Early Disease Course and Predictors of Disability in Juvenile Rheumatoid Arthritis and Juvenile Spondyloarthropathy: A 3 Year Prospective Study

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ABSTRACT. ***Objective***. To describe the 3 year disease course in early juvenile rheumatoid arthritis (JRA) and juvenile spondyloarthropathy (JSpA), to compare the health status after 3 years of followup with that of normal controls, and to investigate the relationship between physical function at followup and disease characteristics recorded during the first 6 months.

Methods: One hundred and ninety-seven children (median age 6.6 yrs) with JRA and JSpA and disease duration < 1.5 years were examined by a pediatric rheumatologist every 6 months for a median of 3.1 years. Controls were randomly selected from the National Population Register. Physical and psychosocial health was assessed by means of the Child Health Questionnaire and the Childhood Health Assessment Questionnaire (CHAQ). Disease course was analyzed by analysis of variance for repeated measurements.

Results. Health status and disease activity improved over time. Treatment with disease modifying antirheumatic drugs was started in 58% of the patients at baseline. Patients with persistent oligoarthritis had the most favorable disease course. The patients with juvenile ankylosing spondylitis (JAS), syndrome of seronegative enthesopathy and arthropathy (SEA), and rheumatoid factor (RF) positive polyarthritis had the poorest health status. A significant improvement for the whole group was observed after 3 years in all measures of disease activity and health status, except pain. Patients had poorer physical function and general health and more pain than controls. Predictors of reduced physical function at followup were a high CHAQ disability index and a poor well-being assessed during the first 6 months.

Conclusion. Health status and disease activity improved over time in patients under medical treatment. The patients with JAS/SEA and RF positive polyarthritis had poorer health than the patients in other subtypes. A high disability index and a poor well-being at baseline predicted reduced physical function after 3 years. (J Rheumatol 2005;32:1122–30)

Key Indexing Terms:
JUVENILE RHEUMATOID ARTHRITIS DISEASE PROGRESSION
DISABILITY PROGNOSIS RISK FACTORS

Juvenile rheumatoid arthritis (JRA) and juvenile spondyloarthropathy (JSpA) are a potential cause of disability among children. Medical regimes that are effective in treating childhood arthritis have recently been developed[1-5], but treatment must be started at an early stage of disease to be effective in preventing joint damage and loss of physical function[6]. Thus it is important to recognize at an early stage patients who will develop severe disease.

Studies have shown that about 40% of children with JRA and JSpA develop functional disability after 10-15 years[6,7]. Not much is known about the development of disability during the first years of the disease. Most of the studies are retrospective outcome studies, which focus on an endpoint for a given measure at the time of followup. There are currently few prospective studies and none of them include serial measurements over time, which would measure the clinical course of the disease and reveal the disease process leading to the outcome at followup. Repeated measurements can also increase the predictive ability of a variable[8]. Further, to our knowledge, health status in early JRA and JSpA has not been compared with that of the general population.

We therefore conducted a prospective study of the course of JRA and JSpA based on repeated assessments every 6 months during a 3 year followup. The aims were to describe the early disease course as measured by internationally standardized and accepted instruments in children with JRA and JSpA, to identify predictors of 3 year functional outcome among disease variables measured during the first 6 months of followup, and to compare the physical and psychosocial short-term outcome in JRA and JSpA with controls from the normal Norwegian population.

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MATERIALS AND METHODS

Patients and controls. Two hundred and twenty-seven patients with JRA or JSpA and less than 18 months of disease duration attended the Department of Rheumatology, Rikshospitalet University Hospital, Oslo, from March 1995 to December 1999. One hundred and ninety-seven (87.2%) JRA and JSpA patients [age 1 to 16 yrs (median 6.6), median disease duration of 3.7 mo, 61.4% girls] participated in the study and were examined by a pediatric rheumatologist every 6 months for 3.2 ± 0.4 years.

Thirty (13.3%) out of the 227 patients with JRA or JSpA did not participate. Eighteen parents of these children chose not to participate, 4 parents did not know the Norwegian language well enough, and 8 patients were excluded due to incomplete data. The participants were comparable to the non-participants with regard to age, gender, disease subtype, and disease duration (data not shown).

One hundred and eighty-five patients had JRA according to the American College of Rheumatology criteria[9] and 12 had juvenile spondyloarthropathy (JSpA) [3 with juvenile ankylosing spondylitis (JAS)[10], 4 syndrome of seronegative enthesopathy and arthropathy (SEA)[11], and 5 juvenile psoriatic arthritis (JPsA)[12]]. No patient with JPsA had sacroiliitis. Our protocol comprised patients with arthritis only; patients with enthesitis without arthritis were not included. Disease onset was defined as the date of physician documented arthritis or systemic features. Classification criteria for juvenile idiopathic arthritis (JIA) were published in 1998, after the start of the present study[13]. Reclassification of our patients according to these criteria was not done because this would have excluded 33 patients (16.8%) with undifferentiated arthritis.

Remission was defined as using no medical treatment and having no signs of active arthritis, systemic involvement, or active uveitis for the previous 6 months.

One hundred and sixteen children randomly chosen from the National Population Register were used as controls for assessments of health status at followup. Their parents completed the Child Health Questionnaire (CHQ). The controls were comparable to patients with regard to age and gender (mean age 9.3 yrs vs 10.1 yrs, p = 0.070, percentage of females 60.3% vs 61.4%, p = 0.850).

Patients and controls came from all parts of Norway except the counties Nord-Trøndelag, Troms, and Finnmark.

Our study was approved by the Regional Ethics Committee for Medical Research. Informed consent was obtained from all participants.

Measures of physical function. The impact of arthritis on physical function was assessed by the Norwegian version of the Childhood Health Assessment Questionnaire (CHAQ)[14,15]. The CHAQ is a disease-specific instrument that measures physical disability and gives an index with a value of between 0 (no disability) and 3 (severe disability). Parents completed the CHAQ.

Pain, fatigue, and parent's global assessment of child's well-being were measured on a 10 cm visual analog scale (VAS), where 0 means no pain, no fatigue or doing very well, and 10 means very severe pain, very severe fatigue, or doing very poorly.

The Child Health Questionnaire (CHQ) was used to measure physical and psychosocial function in patients and controls[16]. The CHQ is a generic instrument and measures health status in children in general. It assesses the following 10 concepts: the child's physical functioning, bodily pain, changes in role and in social functioning due to physical, emotional or behavioral problems, general health, mental health, behavior problems, self-esteem, and the impact of the child's health on the parent's emotional well-being and the parent's personal time. The scores in each area range from 0 to 100, where 0 means poor health status and 100 means excellent health status. The summary measures for physical function (PhS) and psychosocial function (PsS) are made to have a mean of 50 and a standard deviation of 10 in the general US population[16]. The PhS and PsS in a patient group are calculated by first computing the difference between each of the 10 concept scores and the corresponding mean scores in the US population and then dividing these by the standard deviations for the US population scores (standardization). These standardized concept scores are then weighted according to how much they contribute to the PhS/PsS (using factor score coefficients for each concept score from the same US population) and added together (raw score). The raw score, which is a deviation from a mean of 0, is computed into the final PhS/PsS by multiplying this raw score with 10 (the standard deviation in the US population) and adding this product to 50 (the mean in the US population). We used the parent form of the questionnaire consisting of 50 questions (CHQ-pf50).

The 2 questionnaires, which have been translated and culturally adapted to Norwegians[15,17] were administered to one or both parents of all the children. Parents completed the questionnaires without any help from a health professional.

Clinical and laboratory data. The patients were examined by one of 5 pediatric rheumatologists (BF, DS, OV, GL, or AMS). The clinical examination included registration of number of joints with swelling, tenderness, and limited range of motion, number of active (swelling or both tenderness and limited range of motion) joints, an arthritis severity index[1,9,18], morning stiffness (hours), and physician's global assessment of disease activity (on a 5-point Likert scale, where 1 = inactive, 2 mild, 3 moderate, 4 severe, and 5 very severe). Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were measured by standard methods. Antinuclear antibody (ANA) titer ≥ 32, measured by indirect immunofluorescence using mouse liver sections as substrate, was considered positive. Positive IgM rheumatoid factor (RF) was defined as titer ≥ 64 by the Rose-Waaler test. HLA-B27 was determined by serologic testing[19].

Statistical analyses. Differences between participants and non-participants and between patients and controls were measured by the independent sample t test. The chi-squared test was used for categorical variables. The concept scores general health, bodily pain, and the summary scores (PhS, PsS) from the CHQ were close to normally distributed. We also did a Mann–Whitney test on these variables, which gave the same results as the independent sample t test, but we chose to present the t test. The differences between baseline and 3 year followup were normally distributed and tested by the paired samples t test. One-way analysis of variance (ANOVA) was used to compare patients with active disease, patients in remission, and controls.

To study disease course, we performed an ANOVA for repeated measurements on each of the study variables (CHAQ, PhS, PsS, pain, global assessment of well-being, physician's global assessment of disease activity, number of active and mobility restricted joints, and ESR as dependent variables). Disease subtype and months of followup (0, 6, 12, 18, 24, 30, 36) were used as fixed factors and identification numbers as random factors (nested to disease subtype). Residuals were normally distributed. Scheffé correction for multiple comparisons was used. The analysis tells if there is a difference in mean estimated level for each subgroup during the 3 years and if there is a change over time for the total patient group. We used ANOVA to examine if each subgroup within each variable improved during the 3 years (corrections for multiple comparisons were not performed).

A multiple linear regression analysis was performed to identify predictors of the CHAQ disability index at 3 year followup (dependent variable). The CHAQ score, parent's global assessment of child's well-being, physician's global assessment of disease activity, number of active and mobility restricted joints and ESR were chosen as possible predictors (independent variables) calculated as the area under the curve (AUC)[20] between baseline and 6 months. These variables were chosen because they have been shown to be the most important factors for defining improvement in juvenile arthritis[21]. In addition we included pain. Variables with p value < 0.10 in the univariate analysis were analyzed as possible predictors in the multivariate analysis. Highly intercorrelated independent variables ($r > 0.7$) were avoided in the analysis. Backward and forward regression methods were used. Residuals were normally distributed. Missing data were replaced with the variable from the previous or the next visit. For all the analyses, p values < 0.05 (2-tailed tests) were considered statistically significant. All statistical analyses were performed by the SPSS software program (SPSS Inc., Chicago, IL, USA) versions 10.0/11.0.

Table 1. Demographic and clinical characteristics of patients with JRA and JSpA (n = 197). * Values refer to the numbers of subjects (%) unless otherwise stated.

Characteristic	Value
Females	121 (61.4)
Males	76 (38.6)
Age at baseline, yrs (SD)	6.9 (4.2)
Disease subtypes	
Oligoarticular, persistent	95 (48.2)
Oligoarticular, extended	16 (8.1)
Polyarticular, RF negative	55 (27.9)
Polyarticular, RF positive	5 (2.5)
Systemic	14 (7.1)
JAS/SEA	7 (3.6)
Juvenile psoriatic arthritis	5 (2.5)
Disease duration at baseline, mo (SD)	4.7 (6.5)
HLA-B27-positive	43 (21.9)
ANA positive	96 (48.7)
RF positive	8 (4.1)

* Patients with JRA and JSpA and a disease duration < 1.5 years admitted to hospital between March 1995 and December 1999. JAS: juvenile ankylosing spondylitis. SEA: syndrome of seronegative enthesopathy and arthropathy in children.

RESULTS

Demographic and clinical data for the patients are shown in Table 1. The patient group comprised 95 patients (48.2%) with persistent oligoarthritis, 16 patients (8.1%) with extended oligoarthritis, 55 patients (27.9%) with RF negative polyarthritis, 5 patients (2.5%) with RF positive polyarthritis, 14 patients (7.1%) with systemic arthritis, 7 patients with JAS (n = 3)/SEA (n = 4) (3.6%), and 5 patients (2.5%) with JPsA. The mean disease duration at baseline was 4.7 ± 6.5 months and the mean symptom duration at baseline was 10.1 ± 9.9 months.

Changes over time in health status and disease activity. Table 2 shows the levels of health status and disease activity every 6 months during the 3 years of followup for the whole group of patients. There were significant improvements over time for physical function as assessed by the PhS, physician's global assessment of disease activity, and ESR (p = 0.016, < 0.001 and < 0.001, respectively). The statistically significant differences appeared from baseline to 12 months for PhS and from baseline to 6 months for physician's global assessment of disease activity and ESR (as measured by variances).

Disease progression in subgroups of JRA and JSpA over time. Figure 1 illustrates the disease activity and health status in patients with different subtypes of JRA and JSpA during the 3 years of followup. The subgroups with persistent oligoarthritis and RF negative polyarthritis had a significant improvement in physician's global assessment of disease activity ($p < 0.001$ for both), number of active joints ($p < 0.001$, $p = 0.005$), number of joints with limitation of motion ($p < 0.001$, $p = 0.017$), and ESR ($p = 0.001$, $p < 0.001$). Additionally, the patients with RF negative polyarthritis had a statistically significant improvement in PhS over the 3 years ($p = 0.048$). The subgroup with systemic JRA had a significant improvement in physician's global assessment of disease activity the first 1.5 years ($p = 0.015$) and in ESR the first year ($p = 0.043$), but not over the 3 years. The extended oligoarthritis group had a significant improvement in ESR the first year ($p < 0.001$), but not over the 3 years.

The CHAQ, pain, well-being, and PsS scores did not change statistically in any of the subgroups during the 3 years of followup. In general the groups with RF positive polyarthritis, JAS/SEA, and JPsA comprised few cases, and changes over the 3 years were not statistically significant.

Subgroup differences in the course of JRA and JSpA. Over the 3 years of followup, the mean estimated levels of phys-

Table 2. Health status and disease activity over 3 years of followup in 197 children with early JRA and JSpA. Values are mean ± SD.

Measure	Baseline	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo	p*
CHAQ (range 0–3)†	0.52 ± 0.58	0.49 ± 0.55	0.44 ± 0.61	0.47 ± 0.60	0.36 ± 0.51	0.33 ± 0.47	0.35 ± 0.51	0.447
Physical summary score CHQ‡	38.4 ± 15.3	43.0 ± 12.9	46.0 ± 12.0	44.7 ± 11.6	45.7 ± 11.5	46.2 ± 11.9	46.3 ± 12.4	0.016
Psychosocial summary score CHQ‡	51.1 ± 7.1	49.5 ± 8.9	52.9 ± 6.9	51.8 ± 8.6	54.2 ± 7.0	53.7 ± 6.7	52.8 ± 7.2	< 0.001
Pain (10 cm VAS)§	2.5 ± 2.4	2.2 ± 2.4	2.3 ± 2.4	2.5 ± 2.4	2.3 ± 2.4	2.3 ± 2.5	2.3 ± 2.5	0.776
Patient's global well-being (10 cm VAS)§	2.6 ± 2.3	2.3 ± 2.2	2.2 ± 2.2	2.4 ± 2.3	1.9 ± 2.0	2.0 ± 2.1	2.0 ± 2.2	0.637
Physician global disease activity (Likert scale 1–5)#	3.0 ± 0.9	2.3 ± 0.9	2.1 ± 0.9	1.9 ± 0.9	1.9 ± 1.0	1.8 ± 0.9	1.8 ± 1.0	< 0.001
No. of active joints (range 0–69)	3.1 ± 3.8	2.1 ± 3.4	1.5 ± 2.5	1.3 ± 2.6	1.5 ± 3.5	1.3 ± 2.9	1.3 ± 3.1	0.098
No. of joints with LOM (range 0–69)	2.3 ± 2.9	1.6 ± 2.2	1.2 ± 1.8	1.2 ± 2.1	1.5 ± 2.8	1.2 ± 2.8	1.2 ± 2.8	0.300
ESR (mm/h)	26.2 ± 23.7	16.7 ± 14.8	13.4 ± 12.9	13.2 ± 12.5	13.0 ± 12.5	14.5 ± 22.5	11.3 ± 9.4	< 0.001

* Analysis of variance for repeated measurements, time effect. † CHAQ: Childhood Health Assessment Questionnaire, 0 (no disability), 3 (severe disability). ‡ CHQ: Child Health Questionnaire, a score where 50 ± 10 corresponds to the mean value ± SD in the normal population (> 50 better than mean, < 50 worse than mean). § Scores could range from 0 cm (best) to 10 cm (worst). # Scores could range from 1 (best) to 5 (worst). LOM: limitation of motion.

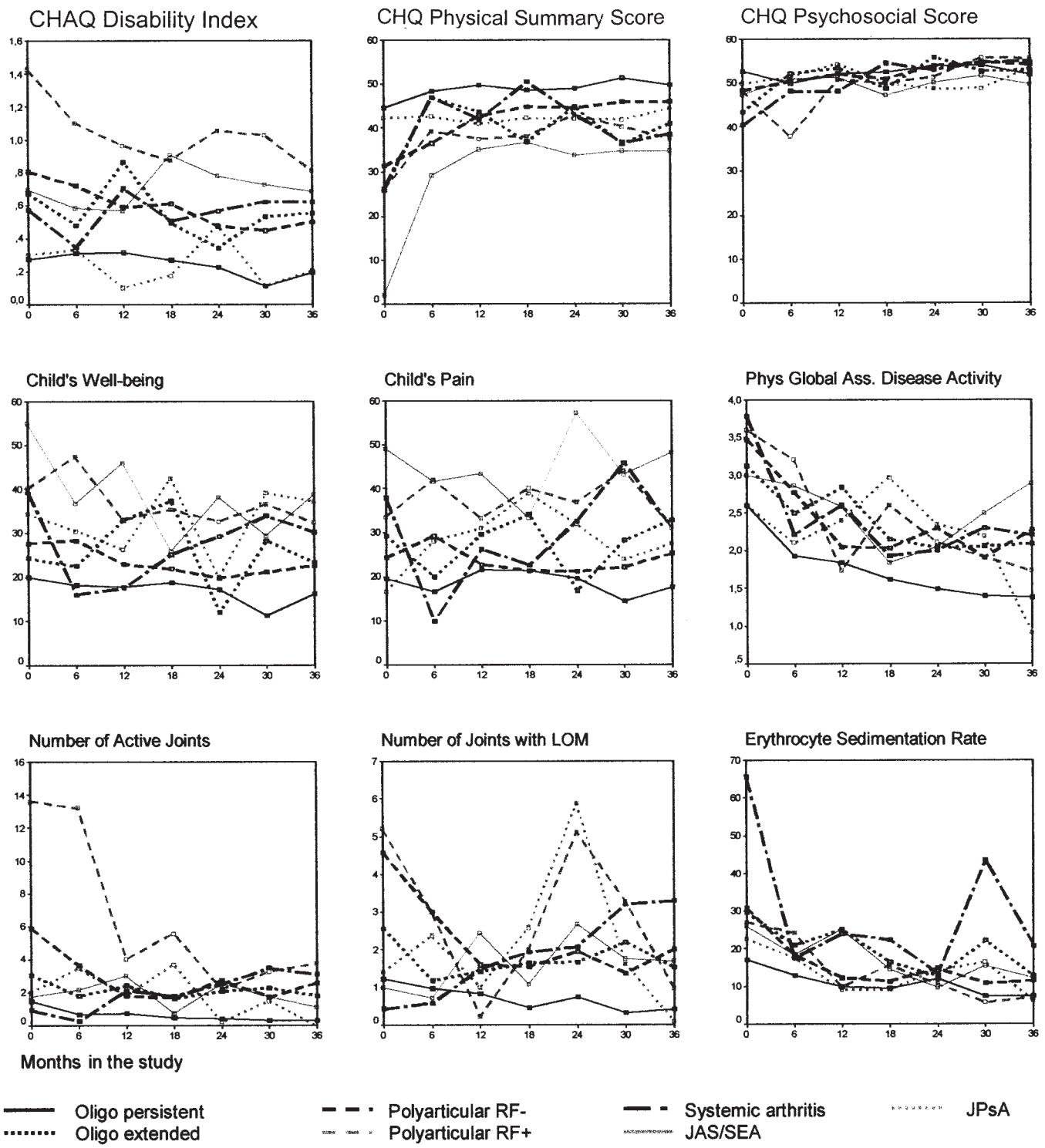

Figure 1. The disease course in the different disease subtypes during 3 years of followup for the variables Child Health Assessment Questionnaire disability index (range 0-3), physical and psychosocial function measured by the Child Health Questionnaire (50 ± 10 corresponds to the mean value ± SD in the normal population), parent's global assessment of child's well-being (0–10 cm VAS), pain (0-10 cm VAS), physician's global assessment of disease activity (Likert scale 1-5), number of active joints (range 0-69), number of joints with limitation of motion (LOM) (range 0-69) and erythrocyte sedimentation rate (range 0-100 mm/h). The x axis represents the number of months in the study. The y axis represents the measurement scale for each variable. JAS: juvenile ankylosing spondylitis. SEA: syndrome of seronegative enthesopathy and arthropathy in children. JPsA: juvenile psoriatic arthritis.

ical function as assessed by the CHAQ and PhS were significantly better in patients with persistent oligoarthritis than in those with extended oligoarthritis, RF negative and RF positive polyarthritis, systemic JRA, and JAS/SEA ($p < 0.005$ vs all, but not significantly different from JPsA). The RF positive polyarthritis group had the poorest physical function as measured by CHAQ ($p \leq 0.008$ vs persistent and extended oligoarthritis, RF negative polyarthritis, systemic arthritis, and JPsA, but not significantly different from JAS/SEA). The patients with JAS/SEA had the poorest physical function as measured by PhS ($p \leq 0.005$ vs persistent oligoarthritis, RF negative polyarthritis, systemic arthritis, and JPsA but not significantly different from extended oligoarthritis and RF positive polyarthritis). There were no significant differences among subgroups in mean levels of psychosocial summary scores.

Parent's global assessment of well-being showed the lowest scores for the patients with persistent oligoarthritis ($p \leq 0.005$ vs all other subtypes) and the worst scores for JAS/SEA ($p \leq 0.018$ vs persistent and extended oligoarthritis, RF negative polyarthritis, and systemic arthritis but not significantly different from RF positive polyarthritis and JPsA).

Pain intensity was significantly higher in patients with JAS/SEA than in those with persistent and extended oligoarthritis, RF negative polyarthritis, and systemic arthritis ($p \leq 0.001$ vs all, but not significantly different from RF positive polyarthritis and JPsA).

Physician's global assessment of disease activity was lowest in patients with persistent oligoarthritis ($p \leq 0.046$ vs all other subgroups) and highest in patients with JAS/SEA ($p \leq 0.001$ vs persistent oligoarthritis but not significantly different from the scores of the other subtypes).

The numbers of active and mobility restricted joints were lowest in patients with persistent oligoarthritis ($p \leq 0.003$ vs extended oligoarthritis, RF negative and RF positive polyarthritis, and systemic arthritis but not different from those with JAS/SEA and JPsA). The highest numbers of active and mobility restricted joints were found in RF positive polyarthritis. This number of active joints was significantly higher than in all other subtypes ($p < 0.001$ vs all). The number of mobility restricted joints in RF positive polyarthritis was significantly higher than in persistent oligoarthritis ($p < 0.001$, but not different from extended oligoarthritis, RF negative polyarthritis, systemic arthritis, JAS/SEA, and JPsA).

ESR was lowest in patients with persistent oligoarthritis ($p < 0.001$ vs extended oligoarthritis, RF negative polyarthritis and systemic arthritis, but not significantly different from RF positive polyarthritis, JAS/SEA, and JPsA), and those with systemic arthritis had the highest ESR ($p < 0.001$ vs all).

Short-term outcome after 3 years. Table 3 shows that in the total group of JRA and JSpA patients there were statistically significant improvements for most disease variables after 3 years of followup compared with baseline. CHAQ disability index was 0.0 (range 0-2.4) in 51.8% (68.4% in persistent oligoarthritis, 37.5% in extended oligoarthritis, 41.8% in RF negative polyarthritis, 40.0% in RF positive polyarthritis, 28.6% in systemic, 0% in JAS/SEA, and 40% in JPsA).

PhS, general health score, and pain score from the generic CHQ at followup were significantly worse in our patient group compared with those of a group of children from the normal population (Table 4). There was no difference in PsS. We divided patients into those with active disease and those in remission. Poor scores in PhS, general health, and pain were mainly found in patients with active disease. The patients in remission had PhS and pain comparable to controls, but a lower general health (Table 4). After 3 years of followup, 53 (26.9%) of the 197 JRA and JSpA patients were in remission. At baseline 93.4% of the patients used nonsteroidal antiinflammatory drugs (NSAID) and 57.9% had started disease modifying antirheumatic drugs (DMARD). After 3 years 47.2% used NSAID and 40.1% used DMARD.

Predictors of disability. We performed a regression analysis looking for predictors of CHAQ disability index after 3 years of followup. The CHAQ score, global assessment of well-being, pain, physician's global assessment of disease activity, number of active and mobility restricted joints, and ESR during the first 6 months were used as independent variables (calculated as AUC between baseline and 6 mo). There was a high correlation between global assessment of well-being and pain ($r = 0.815$, $p < 0.001$). We chose to use well-being in the analysis. The CHAQ score and parent's global assessment of the child's well-being during the first 6 months were predictors of CHAQ disability index after 3 years (standardized beta 0.324 and 0.231, $p < 0.001$ and $p = 0.006$ respectively, $R^2 = 25.1\%$) (Table 5). We also looked separately at predictors for CHAQ disability index at followup in patients with oligoarthritis ($n = 111$) and included course type as an independent variable. Parent's global assessment of the child's well-being during the first 6 months (standardized beta 0.353, $p < 0.001$) and course type (standardized beta 0.345, $p < 0.001$) were predictors of disability after 3 years in the patients with oligoarthritis ($R^2 = 22.2\%$) (Table 6). CHAQ score during the first 6 months was the only predictor of CHAQ disability index after 3 years in the 60 patients with polyarthritis (standardized beta 0.636, $p < 0.001$, $R^2 = 39.4\%$) (Table 7).

DISCUSSION

This is the first prospective study with repeated assessments of health status and disease activity at standardized intervals in JRA and JSpA. We found that health status and disease activity improved over time. The patients had worse physical function, general health, and pain than normal controls. The 2 predictors of the CHAQ disability index after 3 years

Table 3. Meaures of disease activity at first admission and at 3 year followup in 197 children with JRA and JSpA.

Measures of Disease Activity	Baseline Mean (SD)	Followup Mean (SD)	p
CHAQ (range 0–3)*	0.5 (0.6)	0.4 (0.5)	< 0.001
Parent's assessment of child's pain (0–10 cm VAS)†	2.5 (2.4)	2.3 (2.5)	0.586
Parent's assessment of child's fatigue (0–10 cm VAS)†	2.4 (2.5)	2.4 (2.5)	0.857
Parent's global assessment of child's well-being (0–10 cm VAS)†	2.6 (2.3)	2.0 (2.2)	0.001
Morning stiffness (range 0–5 h)	0.5 (0.5)	0.2 (0.4)	< 0.001
Physician's global assessment of disease activity (Likert scale 1–5)‡	3.0 (0.9)	1.8 (1.0)	< 0.001
No. of swollen joints (range 0–66)	3.0 (3.8)	1.2 (3.0)	< 0.001
No. of tender joints (range 0–68)	1.5 (2.7)	0.8 (2.5)	0.004
No. of joints with limited range of motion (range 0–69)	2.3 (2.9)	1.2 (2.9)	< 0.001
No. of active joints (range 0–69)	3.1 (3.8)	1.3 (3.1)	< 0.001
Arthritis severity index (range 0–668)§	8.6 (9.9)	4.6 (12.4)	< 0.001

* CHAQ: Childhood Health Assessment Questionnaire, 0 (no disability), 3 (severe disability). † VAS: Visual analog scale, scores could range from 0 cm (best) to 10 cm (worst). ‡ Scores could range from 1 (best) to 5 (worst). § Scores could range from 0 (best) to 668 (worst).

Table 4. Health status in JRA and JSpA patients after 3 years of followup compared with controls.

	Patients			Controls
	Total N = 173/180	Active Disease N = 124	In Remission N = 49	N = 116
CHQ scores				
Physical summary score*	47.1 ± 12.0†	44.2 ± 12.7‡	54.4 ± 4.7	55.2 ± 7.3
Psychosocial summary score*	53.5 ± 6.9	53.2 ± 7.0	54.4 ± 6.7	54.1 ± 5.7
General health§	64.2 ± 19.1†	61.1 ± 19.5‡	72.4 ± 15.8#	82.7 ± 14.8
Pain§	65.1 ± 29.6†	58.4 ± 29.6‡	83.9 ± 19.9	83.1 ± 19.5

* According to the parent-completed Child Health Questionnaire (CHQ) the summary scores are computed as scores where 50 ± 10 corresponds to the mean value ± SD in the normal population (> 50 better than mean, < 50 worse than mean). † $p < 0.001$ for independent t test between total patient group and controls. ‡ $p < 0.001$ for the difference between patients with active disease and controls. § General health and pain range from 0 to 100, where 0 means poor health status and 100 means excellent health status. # $p = 0.001$ for the difference between patients in remission and controls.

Table 5. The relationship between the Child Health Assessment Questionnaire (CHAQ) disability index at 3 year followup and measures of disease activity in JRA and JSpA (n = 197). Measures of disease activity are analyzed as area under the curve (AUC) between first admission and 6 months.*

	Univariate Analysis			Multiple Regression Analysis‡	
	Area Under the Curve During the First 6 mo (SD)	Pearson's Correlation Coefficient with CHAQ	p	Standardized Beta	p
Measures of disease activity†					
CHAQ	92.4 (107.2)	0.478	< 0.001	0.324	< 0.001
Parent's global assessment of child's well-being	4648.7 (4356.5)	0.447	< 0.001	0.231	0.006
Physician's global assessment of disease activity	509.8 (220.6)	0.079	0.135		
No. of joints with limited range of motion	361.7 (402.4)	0.030	0.336		
No. of active joints	459.1 (503.4)	0.120	0.047		
ESR	3842.9 (3005.0)	0.185	0.005		

* For the measurements y_1 and y_2 at times t_1 and t_2, the AUC between these 2 times is calculated as the product of the time difference and the average of the 2 measurements $(t_2–t_1) \times (y_1 + y_2)/2$. † Pain correlated with the CHAQ after 3 years in the univariate analysis, but was not analyzed in the final model because of a high correlation with well-being. ‡ Results of the final model of multiple linear regression analysis with the CHAQ score at 3 year followup as the dependent variable. Adjusted $R^2 = 25.1\%$.

Table 6. The relationship between the Child Health Assessment Questionnaire (CHAQ) disability index at 3 year followup and measures of disease activity and disease course in oligoarticular JRA (n = 111). Measures of disease activity were analyzed as area under the curve (AUC) between first admission and 6 months.*

	Univariate Analysis			Multiple Regression Analysis§	
	AUC During the First 6 Mo (SD)‡	Pearson's Correlation Coefficient with CHAQ	p	Standardized Beta	p
Measures of disease activity†					
CHAQ	62.5 (80.4)	0.288	0.002		
Parent's global assessment of child's well-being	3752.3 (3846.6)	0.343	< 0.001	0.353	< 0.001
Physician's global assessment of disease activity	458.0 (194.0)	–0.016	0.864		
No. of joints with limited range of motion	233.6 (180.7)	0.108	0.261		
No. of active joints	244.5 (183.8)	0.179	0.060		
ESR	2992.2 (2267.6)	0.257	0.007		
Polyarticular course, n (%)	16 (14.4)	0.334	< 0.001	0.345	< 0.001

* For the measurements y_1 and y_2 at times t_1 and t_2, the AUC between these 2 times is calculated as the product of the time difference and the average of the 2 measurements $(t_2–t_1) \times (y_1 + y_2)/2$. † Pain correlated with the CHAQ after 3 years in the univariate analysis, but was not analyzed in the final model because of a high correlation with well-being. ‡ Unless otherwise stated. § Results of the final model of multiple linear regression analysis with the CHAQ disability index score at 3 year followup as the dependent variable. Adjusted $R^2 = 22.2\%$.

Table 7. The relationship between the Child Health Assessment Questionnaire (CHAQ) disability index at 3 year followup and measures of disease activity in polyarticular JRA (n = 60). Measures of disease activity were analyzed as area under the curve (AUC) between first admission and 6 months.*

	Univariate Analysis			Multiple Regression Analysis‡	
	AUC During the First 6 Mo (SD)	Pearson's Correlation Coefficient with CHAQ	p	Standardized Beta	p
Measures of disease activity†					
CHAQ	154.7 (135.6)	0.636	< 0.001	0.636	< 0.001
Parent's global assessment of child's well-being	5909.0 (5233.7)	0.530	< 0.001		
Physician's global assessment of disease activity	601.9 (252.9)	0.094	0.474		
No. of joints with limited range of motion	686.2 (547.1)	–0.129	0.328		
No. of active joints	946.8 (601.0)	–0.017	0.898		
ESR	4577.7 (3470.2)	–0.014	0.912		

* For the measurements y_1 and y_2 at times t_1 and t_2, the AUC between these 2 times is calculated as the product of the time difference and the average of the 2 measurements $(t_2–t_1) \times (y_1 + y_2)/2$. † Pain correlated with the CHAQ after 3 years in the univariate analysis, but was not analyzed in the final model because of a high correlation with well-being. ‡ Results of the final model of multiple linear regression analysis with the CHAQ disability index score at followup as the dependent variable. Adjusted $R^2 = 39.4\%$.

were the CHAQ score and parent's global assessment of the child's well-being during the first 6 months.

During the first year of followup, physical function, physician's assessment of disease activity, and ESR all improved significantly for the patient group as a whole and for the major subgroups. About 60% of our patients started DMARD at baseline, and it is difficult to know whether the improvement over time is due to the natural course of the disease or whether the changes reflect the effect of starting treatment. There are few data on health status and disease activity during the first years of JRA and JSpA. Bowyer, *et al* found that 50% of patients with persistent pauciarticular disease and 45% of those with systemic onset type did not require medication 1 year after onset[22]. This could indicate an improvement during the first year, and our results support this.

Our patients with RF negative and RF positive polyarticular JRA had higher levels of disease activity and severity than those with persistently oligoarticular JRA throughout the study. For patients with systemic arthritis, the level of disease activity fluctuated mainly between the disease activity levels for oligoarthritis and polyarthritis, but over time they tended to move towards the same or higher levels than the polyarticular onset types. The finding that the persistent oligoarthritis group was the one with least disease activity is in accordance with the findings of several other studies of longer disease duration. However, as far as we can see, ours is the first study that has followed a patient group prospectively using repeated measurements of disease variables. Most studies of disease outcome have one endpoint, and the value of comparing these outcomes with our disease levels over 3 years is limited. Bowyer, *et al* found no patients with pauciarticular onset JRA who had significant limitations in physical function as measured by the Steinbrocker functional class, either one or 5 years after onset. In contrast, 12% of the patients with polyarticular onset and 30% of those with systemic onset were in class 3 or 4 after 5 years[22]. Andersson Gäre, *et al* found after 7 years that CHAQ showed significant differences in physical functioning in girls, where patients with polyarticular disease had higher scores than those with monoarticular, pauciarticular, or sys-

temic disease[23]. In the study of Flatø, *et al* the patients with polyarticular course had significantly more disability than those with persistently pauciarticular JRA after 10 years of disease duration[6]. This was also found by Oen, *et al*[24]. Ruperto, *et al* found the best CHAQ/HAQ scores in patients with pauciarticular JRA and the worst in patients with polyarticular and systemic JRA after 15 years of disease duration[25]. Minden, *et al* compared the HAQ scores for juvenile idiopathic arthritis (JIA) subgroups after 16.5 years of disease duration and found a tendency towards worse functional status in patients with polyarthritis than in those with systemic and oligo/enthesitis-related JIA[26].

The JAS/SEA patients seemed to have poor health status in our study. Their physical function, well-being, and pain were markedly worse than that of the other disease subtypes throughout the study, except for the levels of RF positive polyarthritis. Due to the small number of patients in the JAS/SEA group, these results should be interpreted with caution. The JAS patients represent probably those with the most severe spondyloarthropathies. All the patients with SEA syndrome had arthritis. Thus our JAS/SEA patient group have a bias towards more severe forms of disease. However, the poor health in the JAS/SEA group compared with the other onset groups is in accordance with findings in other studies. Burgos-Vargas, *et al* reported that peripheral joint disease became polyarticular in most patients with JAS[27]. Pain is the most frequent symptom in JSpA[28]. Andersson Gäre, *et al* found that girls with JAS had higher CHAQ scores than those with monoarticular, pauciarticular, or systemic disease after 7 years[23]. Flatø, *et al* found that radiographic changes in the hips, and erosion of a peripheral joint were more frequent in juvenile arthritis patients with sacroiliitis than in those without[29]. On the other hand, Flatø, *et al* did not find a statistically significant difference in the median disability index between JRA and JSpA after 10 years of followup[6]. More prospective studies are needed to settle this issue.

Health status and disease activity generally improved in the patient group after 3 years except for pain and fatigue, which remained mainly unchanged. According to Dempster, *et al* an improvement in disability index of more than 0.13 is of clinical importance[30], and the change in disability index for our patients was higher than this. In our study, patients with active disease had worse physical function, pain, and general health than the control group at followup. The patients in remission had pain and physical function comparable to those of the controls, indicating that these variables are reversible in most patients during early disease. However, the patients in remission considered their general health to be inferior to that of the controls. This is in accordance with other studies of longer disease duration[7,31].

In our study we saw that the level of pain had not significantly improved after 3 years in spite of the significant reduction in most other disease activity variables. Our data support the view that pain is an important dimension in the burden of disease in JRA and JSpA[15,28,32].

There was a minor change over time in psychosocial function for the patient group as a whole, but this was not considered to be clinically relevant since it was within the normal range[33].

Physical function and well-being during the first 6 months were of importance for predicting physical function at 3 years in our study. Disability index at disease onset has not previously been assessed as a possible predictor in JRA and JSpA, but has been shown to be important in RA[34,35]. Our results are in accordance with those of Ruperto, *et al*[36], indicating that parent's global assessment is a sensitive instrument. Our finding that disability and well-being at baseline are important and sensitive predictors of functional disability over time suggests that these variables might be of value in clinical practice. However these variables explained only 25% of the variance in our analysis, implying that factors other than disease variables and patient characteristics influence the level of disability.

Our patient group is a referral-based cohort, which probably represents about half of the estimated JRA and JSpA patients in Norway. These patients probably have more severe disease than cohorts selected from the general population. However, our patient group is comparable to the JRA/juvenile chronic arthritis patients in a number of epidemiological studies as regards age, gender, and distribution of onset type[7,37,38].

The high percentage of patients with HLA-B27 in our study is in accordance with another Norwegian study[29]. The background frequency of HLA-B27 in the Norwegian population varies from 10% in the south to 16% in the north[39]. If we exclude the patients with JAS/SEA in our study, the frequency of HLA-B27 reduces to 19%. A linkage disequilibrium between HLA-DR8 and HLA-B27 in Norwegian patients with JRA has been found and may explain the excess of HLA-B27 (Rafal Ploski, personal communication). However, as our study covers the first years of the disease course, our patient group with oligoarthritis could still contain patients who will develop JSpA later.

We found that health status and disease activity improved over time in patients under medical treatment. The CHAQ disability index and the child's well-being during the first 6 months were important predictors of physical function at 3 years. The importance of these variables as predictors for the longterm outcome of JRA and JSpA should be further explored.

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REFERENCES

1. Giannini EH, Brewer EJ, Kuzmina N, et al. Methotrexate in

resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. N Engl J Med 1992;326:1043-9.
2. Levinson JE, Wallace CA. Dismantling the pyramid. J Rheumatol 1992;19:6-10.
3. Wallace CA, Sherry DD. Trial of intravenous pulse cyclophosphamide and methylprednisolone in the treatment of severe systemic-onset juvenile rheumatoid arthritis. Arthritis Rheum 1997;40:1852-5.
4. Lovell DJ, Giannini EH, Reiff A, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med 2000;342:763-9.
5. Lahdenne P, Vahasalo P, Honkanen V. Infliximab or etanercept in the treatment of children with refractory juvenile idiopathic arthritis: an open label study. Ann Rheum Dis 2003;62:245-7.
6. Flato B, Aasland A, Vinje O, Forre O. Outcome and predictive factors in juvenile rheumatoid arthritis and juvenile spondyloarthropathy. J Rheumatol 1998;25:366-75.
7. Peterson LS, Mason T, Nelson AM, O'Fallon WM, Gabriel SE. Psychosocial outcomes and health status of adults who have had juvenile rheumatoid arthritis: a controlled, population-based study. Arthritis Rheum 1997;40:2235-40.
8. van Leeuwen MA, van Rijswijk MH, Sluiter WJ, et al. Individual relationship between progression of radiological damage and the acute phase response in early rheumatoid arthritis. Towards development of a decision support system. J Rheumatol 1997;24:20-7.
9. Brewer EJJ, Bass J, Baum J, et al. Current proposed revision of JRA criteria. JRA Criteria Subcommittee of the Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Section of The Arthritis Foundation. Arthritis Rheum 1977;20:195-9.
10. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361-8.
11. Rosenberg AM, Petty RE. A syndrome of seronegative enthesopathy and arthropathy in children. Arthritis Rheum 1982;25:1041-7.
12. Southwood TR, Petty RE, Malleson PN, et al. Psoriatic arthritis in children. Arthritis Rheum 1989;32:1007-13.
13. Petty RE, Southwood TR, Baum J, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. J Rheumatol 1998;25:1991-4.
14. Singh G, Athreya BH, Fries JF, Goldsmith DP. Measurement of health status in children with juvenile rheumatoid arthritis. Arthritis Rheum 1994;37:1761-9.
15. Flato B, Sorskaar D, Vinje O, et al. Measuring disability in early juvenile rheumatoid arthritis: evaluation of a Norwegian version of the childhood Health Assessment Questionnaire. J Rheumatol 1998;25:1851-8.
16. Landgraf JM, Abetz L, Ware JE. Child Health Questionnaire (CHQ): A user's manual. Boston, MA: The Health Institute, New England Medical Center; 1996.
17. Selvaag AM, Flato B, Lien G, Sorskaar D, Vinje O, Forre O. Measuring health status in early juvenile idiopathic arthritis: determinants and responsiveness of the child health questionnaire. J Rheumatol 2003;30:1602-10.
18. Brewer EJJ, Giannini EH. Standard methodology for Segment I, II, and III Pediatric Rheumatology Collaborative Study Group studies. I. Design. J Rheumatol 1982;9:109-13.
19. Hill AV, Allsopp CE, Kwiatkowski D, Anstey NM, Greenwood BM, McMichael AJ. HLA class I typing by PCR: HLA-B27 and an African B27 subtype. Lancet 1991;337:640-2.
20. Matthews JN, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. BMJ 1990;300:230-5.
21. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum 1997;40:1202-9.
22. Bowyer SL, Roettcher PA, Higgins GC, et al. Health status of patients with juvenile rheumatoid arthritis at 1 and 5 years after diagnosis. J Rheumatol 2003;30:394-400.
23. Gare BA, Fasth A. The natural history of juvenile chronic arthritis: a population based cohort study. II. Outcome. J Rheumatol 1995;22:308-19.
24. Oen K, Malleson PN, Cabral DA, Rosenberg AM, Petty RE, Cheang M. Disease course and outcome of juvenile rheumatoid arthritis in a multicenter cohort. J Rheumatol 2002;29:1989-99.
25. Ruperto N, Levinson JE, Ravelli A, et al. Long-term health outcomes and quality of life in American and Italian inception cohorts of patients with juvenile rheumatoid arthritis. I. Outcome status. J Rheumatol 1997;24:945-51.
26. Minden K, Niewerth M, Listing J, et al. Long-term outcome in patients with juvenile idiopathic arthritis. Arthritis Rheum 2002;46:2392-401.
27. Burgos-Vargas R, Naranjo A, Castillo J, Katona G. Ankylosing spondylitis in the Mexican mestizo: patterns of disease according to age at onset. J Rheumatol 1989;16:186-91.
28. Burgos-Vargas R, Pacheco-Tena C, Vazquez-Mellado J. The juvenile-onset spondyloarthritides: rationale for clinical evaluation. Best Pract Res Clin Rheumatol 2002;16:551-72.
29. Flato B, Smerdel A, Johnston V, et al. The influence of patient characteristics, disease variables, and HLA alleles on the development of radiographically evident sacroiliitis in juvenile idiopathic arthritis. Arthritis Rheum 2002;46:986-94.
30. Dempster H, Porepa M, Young N, Feldman BM. The clinical meaning of functional outcome scores in children with juvenile arthritis. Arthritis Rheum 2001;44:1768-74.
31. Flato B, Lien G, Smerdel A, et al. Prognostic factors in juvenile rheumatoid arthritis: a case-control study revealing early predictors and outcome after 14.9 years. J Rheumatol 2003;30:386-93.
32. Schanberg LE, Anthony KK, Gil KM, Maurin EC. Daily pain and symptoms in children with polyarticular arthritis. Arthritis Rheum 2003;48:1390-7.
33. Noll RB, Kozlowski K, Gerhardt C, Vannatta K, Taylor J, Passo M. Social, emotional, and behavioral functioning of children with juvenile rheumatoid arthritis. Arthritis Rheum 2000;43:1387-96.
34. 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;39:732-41.
35. Combe B, Cantagrel A, Goupille P, et al. Predictive factors of 5-year health assessment questionnaire disability in early rheumatoid arthritis. J Rheumatol 2003;30:2344-9.
36. Ruperto N, Ravelli A, Falcini F, et al. Responsiveness of outcome measures in juvenile chronic arthritis. Italian Pediatric Rheumatology Study Group. Rheumatology Oxford 1999;38:176-80.
37. Gare BA, Fasth A. Epidemiology of juvenile chronic arthritis in southwestern Sweden: a 5-year prospective population study. Pediatrics 1992;90:950-8.
38. Moe N, Rygg M. Epidemiology of juvenile chronic arthritis in northern Norway: a ten-year retrospective study. Clin Exp Rheumatol 1998;16:99-101.
39. Gran JT, Mellby AS, Husby G. The prevalence of HLA-B27 in Northern Norway. Scand J Rheumatol 1984;13:173-6.