EXTENDED REPORT

Disease activity and health status in rheumatoid arthritis: a case-control comparison between Norway and Lithuania

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Objective: To compare disease characteristics and health status in patients with rheumatoid arthritis (RA) from two countries, Norway and Lithuania.
Methods: Patients were recruited from the RA registers in Vilnius (Lithuania) and Oslo (Norway). For each patient from Vilnius, a patient matched for age and sex from the Oslo register was selected. Sociodemographic characteristics, disease process, and health status were compared between the patient groups.
Results: 201 Lithuanian patients and 201 Norwegian patients were included. Mean (SD) age in both groups was 55.9 (10.0) years, and 83% were women. Patients from Lithuania were less often employed (27% *v* 42%; p=0.001), had higher disease activity expressed by the disease activity score (DAS28; mean (SD) 5.3 (1.0) *v* 4.4 (1.4); p<0.001), had worse physical function by the modified Health Assessment Questionnaire (MHAQ; mean (SD) 2.3 (0.8) *v* 1.6 (0.5); p<0.001), had more often comorbidity (73% *v* 53%; p<0.001) and they reported worse general health measured by Short Form-36 Health Survey (SF-36; mean (SD) 23.2 (13.5) *v* 44.5 (21.3); p<0.001). The proportions of patients who had used disease modifying drugs were similar, but the pattern of use differed.
Conclusion: Important differences in employment, disease activity, physical function, and self reported health status were observed in patients with RA from two northern European countries. Socioeconomic inequalities, differences in disease management, and access to specialised health care, as well as methodological issues regarding instruments and data collection are likely explanations. These data support the view that management of RA should be adapted to country-specific needs.

The burden of inflammatory and degenerative joint disease for patients as well as for society is recognised as a major issue in the Bone and Joint Decade.[1] The magnitude and nature of country-specific differences, however, has been insufficiently explored. There is an overall impression that rheumatoid arthritis (RA) is more prevalent in the northern countries[2–5] and occurs less frequently in southern countries.[6 7] Not only the prevalence, but also the expression of the disease is reported to differ among countries. Classically, differences are attributed to genetic factors, or environmental factors including nutritional habits, ultraviolet radiation, microbial environment, and use of contraceptive pills.[6–9] In addition, the organisation and quality of health care provided to patients can influence the disease severity, and socioeconomic characteristics can influence the perceived health status.[10–12] Comparative studies on the impact of RA across countries can help to provide an understanding of country-specific factors contributing to the burden of disease and can help to target the needs of patients specifically.[13] However, few such studies have been performed in the past decade and many of those available have methodological shortcomings.[14–20]

In this study we compared disease process and health status in patients with RA from two registers established in different, well defined geographical areas with a similar population size—one in Vilnius (Lithuania, Baltic state) and the other in Oslo (Norway, Scandinavia). We assumed that genetic and environmental discrepancies in these neighbouring populations were likely to be small and that possible differences in disease expression and health status were more likely to be explained by differences in socioeconomic status and healthcare organisation and provision.

PATIENTS AND METHODS

Settings and patients

Patients were sampled from the RA registers of Vilnius (Lithuania) and Oslo (Norway), two cities with about 500 000 inhabitants. The Vilnius RA register was established in 1998 and comprised 1018 patients with RA for 486 500 adult inhabitants at the time of the study. The Oslo RA register was established in 1994 and comprised 1552 patients from 472 000 adult inhabitants at the time of the study. The completeness of the Oslo RA register was shown to be 85% and was used to estimate prevalence (44 per 1000)[21] and incidence figures (25.7 per 100 000 inhabitants)[22] of RA in Oslo. Criteria for enrolment into the registers comprised a diagnosis of RA[23] and a residential address in Vilnius or Oslo, respectively. Both registers are continuously updated with new cases and withdrawals due to mortality or changes of address outside the cities. In Vilnius, the general practitioners or rheumatologist, working in one of the 14 outpatient clinics of the town, are asked annually to provide an updated list of patients with RA registered at their outpatient clinic, and the charts of the rheumatology department are continuously reviewed for RA cases (JD). In 1999 a random sample of 359 patients was invited for interview and examination and 201 patients agreed to participate. In Oslo, between 1996 and 1997, 883 patients aged 20–70 years were invited for interview and examination, of whom 636 agreed to participate in the study. Mainly the

Abbreviations: DAS28, disease activity score; DMARD, disease modifying antirheumatic drug; MHAQ, modified Health Assessment Questionnaire; RA, rheumatoid arthritis; SF-36, Short Form-36 Health Survey

hospital chart reviews from the two hospitals serving the county are used to identify patients with RA in the town and mortalities are recorded from the population register. The charts of all patients with RA or possible RA referred to members of the multidisciplinary team in the county hospital are also checked.

The primary cases for this study were patients of the Vilnius RA register. For each patient a control from the Oslo RA register, matched for sex and age, was identified. Patients enrolled in the study came for interview and clinical examinations, performed in Vilnius from 1999 to 2000 and in Oslo from 1996 to 1997. The attendance rate for clinical examination in Vilnius was 56% and in Oslo 72%.[24]

Access to health services for patients with RA and social security in Vilnius and Oslo

Five full time and three part time rheumatologists work in half of the 14 outpatient clinics (polyclinics) in Vilnius. These rheumatologists provide about 10 000 consultations a year. The waiting time for a first referral to a rheumatologist varies from one to three months, but only one fifth of all patients with RA in the register had attended a consultation with a rheumatologist during the past year. When admission to hospital is necessary, patients are admitted to the rheumatology department of the University Hospital, which has 40 rheumatology beds. Mean duration of admission for each patient is 10 days. Six fully employed rheumatologists provide the hospital care and there is no outpatient consultation attached to the hospital.

The specialised rheumatology healthcare services in Oslo were in 1997 mainly concentrated in two referral centres providing about 12 000 consultations given by 10 rheumatologists. About 10% of the consultations are with patients seen within 1–3 days, the rest having a waiting time of between one week and six months. About 45 rheumatology beds were available for citizens from Oslo, including 25 beds for orthopaedic surgery of patients with inflammatory rheumatic diseases. On average, patients were admitted for 10 days.

Both countries have an obligatory health insurance, which is paid by social taxes to the State social insurance fund. In addition, there are small patient out of pocket contributions for drugs. Lithuania spends 4.6% of its gross domestic product on health care compared with 7.1% in Norway. Unemployment figures, a surrogate marker for economic welfare, are 13% in Lithuania and 5.6% in Norway.

Data collection

The procedures for data collection were similar in both settings. After giving consent, the patients were invited for a structured interview and clinical examination. The interview and examination was performed by a rheumatologist (SS) in Vilnius and by a specially trained research nurse in collaboration with a rheumatologist (TU) in Oslo.[24] The interviews comprised questions about sociodemographic status, including years of formal education and current working status, RA cases in the family, questions on disease activity, current and previous treatment, surgical interventions, comorbidity and extra-articular manifestations. When appropriate, the information obtained by interview was supplemented by information from the patient's hospital record.

The disease activity was assessed by the 28 swollen and 28 tender joint counts, joint pain (scale 1–10 in Vilnius rescaled to 0–100), patient's global assessment of disease activity (scale 1–5 in Oslo and scale 1–10 in Vilnius, rescaled to 0–100), and investigator's global assessment (being rescaled from 1–5 to a 100 mm VAS in Vilnius). Laboratory tests were performed locally at the time of examination according to routine guidelines and included erythrocyte sedimentation rate (mm/1st h), haemoglobin (g/l), and white blood cell count. From these measures the disease activity score (DAS28) was calculated.[25 26] In addition, IgM rheumatoid factor was determined by the Waaler-Rose test in Oslo (positive for a titre ⩾1/64) and by latex fixation in Vilnius (positive for ⩾40 IU/ml).

Finally, patients completed various health status questionnaires, including the modified Health Assessment Questionnaire (MHAQ; scale 1–4, 4=worst health)[27] and the Short Form-36 Health Survey (SF-36; scale 0–100, 0=worst health).[28]

Table 1 Demographic characteristics of patients with RA from Vilnius and Oslo (mean (SD) for continuous variables, % (n/total) for dichotomous variables)

	Vilnius (n=201)	Oslo (n=201)	p Value
Age	55.9 (10.0)	55.9 (10.0)	
Women	83% (167/201)	83% (167/201)	
Disease duration	11.9 (9.5)	12.7 (9.2)	0.05
Years of education	12.0 (4.4)	11.7 (3.4)	0.28
Employment	27% (54/201)	42% (83/199)	0.001
RA in the family	24% (48/199)	30% (51/170)	0.17

Statistical analysis

SPSS was used for data entry and analyses. Results are expressed as mean (SD) or proportions (counts) when appropriate. Statistical analysis was performed using a paired test for continuous variables and the McNemar test for dichotomous variables. The differences were considered significant at $p<0.05$.

RESULTS

Patients

For each 201 patients with RA from the Vilnius RA register a patient from the Oslo RA register, matched for age and sex, was identified. Mean age was 55.9 (10.0) years and 83% were female. Table 1 shows that the mean disease duration for patients from Vilnius was slightly shorter (11.9 (9.5) *v* 12.9 (9.5) years), but this difference was not significant. The table also contrasts the sociodemographic features of the patient groups. There was an important difference in employment rate (27% *v* 42%; p=0.001), despite similar educational level (12.0 (4.4) *v* 11.7 (3.4); p=0.28).

Disease activity and health status

Table 2 presents the disease process and health status for patients from both countries. Disease activity, including doctor's global assessment, acute phase reactants, and all components of the DAS28, with the exception of the 28 swollen joint counts, were consistently worse for patients from Vilnius. Comorbidity was more frequently recorded in the Vilnius group, but the occurrence of extra-articular manifestations was similar. The health status was rated worse in Vilnius for joint pain (59.5 (20.0) *v* 36.2 (22.1); p<0.001), physical disability (MHAQ score 2.3 (0.8) *v* 1.6 (0.5); p<0.001), and several of the domains of the SF-36. Domains of the SF-36 showing significant differences (p<0.001) were physical functioning, role emotional, mental and general health.

Treatment

Nearly all patients both in Vilnius and Oslo had ever used non-steroidal anti-inflammatory drugs. The proportions of patients having ever used disease modifying antirheumatic drugs (DMARDs) were also similar (94% and 90%; p=0.17), but the pattern of use of specific drugs used differed considerably (table 3). Vilnius patients had been treated more widely with azathioprine (p<0.001), sulfasalazine (p=0.002), and antimalarial drugs (p=0.02), whereas methotrexate (p=0.02), gold drugs (p<0.001), cyclosporin (p=0.001), and

Table 2 Disease process and health status measures in patients with RA from Vilnius and Oslo (mean (SD) for continuous variables, % (n/total) for dichotomous variables)

	Vilnius (n=201)	Oslo (n=201)	p Value
Pain VAS (0–100)	59.5 (20.0)	36.2 (22.1)	<0.001
Patient's global assessment (1–10)	49.2 (18.0)	41.8 (20.0)	<0.001
Investigator's global assessment (1–100)	47.5 (22.8)	29.2 (24.7)	<0.001
28 TJC	12.6 (7.9)	6.6 (6.5)	<0.001
28 SJC	4.7 (5.2)	7.8 (6.0)	<0.001
DAS28	5.3 (1.0)	4.4 (1.4)	<0.001
MHAQ (1–4)	2.3 (0.8)	1.6 (0.5)	<0.001
RF positive	61% (82/134)	49% (93/190)	0.03
ESR (mm/1st h)	28.6 (13.4)	20.5 (17.3)	<0.001
Haemoglobin (g/l)	118 (13)	137 (13.2)	<0.001
WBC (×10⁹/l)	8.0 (2.0)	8.3 (2.7)	0.14
Extra-articular manifestations present	59% (118/200)	62% (116/187)	0.60
Comorbidity	73% (141/192)	53% (102/192)	<0.001
SF-36			
Physical functioning	35.2 (25.2)	48.5 (25.6)	<0.001
Role physical	23.1 (34.8)	25.7 (33.7)	0.47
Bodily pain	42.0 (21.2)	42.6 (21.1)	0.99
General health	23.2 (13.5)	44.5 (21.3)	<0.001
Vitality	43.7 (22.4)	41.9 (20.9)	0.25
Social functioning	61.1 (27.0)	64.6 (27.3)	0.26
Role emotional	34.0 (42.4)	52.1 (40.3)	<0.001
Mental health	54.6 (21.0)	68.7 (19.7)	<0.001

VAS, visual analogue scale; TJC, tender joint count; SJC, swollen joint count; DAS, disease activity score; MHAQ, modified Health Assessment Questionnaire; RF, rheumatoid factor; ESR, erythrocyte sedimentation rate; WBC, white blood cell count; SF-36, Short Form-36 Health Survey.

Table 3 Drugs ever used and joint replacement surgery in patients with RA from Vilnius and Oslo (% (n/total))

	Vilnius (n=201)	Oslo (n=201)	p Value
NSAIDs	98 (194/197)	96 (192/200)	0.23
Oral corticosteroids*	77 (152/198)	60 (121/201)	0.001
DMARDs ever used	94 (188/199)	90 (161/179)	0.17
D-pencillamine	2 (5/201)	17 (33/198)	<0.001
Azathioprine*	29 (58/201)	13 (26/201)	<0.001
Cyclophosphamide	3 (7/201)	0 (0/200)	–
Cyclosporin	1 (3/201)	9 (18/201)	0.001
Sulfasalazine*	49 (98/201)	34 (68/198)	0.002
Gold drugs	28 (56/199)	57 (67/118)	<0.001
Methotrexate	36 (72/201)	49 (98/201)	0.02
Antimalarial drugs*	50 (100/201)	38 (75/200)	0.02
Joint replacements	7 (15/201)	24 (48/198)	<0.001

*Drugs more often used in Vilnius than in the Oslo group.
NSAIDs, non-steroidal anti-inflammatory drugs; DMARDs, disease modifying antirheumatic drugs.

D-penicillamine ($p<0.001$) had been used relatively more often in Oslo than in Vilnius. Surgery with joint replacements was more prevalent in the Oslo group ($p<0.001$) (table 3).

DISCUSSION

Our study shows that the expression and impact of RA differs between two northern European populations. Disease activity (DAS28) as well as functional impact (employment and HAQ) and perceived general health (SF-36) were worse in patients from Lithuania.

To the best of our knowledge only six studies in the past 10 years have examined differences in disease expression in RA across countries.[9 15 17–20] All focused on disease activity and damage while health related quality of life was not studied. Remarkably, five out of the six studies compared British patients with ethnically remote patients like Greeks,[9] Pakistanis,[15] Malaysians,[17] ethnic black Zimbabweans,[18] and West Africans,[19] and one study compared Dutch and Egyptian patients.[20] Table 4 summarises the data from these studies. The overall impression from these studies is that British patients tend to develop more severe disease with more expressed functional disability and higher prevalence of extra-articular manifestations than southern populations. In contrast, in the study comparing Dutch and Egyptian patients with RA, the Egyptian group showed higher disease activity and more pronounced impact on activities of daily living. The authors suggested that these differences might be attributed to the higher use of contraceptives among Dutch patients, on the one hand, and a more stressful lifestyle in Arabs, on the other.[20] Overall, genetic factors may be an explanation but environmental factors also, such as use of contraceptive pills, microbial factors, life expectancy, educational level, and diet, may contribute to differences in disease expression across countries.[13 29] However, it is methodologically difficult—if not impossible—to evaluate the individual contribution of each of these variables to the observed differences. We feel that the role of socioeconomic factors has been underestimated. Even in welfare societies increased mortality in RA was shown to be associated with access to health care.[30] A recent study, comparing two socioeconomically contrasting regions of Oslo, showed similar disease activity but worse health status across several dimensions of self reported health in those living in the less affluent area.[12]

Difference in socioeconomic status may also be an explanatory factor in the present study. It is of note that differences between Vilnius and Oslo were not only seen in measures influenced by the disease perceptions of individual patients but also in disease activity.

This study is the first to compare RA among white populations in two different countries, with the exception of some preliminary data from a survey on patients with RA reported in England, the Netherlands, and Oslo.[31] Our comparative study has several strengths. Firstly, both patient groups derived from urban populations comparable in size and with a similar low prevalence of RA. The reported prevalence of RA for Oslo is 0.44%,[21] according to a population survey, and 0.36% for Vilnius, according to the Lithuanian health information centre.[32] Patients in Vilnius had slightly shorter disease duration, but this difference was not statistically significant. Secondly, all outcomes recommended for observational studies[33] were included, with the exception of radiographic damage. Prevalence of joint replacement surgery might be

Table 4 Results of comparative cross cultural studies

Author, year [ref]	Populations compared	Patients/place	Disease variables compared	Results
Hameed K, 1996 [15]	British-Pakistani	176 Matched patients/centre based	MS, joint count, RAI, EAM, HAQ, laboratory measures, *x* ray scores	**British** had **worse** *x*-ray damage and more nodules. **Pakistani** had **worse** scores for MS, RAI, HAQ and laboratory measures.
Drosos AA, 1992 [9]	British-Greek	215 Consecutive patients/centre based	MS, joint count, GS, EAM, *x* ray stage, laboratory measures	**British** had **worse** scores in all clinical measures except for sicca symptoms.
Veerapen K, 1993 [17]	British-Malaysian	140 Consecutive matched cases/centre based	MS, joint count, EAM, *x* ray damage, laboratory measures	**British** had more **severe** disease in feet and higher prevalence of EAM; other variables were similar.
Chinkanza IC, 1994 [18]	British-Zimbabwean	168 Consecutive matched patients/centre based	MS, joint count (swollen, deformed), GS, EAM, *x* ray damage, laboratory measures	**British** had **worse** disease judged clinically and radiographically with fewer EAM.
Adebajo AO, 1991 [19]	British-Nigerian	Consecutive patients/centre based	Joint count, EAM, *x* ray damage, laboratory measures	**British** had more **severe** disease and higher prevalence of EAM.
Abdel-Nasser AM, 1996 [20]	Egyptian-Dutch	200 consecutive patients/centre based	Activity, disability indices, *x* ray stage, comorbidities, EAM	**Egyptian** had **higher** disease activity; more pronounced pain and limitation of activities of daily living.

MS, morning stiffness; RAI, Ritchie articular index; EAM, extra-articular manifestations; HAQ, Health Assessment Questionnaire; GS, grip strength.

considered as a measure of damage,[34] although the difference in joint replacements in favour of Oslo might be explained by differences in access to surgery. In Oslo, orthopaedic and medical treatment of patients with RA is performed within the same department, the so-called "combined unit"; whereas in Vilnius the facilities are separated. Otherwise, access to rheumatological health care appears to be rather similar based on the number of outpatient consultations, number of rheumatologists, number of beds, and admission time in hospital, but similarities in these numbers do not exclude possible differences in the organisation and provision of health care. Ideally, genetic factors should also have been compared, but DNA samples were not available for examination.

Although we have chosen to compare recommended outcomes, there is methodological concern about the validity of the instruments. The measures chosen for assessment of the different outcome domains were instruments accepted world wide for disease activity and health status that have been shown to be valid across countries.[28 35 36] The validation of SF-36 was thoroughly performed in a Norwegian setting of patients with RA.[37] The Lithuania translation, was followed by back translation and adaptation, but full validation was not performed, possibly, causing incomplete comparability. In addition, differences in joint counts might be caused by different interpretation of joint swelling, in particular. The latter observation indicates that regardless of careful description of procedures,[38] training of the investigators in joint assessments should be emphasised. Examination of the patients in both groups by the same trained observer would be the ideal option but was impossible to achieve owing to geographical and cultural barriers.

Other limitations of this study comprise the possibility of selection bias. Although the completeness of the Oslo RA register was examined and found to be 85%,[21] a similar study was not performed in Vilnius. However, it is assumed that most patients with RA are incorporated in the register because referrals from primary care are considered to be fair.[39] This assumption is supported by the prevalence of RA, which was suggested to be 0.36%,[32] indicating that about 1600–1700 patients should have been registered, compared with an actual recorded number of 1018. Another possible source of bias is the differences in response to invitation to participate in this study, which was somewhat lower in Vilnius than in Oslo. Response bias to participate in the study might have influenced the composition of the groups studied. Patients not included may comprise contrasting extremes: those with either mild disease who are uninterested in participating or those with severe disease who are unable to attend. Moreover, the possibility cannot be excluded that response bias acted in opposite ways in the two countries: more patients who were more highly educated and had less severe RA being less likely to participate in Norway and fewer educated and more severely ill patients being less likely to participate in Lithuania. Age and sex of participants and non-participants from both countries were similar within the country[24] and between the countries.

It is also of note that assessment of the patients took place over different periods of time. As no important economic changes or changes in management strategies of RA occurred during those three years it is unlikely that the different period of time had a significant effect on working status and disease characteristics of patients in this cross sectional study, which included patients with a mean disease duration of 12 years.

Therefore, taken together, it is unlikely that the observed differences in disease expression can be explained by bias and lack of full validation of outcome measures. Explaining the observed differences remains difficult. Classically, geo-environmental factors (nutrition, ultraviolet radiation, microbial factors, contraceptive pills) are advocated to explain the differences in RA outcome among countries. Because both countries are located in the north of Europe and geographically not far from each other, the contribution of such factors will be low. However, additional research may add knowledge to RA genetic variety in the region and over the world.

A more likely explanation is the difference in social background and provision of specialised rheumatologists and therefore differences in medical RA management in Vilnius.[39] This hypothesis is supported by the lower employment rate, differences in number of joints replacements, and differences in the use of methotrexate. Several factors might explain the phenomenon of the different use of DMARDs between the countries. All DMARDs are now available in Lithuania, but some drugs have been prescribed more often in the past than others. The higher use of antimalarial drugs and sulfasalazine in Lithuania might be explained because these drugs are considered by Lithuanian doctors to be less toxic and are preferable for patients who have limited access to highly qualified rheumatological care. Among the immunosuppressive drugs, the more frequent use of azathioprine probably reflects a historical difference. Azathioprine was for long time the only immunosuppressive drug, whereas methotrexate only became widely available and accepted later than in Western European countries. Finally, an economic consideration might play a

part. Prednisone is inexpensive for patients, which might be an incentive for patients to accept this drug as the treatment option.

In conclusion, important differences in disease activity, physical function, and self perceived wellbeing are seen in white patients with RA from two northern European countries, the burden of disease being increased in patients from Vilnius. Differences in economic prosperity and health-care organisation as well as methodological differences in instruments and methods used to assess the outcomes are the more likely explanations. In the light of the Bone and Joint Decade, further research into the influence of healthcare organisation on the outcome of RA should be stimulated.

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