANOVA

with age and reaches a plateau at around age 60 (18, 25). This increase is relatively stronger for males. Thus, the female: male ratio for new cases of RA is lower in older than in younger patient populations. The implication of this finding is that nearly half of the new cases of RA can be expected to be seen after age 60.

*Disease course and outcome in relation to disease duration*

In the EURIDISS cohort, the progression rate of radiographic damage was compared across subgroups of patients with RA defined according to the disease duration at the baseline examination. In 183 patients (77%), x-rays of the hands were taken at baseline and after 2 years and were scored by one observer using the Sharp/van der Heijde method. Only the total modified Sharp score was available in these analyses.

No difference was observed across the cohorts (Table I), indicating that the progression is linear and independent of disease duration early in the disease. These patients were treated according to standard recommendations and opportunities in the 1990s.

Cross-sectional data examining the association between disease duration and health status from the ORAR revealed no major differences in health status and disease activity measures in subgroups of patients with different disease durations (data not shown).

*Relevance of classification criteria in early RA*

The RA classification criteria include 7 items, of which 4 must be met to classify a patient as having RA (1). These criteria were developed primarily for research use, but are to some extent also used in many clinical settings to assist in the diagnosis of RA. Four of the criteria are related to disease activity (morning stiffness ≥ 45 minutes, arthritis in at least 3 areas, symmetric arthritis, and arthritis of hand joints), whereas 3 other criteria are more directly related to disease severity (rheumatoid nodules, RF, radiographic bone erosions). These latter 3 items are more likely to develop with time.

We used the ORAR setting to examine the proportion of RA patients with different disease durations who cumulatively fulfilled the various items, i.e., the items had not necessarily been fulfilled exactly at the time of examination. The ORAR patients born in 1926 or later underwent a complete clinical examination in 1996-1997, including assessment of whether they fulfilled the criteria items. Of 894 eligible patients, 636 (71.1%) underwent examination. Attending and non-attending patients did not differ in age, sex, disease duration and seropositivity. The numbers of patients with different disease duration were: Less than 1 year n = 17, 1-2 years n = 33, 2-3 years n = 41, 3-4 years n = 49, 4-5 years n = 42, > 5 years n = 454. These sub-groups did not differ regarding fulfillment of the 7 individual items of the ACR classification criteria, except for radiographic abnormalities, which were related to disease duration. In patients with less than 1 year's disease duration, 35.3% had erosions; this proportion increased to 76.7% in patients with a disease duration of more than 5 years. The first 3 items were fulfilled by 81.6-100% of the patients in all subgroups (Table II).

A similar approach was used in the EURIDISS cohort. The patients were rigorously assessed at baseline with regard to the current fulfillment of the items in the ACR classification criteria. Comparisons were performed across subgroups of patients with a disease duration of 1-4 years. The number (%) of patients with a disease duration of less than 1 year was 46 (19.3%), between 1 and 2 years 47 (19.7%), between 2 and 3 years 66 (27.7%), and more than 3 but less than 5 years (33.2%).

Table III shows the numbers (percentages) of patients fulfilling the ACR criteria in groups with varying disease duration at baseline examination. "Swelling in 3 areas" was more prevalent in patients with a short disease duration. Radiographic damage was less frequent in the group with less than 1 year disease duration than in the groups with longer disease course, and only a small proportion of patients fulfilled the rheumatoid nodules item (Table III). Thus, these data overall support the hypothesis that the four clinical criteria are much more effective for the identification of RA patients with early disease than the three items involving

**Table II.** Patients in ORAR with different disease duration (proportions %) fulfilling individual items of the ACR classification criteria (cumulative approach).

| | Disease duration | | | | | | |
|---|---|---|---|---|---|---|---|
| | < 1 year (n = 17) | 1-2 yrs. (n = 33) | 2-3 yrs. (n = 41) | 3-4 yrs. (n = 49) | 4-5 yrs. (n = 42) | > 5 yrs. 454 | P value* |
| Morning stiffness | 94.1 | 93.9 | 82.9 | 81.6 | 88.1 | 85.2 | 0.55 |
| Swelling in 3 joint areas | 100 | 90.9 | 87.8 | 87.8 | 90.5 | 92.7 | 0.53 |
| Swelling wrists, MCP, or PIP | 94.1 | 90.9 | 92.7 | 89.8 | 92.9 | 93.2 | 0.97 |
| Symmetric swelling | 64.7 | 72.7 | 65.9 | 79.6 | 78.6 | 74.7 | 0.62 |
| X-ray | 35.3 | 42.4 | 48.8 | 55.1 | 69.0 | 76.7 | < 0.001 |
| Rheumatic noduli | 47.1 | 36.4 | 29.3 | 32.7 | 33.3 | 46.5 | 0.08 |
| RF (Waaler ≥ 64) | 52.9 | 60.6 | 56.1 | 49.0 | 57.1 | 58.1 | 0.87 |

* Pearson chi-square tests

**Table III**. Patients in the EURIDISS cohort with different disease duration (proportions %) fulfilling individual items of the ACR classification criteria at baseline (current approach).

| | All pts. n = 238 | < 1 yr. n = 46 | 1-2 yrs n = 47 | 2-3 yrs n = 66 | 3-4 yrs n = 79 | P value* |
|---|---|---|---|---|---|---|
| Morning stiffness | 118 (50) | 23 (59) | 16 (34) | 36 (54) | 43 (55) | 0.10 |
| Swelling in three joint areas | 187 (79) | 41 (89) | 37 (79) | 44 (68) | 65 (83) | 0.02 |
| Swelling wrists, MCP, or PIP | 206 (87) | 43 (94) | 43 (92) | 53 (80) | 67 (86) | 0.16 |
| Symmetric swelling | 200 (84) | 41 (89) | 35 (74) | 57 (86) | 67 (86) | 0.20 |
| X-ray | 115 (49) | 10 (22) | 26 (55) | 28 (42) | 51 (65) | <0.001 |
| Rheumatic noduli | 35 (15) | 9 (20) | 6 (13) | 10 (15) | 10 (13) | 0.76 |
| RF (Waaler ≥ 64) | 105 (44) | 21 (46) | 26 (55) | 27 (41) | 31 (40) | 0.37 |

* Pearson chi-square tests.

structural damage, nodules and RF.

We also used this cohort to examine whether the duration of symptoms before disease classification was related to the presence of the seven 1987 ACR classification criteria and to disease outcome in 238 patients with a short disease duration. The time of disease classification was set at when patients had met at least 4 of the 7 cumulatively applied items of the 1987 ACR criteria. The duration of symptoms before the classification diagnosis was reported by the patients at the baseline visit of the study. The median duration of symptoms before classification of RA was 8.1 (IQR 12.8) months. The distribution in the presence of the individual ACR criteria was not different in patients with at least 1 year of symptoms before diagnosis compared to patients with shorter symptom duration (Pearson chi-square test). No association was observed between the duration of symptoms and age or sex, or with 5-year progression and outcome in radiographic damage or physical and psychological function. Thus, the selected methods of determining disease onset in RA – by the start of symptoms or by the time when ACR classification criteria were satisfied – do not affect the distribution of classification criteria or the observed disease outcome. This observation indicates that disease onset may be defined either by start of symptoms or by disease classification, and that the choice between these options does not influence outcome.

## Discussion

Although traditional approaches to RA did not emphasize early treatment with disease modifying anti-rheumatic drugs (DMARDs), recent research has supported the value of such early treatment (8-14). Some studies have even indicated that institution of DMARDs as early as less than 4 months after diagnosis is important (11, 15).

The majority of patients with arthritides will initially be examined by their general practitioners. These physicians cannot be expected to manage RA adequately at an early stage. This fact is also related to the increasing complexity of drug treatment, with the availability of combination regimens and new biological therapies. The essential role of general practitioners will be to identify patients suspected of having RA for referral to a rheumatologist (26-28). Importantly, the incidence of RA over the last years has shifted to older persons, especially females (29, 30). Results presented in this report, as well as other studies, have demonstrated clearly that RA most frequently starts after the age of 60 (18, 25). Thus, other joint diseases appearing frequently in this age group would also be the most important differential diagnoses. Among these, generalized osteoarthritis with hand involvement must in particular be considered. Previous studies of the whole spectrum of arthritides also clearly indicate that reactive arthritis is a frequently occurring type of arthritis in younger age groups and appears to be as frequent as RA in persons under the age of 40.

It has been suggested that the progression of RA is more rapid early in the disease course (31, 32). Such findings may be related to scaling properties of measures of damage. For example, the intervals in the Larsen score from 0 to 1 and from 2 to 3 are numerically identical, but do not reflect the same amount of damage. At present, radiographic scoring methods for joint damage do not capture the exact volume of destructed bone, and because the magnitude of damage does not clearly correlate with physical function, scaling properties of damage measures are an important issue. Data from the EURIDISS study do not support the relationship between disease duration and the rate of progression. An alternative interpretation of this conflicting finding is that some of the studies showing rapid progression early in the disease were performed in the 1970s and 1980s (31, 32), when the treatment philosophy was less aggressive than in the 1990s and especially today.

To identify patients with RA at an early stage we need classification criteria that are suitable for this purpose. Three of the items in the ACR classification criteria are related to the severity of the disease and may develop with time. This was clearly shown in data from the Norfolk Arthritis Register, where the initial incidence of 25 per 100,000 increased to 41 per 100,000 with 5 years of observation, when the individual items were applied cumulatively over time (33). Data from the ORAR and EURIDISS also suggest that these items are not frequently met early in the disease course (Tables II and III). The results from the RA register and the EURIDISS cohort also demonstrate the variable presence of the items according to whether they are recorded cumulatively or cross-sectionally, i.e., either present at any time during the course of the disease or present at the time of examination.

Epidemiological studies have clearly shown the heterogeneity of arthritides at an early stage of the disease (16, 34, 35). Actually, unspecified polyarthritis is a very frequent condition (36) and appears to be as frequent as RA when patients are diagnosed early (34, 35). Follow-up studies on polyarthritides have suggested that the disease course, both in terms of disability and radio-

graphic damage, is related to the activity of the disease at baseline, but also that early therapy with disease-modifying antirheumatic drugs is beneficial for the disease course (37).

It has been shown clearly in established disease that early erosions, RF and acute phase reactants are consistent predictors of future structural damage (24). The most important current research agenda in the very early stages of the disease is to identify markers that predict persistent arthritic disease as well as a progressive disease course. This latter group of patients will be obvious candidates for an active and aggressive therapeutic approach.

## References


1. ARNETT FC, EDWORTHY SM, BLOCH DA *et al.*: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
2. FELSON DT, ANDERSON JJ, BOERS M *et al.*: American College of Rheumatology core set of disease activity measures for rheumatoid arthritis clinical trials. *Arthritis Rheum* 1993; 36: 729-40.
3. TUGWELL P, BOERS M: Developing consensus on preliminary core efficacy endpoints for rheumatoid arthritis clinical trials. *J Rheumatol* 1993; 20: 555-6.
4. SCOTT DL, PANAYI GS, VAN RIEL PL, SMOLEN J, VAN DE PUTTE LB: Disease activity in rheumatoid arthritis:preliminary report of the Consensus Study Group of the European Workshop for Rheumatology Research. *Clin Exp Rheumatol* 1992; 10: 521-5.
5. FELSON DT, ANDERSON JJ, BOERS M *et al.*:American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 727-35.
6. VAN GESTEL AM, PREVOO ML, VAN 'T H, VAN RIJSWIJK MH, VAN DE PUTTE LB, VAN RIEL PL: Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism criteria. *Arthritis Rheum* 1996; 39: 34-40.
7. WOLFE F, LASSERE M, VAN DER HEIJDE D, *et al.*: Preliminary core set of domains and reporting requirements for longitudinal observational studies in rheumatology. *J Rheumatol* 1999; 26: 484-9.
8. VAN DER HEIJDE D, JACOBS JW, BIJLSMA JW, *et al.*: The effectiveness of early treatment with "second-line" antirheumatic drugs. A randomized, controlled trial. *Ann Intern Med* 1996; 124: 699-707.
9. WILES NJ, LUNT M, BARRETT EM, *et al.*: Reduced disability at 5 years with early treatment of inflammatory polyarthritis: Results from a large observational cohort, using propensity models to adjust for disease severity. *Arthritis Rheum* 2001; 44: 1033-42.
10. STENGER AA, VAN LEEUWEN MA, HOUTMAN PM: Early effective suppression of inflammation in rheumatoid arthritis reduces radiographic progression. *Br J Rheumatol* 1998; 37: 1157-63.
11. MOTTONEN T, HANNONEN P, KORPELA M, *et al.*: Delay to institution of therapy and induction of remission using single-drug or combination-disease-modifying antirheumatic drug therapy in early rheumatoid arthritis. *Arthritis Rheum* 2002; 46: 894-8.
12. BUKHARI MA, WILES NJ, LUNT M, *et al.*: Influence of disease-modifying therapy on radiographic outcome in inflammatory polyarthritis at five years:Results from a large observational inception study. *Arthritis Rheum* 2003; 48: 46-53.
13. LARD LR,VISSER H, SPEYER I, *et al.*: Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. *Am J Med* 2001; 111:446-51.
14. EGSMOSE C, LUND B, BORG G, *et al.*: Patients with rheumatoid arthritis benefit from early 2nd line therapy: 5 year followup of a prospective double blind placebo controlled study. *J Rheumatol* 1995; 22: 2208-13.
15. NELL VPK, MACHOLD KP, EBERL G, UFFMANN M, STAMM T, SMOLEN JS: Benefit of very early referral and therapy with disease modifying antirheumatic drugs in patients with early rheumatoid arthritis. *Ann Rheum Dis* 2002; 61(Suppl. 1) :37.
16. KVIEN TK,GLENNAS A,MELBY K *et al.*: Reactive arthritis: incidence, triggering agents and clinical presentation. *J Rheumatol* 1994; 21: 115-22.
17. KVIEN TK, GLENNAS A, KNUDSROD OG, SMEDSTAD LM, MOWINCKEL P, FORRE O: The prevalence and severity of rheumatoid arthritis in Oslo. Results from a county register and a population survey. *Scand J Rheumatol* 1997; 26: 412-8.
18. UHLIG T, KVIEN TK, GLENNAS A, SMEDSTAD LM, FORRE O: The incidence and severity of rheumatoid arthritis, results from a county register in Oslo,Norway. *J Rheumatol* 1998; 25: 1078-84.
19. HAGEN KB, SMEDSTAD LM, UHLIG T, KVIEN TK: The responsiveness of health status measures in patients with rheumatoid arthritis: comparison of disease-specific and generic instruments. *J Rheumatol* 1999; 26: 1474-80.
20. KVIEN TK, GLENNAS A, KNUDSROD OG, SMEDSTAD LM: The validity of self-reported diagnosis of rheumatoid arthritis: results from a population survey followed by clinical examinations. *J Rheumatol* 1996; 23: 1866-71.
21. UHLIG T, KVIEN TK, JENSEN JL, AXELL T: Sicca symptoms, saliva and tear production, and disease variables in 636 patients with rheumatoid arthritis. *Ann Rheum Dis* 1999; 58: 415-22.
22. HAUGEBERG G, ORSTAVIK RE, UHLIG T, FALCH JA, HALSE JI, KVIEN TK: Bone loss in patients with rheumatoid arthritis: results from a population-based cohort of 366 patients followed up for two years. *Arthritis Rheum* 2002; 46: 1720-8.
23. SMEDSTAD LM, VAGLUM P, KVIEN TK, MOUM T: The relationship between self-reported pain and sociodemographic variables, anxiety, and depressive symptoms in rheumatoid arthritis. *J Rheumatol* 1995; 22: 514-20.
24. UHLIG T, SMEDSTAD LM, VAGLUM P, MOUM T, GERARD N, KVIEN TK: The course of rheumatoid arthritis and predictors of psychological, physical and radiographic outcome after 5 years of follow-up. *Rheumatology* (Oxford) 2000; 39: 32-41.
25. SYMMONS DP, BARRETT EM, BANKHEAD CR, SCOTT DG, SILMAN AJ: The incidence of rheumatoid arthritis in the United Kingdom: results from the Norfolk Arthritis Register. *Br J Rheumatol* 1994; 33: 735-9.
26. HOUSSIEN DA, SCOTT DL: Early referral and outcome in rheumatoid arthritis. *Scand J Rheumatol* 1998; 27: 300-2.
27. EMERY P, BREEDVELD FC, DOUGADOS M, KALDEN JR, SCHIFF MH, SMOLEN JS: Early referral recommendation for newly diagnosed rheumatoid arthritis: evidence based development of a clinical guide. *Ann Rheum Dis* 2002; 61: 290-7.
28. VISSER H, LE CESSIE S, VOS K, BREEDVELD FC, HAZES JM: How to diagnose rheumatoid arthritis early:a prediction model for persistent (erosive) arthritis. *Arthritis Rheum* 2002; 46: 357-65.
29. IMANAKA T, SHICHIKAWA K, INOUE K, SHIMAOKA Y, TAKENAKA Y, WAKITANI S: Increase in age at onset of rheumatoid arthritis in Japan over a 30 year period. *Ann Rheum Dis* 1997; 56: 313-6.
30. KAIPIAINEN-SEPPANEN O, AHO K, ISOMAKI H,LAAKSO M: Shift in the incidence of rheumatoid arthritis toward elderly patients in Finland during 1975-1990. *Clin Exp Rheumatol* 1996; 14: 537-42.
31. LARSEN A, THOEN J: Hand radiography of 200 patients with rheumatoid arthritis repeated after an interval of one year. *Scand J Rheumatol* 1987; 16: 395-401.
32. FUCHS HA, KAYE JJ, CALLAHAN LF, NANCE EP, PINCUS T: Evidence of significant radiographic damage in rheumatoid arthritis within the first 2 years of disease [see comments]. *J Rheumatol* 1989; 16: 585-91.
33. WILES N, SYMMONS DP, HARRISON B, *et al.*: Estimating the incidence of rheumatoid arthritis:trying to hit a moving target? *Arthritis Rheum* 1999; 42: 1339-46.
34. ISOMAKI H, RAUNIO J, VON ESSEN R, HAMEENKORPI R: Incidence of inflammatory rheumatic diseases in Finland. *Scand J Rheumatol* 1978; 7: 188-92.
35. SODERLIN MK,BORJESSON O, KAUTIAINEN H, SKOGH T, LEIRISALO-REPO M: Annual incidence of inflammatory joint diseases in a population based study in southern Sweden. *Ann Rheum Dis* 2002; 61: 911-5.
36. WOLFE F, ROSS K, HAWLEY DJ, ROBERTS FK, CATHEY MA: The prognosis of rheumatoid arthritis and undifferentiated polyarthritis syndrome in the clinic: a study of 1141 patients. *J Rheumatol* 1993; 20: 2005-9.
37. JANSEN LM, VAN SCHAARDENBURG D, VAN DER HORST-BRUINSMA IE, DIJKMANS BA: One year outcome of undifferentiated polyarthritis. *Ann Rheum Dis* 2002; 61: 700-3.