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Early Self-Reported Pain in Juvenile Idiopathic Arthritis as Related to Long-Term Outcomes: Results From the Nordic Juvenile Idiopathic Arthritis Cohort Study

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Objective. To study self-reported pain early in the disease course of juvenile idiopathic arthritis (JIA) as a predictor of long-term disease outcomes.

Methods. Consecutive cases of JIA with disease onset from 1997 to 2000 from defined geographical areas of Norway, Sweden, Finland, and Denmark were prospectively enrolled in this population-based cohort study. Self-reported, disease-related pain was measured on a 10-cm visual analog scale (VAS pain). Inclusion criteria were a baseline visit with a pain score 6 months after disease onset, followed by an 8-year study visit. Remission was defined according to Wallace et al (2004) preliminary criteria. Functional disability was measured by the Childhood Health Assessment Questionnaire and the Child Health Questionnaire Parent Form if the child was age <18 years and by the Health Assessment Questionnaire if age ≥18 years. Damage was scored using the Juvenile Arthritis Damage Index.

Results. The final study cohort consisted of 243 participants, and 120 participants (49%) had oligoarticular onset. At baseline, 76% reported a VAS pain score >0 compared to 57% reporting at 8 years. Half of those who reported baseline pain also reported pain at 8 years but at a lower intensity. Compared to no pain, higher pain intensity at baseline predicted more pain at 8 years, more functional disability, more damage, and less remission without medication. Baseline pain predicted more use of disease-modifying antirheumatic drugs/biologics during the disease course. Participants with oligoarticular JIA reporting pain at baseline were more likely to develop extended oligoarticular JIA or other JIA categories with an unfavorable prognosis.

Conclusion. Early self-reported, disease-related pain among children and adolescents with JIA is common and seems to predict persistent pain and unfavorable long-term disease outcomes.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a diverse chronic disease with onset at age <16 years. This most common rheumatic disease among children is characterized by at least 6 weeks of continuous arthritis of unknown cause in 1 or more joints (1). The incidence rate in the Nordic countries is reported to be approximately 15–22 per 100,000 children (2–4). JIA is a heterogeneous disorder classified into 7 categories, based on defined criteria occurring during the first 6 months after disease onset (5). Among the different categories, and within each category, the disease course and outcome differ markedly (6). Persistent oligoarticular JIA has the best prognosis of all JIA categories (7). Extended oligoarticular JIA has a more unfavorable outcome, similar to that of polyarticular disease (8,9). Predicting outcome is challenging, and several studies have focused on associations between long-term outcome and clinical characteristics and biomarkers, such as the nature of joint involvement, the intensity

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No potential conflicts of interest relevant to this article were reported.

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SIGNIFICANCE & INNOVATIONS

- Pain is a frequent symptom, tends to persist, and affects health-related quality of life for children and adolescents with juvenile idiopathic arthritis (JIA).
- In this study, we showed for the first time that an early pain report is associated with long-term nonremission, functional impairment, more use of disease-modifying antirheumatic drugs/biologics, and, for those with oligoarticular JIA, development into extended disease.
- The study adds to the increasing amount of evidence establishing the importance of pain assessment in routine care of children and adolescents with JIA.

of acute-phase response, and the existence of autoantibodies and genetic variables (10). Because none of those predictors are perfect, and in order to tailor treatment to reach the target of clinical remission, there is a need for more prospective longitudinal studies to evaluate early predictors using validated and multidimensional measures (10). More patient-centered measurements have been needed for assessment of the course and outcome of JIA (11). Among the 6 core variables endorsed by the American College of Rheumatology (ACR) (12), only the parent/patient assessment of overall well-being can be defined as a patient-reported measure. Patients, parents, and clinicians have pointed to more specific quality-of-life measures, and especially pain, as important measures when evaluating the course and outcome of JIA (11).

Pain is a frequent symptom among children and adolescents with JIA (13,14). Pain perception is highly subjective, and different self-reported measures are used to detect pain frequency and intensity (15,16). Pain assessment in young children is especially challenging, because pain reports are dependent on the parents' assumption of their child's pain (17). Both unidimensional and multidimensional tools are available for parent and child/adolescent assessment of pain in JIA (16). Among the unidimensional tools, the visual analog scale (VAS) is a commonly used and validated scoring instrument (18,19). The pathogenesis of pain in children and adolescents with JIA is multifactorial, including both biologic and psychosocial factors (16,20). Pain is a distressing symptom, and several studies have elucidated the relationship between pain, functional disability, and health-related quality of life (21–24), but information about pain as a predictor of long-term disease outcome is lacking.

In our Nordic population-based JIA cohort with comprehensive and prospectively sampled data, we have previously studied different aspects of JIA (2,8). In this project, we aimed to study self-reported pain early in the disease course and the association with long-term disease outcomes.

PATIENTS AND METHODS

Patients. The Nordic JIA cohort is a population-based cohort study. Consecutive cases of newly diagnosed JIA from defined geographical areas of Norway, Sweden, Finland, and Denmark with disease onset from January 1, 1997 to June 30, 2000, were prospectively included. Disease onset was defined as the day the child fulfilled the criteria for active arthritis according to information given by the parents/patient or by a physician. Participants were included consecutively and as soon as possible after the diagnosis was determined. However, the first extensive baseline visit was scheduled for 6 months after disease onset. This time point was chosen to enable classification of the disease into a JIA category, according to the International League Against Rheumatism Edmonton criteria (5). We have no registration of onset symptoms in the database. A detailed description of data collection and patient enrollment has been published previously (2,8). In the current study, participants were included if they had at least a baseline visit 6 months after disease onset with available pain scores, and participation in the 8-year follow-up visit. At both visits, we had data from clinical examinations, disease activity measures, previous and ongoing medication, and damage and remission status, as well as results from blood tests. Health-related quality of life was reported by the children or by their parents.

Measures. Self-reported, disease-related pain intensity during the previous week was measured on a 10-cm VAS for pain (where 0 = no pain and 10 = worst possible pain) by the child if age ≥9 years or by the parents if the child was age <9 years. VAS pain was assessed with the question "How do you rate your/your child's pain due to your/his or her illness in the past week?" As in previous studies on pain in JIA (15,24–26), pain analyses were explored both by categorization of VAS pain (0, >0 to 3, >3 to 7, or >7 to 10), and dichotomized into 0 (no pain) or >0. We performed subanalyses on VAS pain scores in participants age <9 years and ≥9 years to look for any discrepancies between parent- and patient-reported pain (27). Self-reported physical disability questionnaires were the disease-specific and validated Childhood Health Assessment Questionnaire (C-HAQ; where 0 = no difficulty and 3 = unable to do) if the child was age <18 years (28,29), and the Health Assessment Questionnaire (HAQ; where 0 = no difficulty and 3 = unable to do) if age ≥18 years (30). Children age ≥9 years filled out the C-HAQ, and parents filled out the questionnaire for those age <9 years.

For children age <18 years, the parent form of the generic health-related quality-of-life instrument, the Child Health Questionnaire Parent Form (CHQ-PF50, or simply CHQ), was answered by the parents, yielding a physical summary score and a psychosocial summary score (range 0–100, where 0 = worst, with a mean ± SD score of 50 ± 10) (28,31,32). This instrument is designed to capture the child's physical and psychosocial well-being

independent of his/her disease, and it is comparable to norm scores from the general US population. Damage was scored by experienced pediatric rheumatologists using the Juvenile Arthritis Damage Index (JADI) assessment of articular damage (JADI-A) (range 0–72, where 0 = no damage) and extraarticular damage (JADI-E) (range 0–17, where 0 = no damage) (8,32). Damage was defined as either JADI-A and/or JADI-E score >0. As in previous studies, C-HAQ/HAQ and JADI scores were dichotomized into 0 (no disability, no damage) or >0 (8,24,33). Physical and psychosocial summary scores of the CHQ were dichotomized into <40 (poor health) or ≥40 (better health) (28,31). Remission was defined according to the preliminary criteria described by Wallace et al (34). Remission status was dichotomized into remission without medication or not in remission without medication (33). The latter included active disease, inactive disease not yet in remission, and in remission while taking medication.

Ethics approval. Medical research ethics committees from each participating country gave their approval according to national practice and regulations in accordance with the Declaration of Helsinki. Written informed consent was obtained from children age ≥16 years and from their parents if age <16 years.

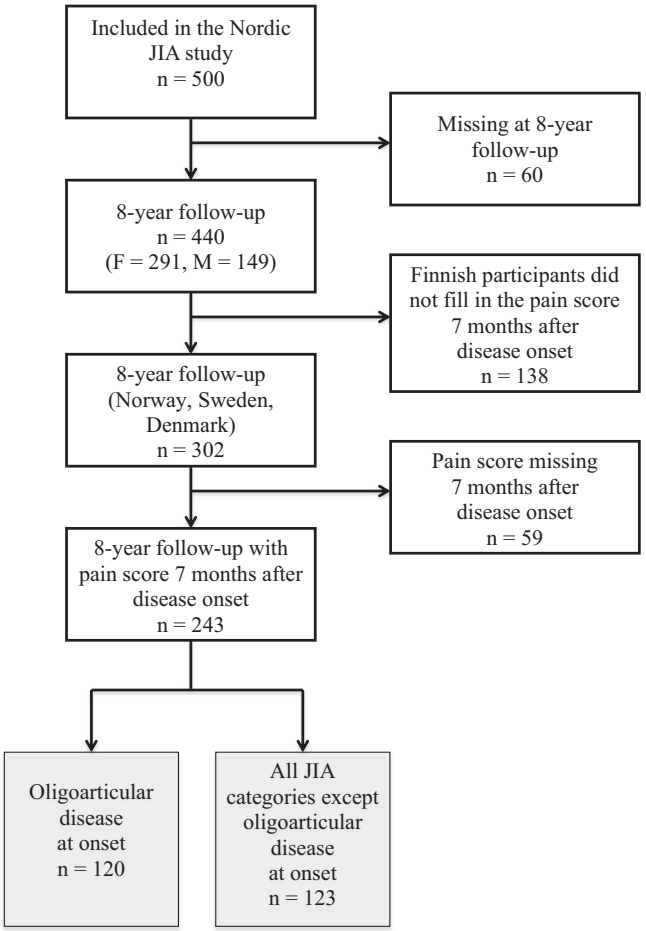

Figure 1. Flow-chart of the study population. JIA = juvenile idiopathic arthritis; F = female; M = male.

Statistical analysis. We used descriptive statistics with median and interquartile ranges (IQRs) for continuous variables, and absolute frequency percentage with 95% confidence intervals (95% CIs) for categorical variables. To evaluate the predictive value of pain at baseline for outcome measures after 8 years and medication during the disease course, model-based absolute risks were estimated after binominal regression using the post-estimation command lincom in Stata software, version 14. Sex adjustment was weighted 0.7 for girls to mimic the distribution in the population. In additional analyses, we also adjusted for age. To estimate absolute risks, we used the mean age at disease onset of 6.8 years. We used logistic regression to estimate the odds ratio with 95% CIs using VAS pain as a continuous variable. In further analyses, we made receiver operator characteristic (ROC) curves based on measures of sensitivity and specificity. The area

Table 1. Clinical characteristics of the juvenile idiopathic arthritis (JIA) study population*

Characteristic	Total no.	Values
Female	243	170 (70)
Oligoarticular JIA at onset	243	120 (49)
Age at disease onset, median (IQR) years	243	6.3 (2.9–10.3)
Age at 8-year follow-up, median (IQR) years	243	14.9 (11.1–18.5)
Disease duration at baseline visit, median (IQR) months	243	7 (6–9)
Disease duration at 8-year follow-up, median (IQR) months	243	97 (95–102)
VAS pain >0 at baseline visit†	243	185 (76)
VAS pain >0 at 8-year follow-up†	204	117 (57)
C-HAQ/HAQ >0 at 8-year follow-up	207	80 (39)
CHQ PhS <40 at 8-year follow-up	132	25 (19)
CHQ PsS <40 at 8-year follow-up	132	7 (5)
JADI >0 at 8-year follow-up	203	46 (23)
Not in remission at 8-year follow-up‡	236	135 (57)

* Values are the number (%) unless indicated otherwise. IQR = interquartile range; VAS = visual analog scale; C-HAQ = Childhood Health Assessment Questionnaire (used for age <18 years); HAQ = Health Assessment Questionnaire (used for age ≥18 years); CHQ PhS = Child Health Questionnaire physical summary score (range 0–100); CHQ PsS = Child Health Questionnaire psychosocial summary score (range 0–100); JADI = Juvenile Arthritis Damage Index.
† Self-reported pain was measured on a 10-cm VAS pain scale.
‡ Not in remission without medication according to the definition by Wallace et al (ref. 34).

under the curve was calculated with 95% CIs, and with the following interpretations: an area of 0.5 or lower was considered to be no discrimination, ≥0.7 to <0.8 as acceptable discrimination, ≥0.8 to <0.9 as excellent discrimination, and ≥0.9 as outstanding discrimination (35). Statistical analyses were carried out using STATA software, version 14.

RESULTS

Clinical characteristics of the study group. Of the 500 patients included from the 4 Nordic countries, 440 participated in the 8-year follow-up. Due to lack of baseline pain scores, all Finnish participants (n = 138) and an additional 59 participants from the other countries were excluded. The final study population consisted of 243 children (Figure 1) with a median baseline visit at 7 months and a final follow-up visit at 97 months (Table 1). Among these participants 70% were female, 49% had oligoarticular disease, and the median age was 6.3 years at disease onset and 14.9 years at follow-up (Table 1). The diagnostic delay was short, and the median interval between disease onset and diagnosis of arthritis by a physician was 50.5 days (IQR 14–101 days). Of these 243 participants, intraarticular glucocorticoid injections had been given to 91 participants, and for 34 of these the drug had been given within the last 3 months of the baseline visit (results not shown). At this baseline visit, none of the participants were taking biologics, but 20 were taking systemic steroids. Methotrexate was used by 31 of the participants, and of those, 8 had cumulative doses ≥100 mg. The 60 participants who did not participate in the 8-year study did not differ significantly in the proportion of oligoarticular JIA or with respect to sex, and had a median follow-up of 47 months (range 5–83 months). At their last registered visit, 30 participants (50%) had a pain assessment, including 21 with VAS pain scores >0, and 9 with VAS pain scores = 0. Participants excluded from the current study due to lack of pain data at baseline had a lower median age (5.1 versus 6.3 years) and the proportion of males was slightly higher (39% versus 30%). There was no difference in the proportion of oligoarticular JIA at onset and remission status at 8 years between the included and excluded participants.

Pain scores. More participants reported a VAS pain score >0 at the baseline visit (76%) than at 8 years (57%). The mean pain intensity score (VAS pain) of those reporting pain was higher at baseline, 3.0 (95% CI 2.6, 3.3) than at 8 years, 2.4 (95% CI 2.0, 2.8). The distribution of pain intensity scores at the baseline visit and at the 8-year follow-up is shown in Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23715/abstract. For participants age <9 years at baseline, 118 of 159 (74%) had a parent-reported pain score >0 with a mean intensity of 2.7 (95% CI 2.3, 3.0), while 67 of 84 participants (79%) age ≥9 years had a patient-reported pain score >0, with a mean intensity of 3.5 (95% CI 2.9, 4.1). Among participants with pain measures both at baseline and 8 years (n = 204), 50% reported a VAS pain score >0 at both visits, and 19% reported no pain at both visits (Figure 2). We divided this group into participants ages <9 and ≥9 years at baseline. Participants age <9 years had parent-reported pain scores at their first visit and patient-reported pain scores at their last visit, and 48% reported a VAS pain score >0 at both visits. Participants age ≥9 years had only patient-reported pain scores, and 55% reported a VAS pain score >0 at both visits (results not shown).

Baseline pain scores and long-term outcome measures. The association between baseline pain scores subdivided into 4 categories of pain intensity and long-term

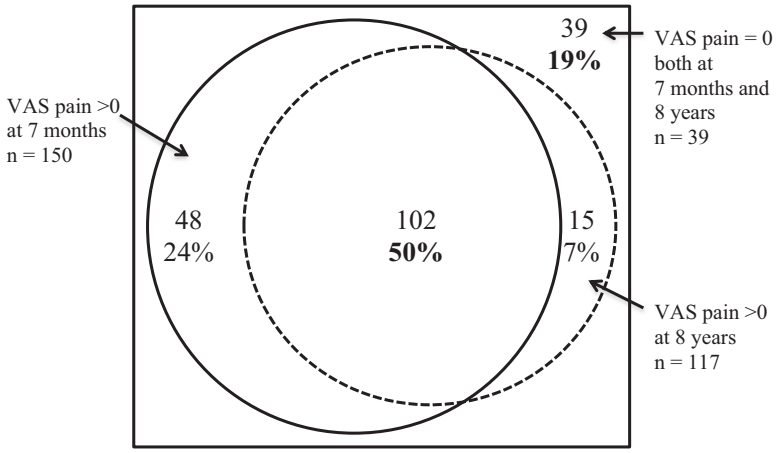

Figure 2. Venn diagram demonstrating pain persistency in the Nordic juvenile idiopathic arthritis study cohort. The cohort included 204 participants with pain measures 7 months after disease onset and at the 8-year follow-up. Disease-related pain was measured on a 10-cm visual analog scale (VAS pain) (where 0 = no pain and 10 = worst possible pain). A continuous circle represents a VAS pain score >0 at 7 months and a broken circle represents a VAS pain score >0 at 8 years.

Table 2. Association between baseline pain report at 7 months after disease onset and outcomes at 8-year follow-up in juvenile idiopathic arthritis*

Baseline VAS pain	VAS pain >0†	C-HAQ/ HAQ >0	CHQ PhS <40	JADI >0	Not in remission‡
0§	15/54, 28 (16, 40)	9/54, 18 (8, 28)	3/32, 11 (1, 21)	4/53, 8 (1, 15)	14/55, 26 (14, 37)
>0–3§	53/86, 62 (51, 72)	31/86, 35 (25, 45)	8/62, 12 (4, 21)	25/83, 30 (20, 40)	61/95, 64 (54, 74)
>3–7§	44/58, 74 (63, 85)	34/60, 56 (44, 69)	14/38, 37 (22, 52)	15/60, 25 (14, 36)	52/73, 71 (61, 81)
>7–10§	5/6, 90 (66, 114)	6/7, 94 (80, 107)	0 0	2/7, 28 (–5, 61)	8/13, 61 (35, 88)
Continuous, OR (95% CI)⁋	1.5 (1.2, 1.7)	1.4 (1.2, 1.6)	1.4 (1.1, 1.7)	1.1 (0.9, 1.2)	1.2 (1.1, 1.4)

* Values are the number/total number, percentage (95% confidence interval [95% CI]) unless indicated otherwise. VAS = visual analog scale; C-HAQ = Childhood Health Assessment Questionnaire (used for age <18 years); HAQ = Health Assessment Questionnaire (used for age ≥18 years); CHQ PhS = Child Health Questionnaire physical summary score (range 0–100); JADI = Juvenile Arthritis Damage Index; OR = odds ratio.
† Self-reported pain was measured on a 10-cm VAS pain scale.
‡ Not in remission without medication according to the definition by Wallace et al (ref. 34).
§ Self-reported pain was measured on a 10-cm VAS pain scale, adjusted for sex, weighted 0.7 for girls.
⁋ Self-reported pain was measured on a 10-cm VAS pain scale, analyzed with VAS pain as a continuous variable, adjusted for sex, weighted 0.7 for girls.

outcome measures is shown in Table 2. Participants reporting a VAS pain score >0 at the baseline visit more frequently reported pain and functional disability (C-HAQ/HAQ >0) at the 8-year follow-up. A distinct dose-response curve was observed with increasing pain intensity at baseline. Using VAS pain as a continuous variable, we observed an increased odds ratio for

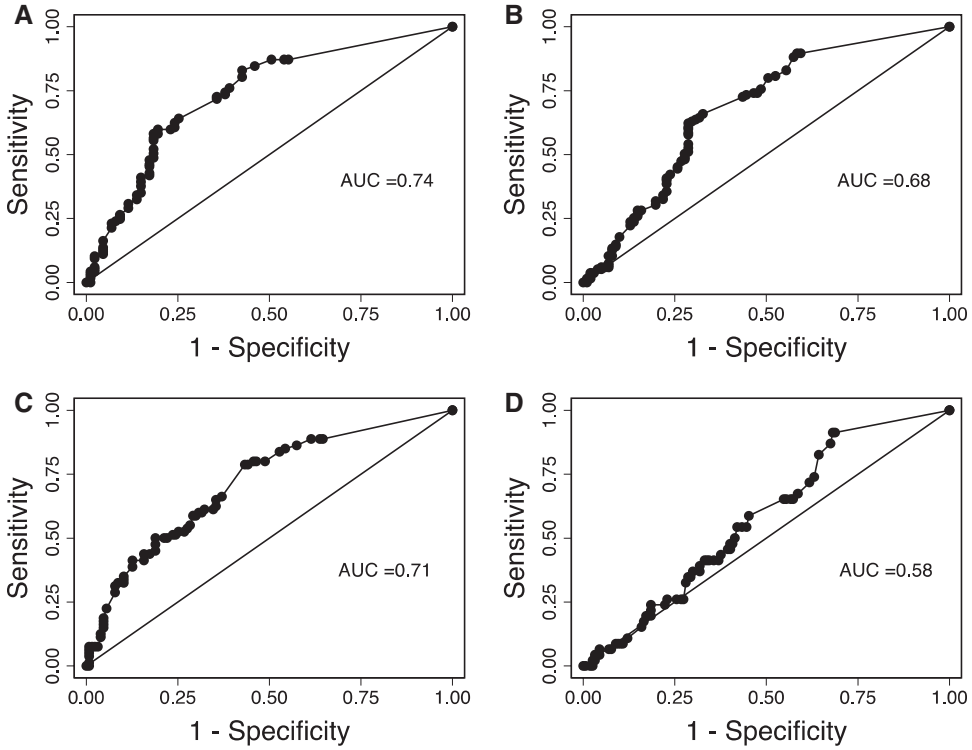

Figure 3. Receiver operator characteristic curves in the Nordic juvenile idiopathic arthritis study cohort for different disease outcomes after 8 years compared to self-reported disease-related pain at 7 months after disease onset, measured on a 10-cm visual analog scale (VAS; where 0 = no pain and 10 = worst possible pain). Remission was defined according to the preliminary criteria described by Wallace et al (34). Functional disability was measured with the Childhood Health Assessment Questionnaire/Health Assessment Questionnaire. Damage was measured with the Juvenile Arthritis Damage Index, articular and extraarticular. The area under the curve (AUC) values were 0.74 (95% CI 0.67, 0.80) for persistent pain, 0.68 (95% CI 0.61, 0.75) for not being in remission, 0.71 (95% CI 0.64, 0.79) for functional disability, and 0.58 (95% CI 0.50, 0.67) for joint damage. **A**, Persistent pain. **B**, Not in remission. **C**, Functional disability. **D**, Damage.

Table 3. Association between baseline pain report at 7 months after disease onset and outcomes at 8-year follow-up in juvenile idiopathic arthritis with oligoarticular onset*

Baseline VAS pain	Extend oligo/others†	VAS pain >0‡	C-HAQ/ HAQ >0	JADI >0	Not in remission§
0⁋	12/40, 30 (16, 44)#	10/37, 26 (12, 40)	7/37, 16 (7, 26)	3/36, 7 (0, 15)	11/38, 29 (14, 43)
>0⁋	39/80, 48 (38, 60)**	40/65, 61 (50, 73)	26/66, 39 (28, 51)	19/65, 29 (18, 40)	51/78, 65 (55, 76)
Continuous, OR (95% CI)††	1.3 (1.1, 1.6)	1.4 (1.1, 1.8)	1.4 (1.1, 1.8)	1.0 (0.8, 1.3)	1.3 (1.0, 1.5)

* Values are the number/total number, percentage (95% confidence interval [95% CI]) unless indicated otherwise. VAS = visual analog scale; Extend oligo = extended oligoarticular juvenile idiopathic arthritis (JIA); C-HAQ = Childhood Health Assessment Questionnaire (used for age <18 years); HAQ = Health Assessment Questionnaire (used for age ≥18 years); JADI = Juvenile Arthritis Damage Index; OR = odds ratio.
† Oligoarticular JIA at 6 months changed to either extended oligoarticular or other JIA categories at the 8-year follow-up.
‡ Self-reported pain was measured on a 10-cm VAS pain scale.
§ Not in remission without medication according to the definition by Wallace et al (ref. 34).
⁋ Self-reported pain was measured on a 10-cm VAS pain scale, adjusted for sex, weighted 0.7 for girls.
Others were 1 with enthesitis-associated arthritis and 2 with undifferentiated arthritis.
** Others were 2 with psoriatic arthritis, 6 with enthesitis-associated arthritis, and 2 with undifferentiated arthritis.
†† Self-reported pain was measured on a 10-cm VAS pain scale, analyzed with VAS pain as a continuous variable, adjusted for sex, weighted 0.7 for girls.

the different long-term outcomes. Functional disability as presented by the CHQ physical summary score demonstrated similar results. Participants reporting pain at baseline more frequently were not in remission without medication at follow-up, compared to those reporting no baseline pain. A similar association between increasing pain intensity at baseline and long-term remission status was observed, but the dose-response relationship tended to level out at the most extreme pain intensities. Participants reporting no pain at baseline rarely reported pain (28%) and functional disability (18%) at 8 years, and 74% were in remission without medication. In all analyses, we adjusted for sex, and additional adjustment for age did not change the results. Similar to the results on long-term remission, pain, and functional disability, baseline pain was associated with the use of disease-modifying antirheumatic drugs (DMARDs) and biologics during the 8-year disease course (see Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23715/abstract). In contrast to the other 8-year outcome measures, psychosocial health assessed with the CHQ psychosocial summary score did not show an association with the baseline pain score (results not shown). The predictive ability of baseline pain was also analyzed using ROC curves, giving acceptable discrimination between early pain scores and long-term outcomes of pain, functional disability, and not being in remission at 8 years, but no clear discrimination was observed for long-term damage (Figure 3).

Baseline pain scores and long-term outcomes in the oligoarticular category. Among participants with oligoarticular JIA reporting a VAS pain score >0 at the baseline visit, 48% (95% CI 38, 60) developed extended oligoarticular disease or other JIA categories during the course of the disease compared to 30% (95% CI 16, 44) of those reporting no pain (Table 3). Also, a higher proportion of participants with a VAS pain score >0 at baseline was not in remission without medication, 65% (95% CI 55, 76), and reported pain, 61% (95% CI 50, 73) at 8 years, compared to those reporting no pain at baseline. In contrast, 70% (95% CI 56, 84) of those reporting no pain at baseline remained in the persistent oligoarticular JIA category at the 8-year follow-up. The associations were strengthened using VAS pain as a continuous variable. In all analyses, we adjusted for sex, and additional adjustment for age did not change the results.

DISCUSSION

Among participants in the population-based Nordic JIA study, a higher proportion reported disease-specific pain 7 months after disease onset, and the pain was of higher intensity, compared to the 8-year follow-up. Half of the participants reporting pain at baseline also reported pain at 8 years. Self-reported pain early in the disease course predicted more pain, more functional disability, more damage, more use of DMARDs/biologics, and more long-term disease activity at 8 years. In addition, participants with oligoarticular JIA and a VAS pain score >0 at baseline more often developed an extended disease or other unfavorable JIA categories.

The strength of our study is the longitudinal and population-based design, a robust international cohort, and the use of validated and multidimensional outcome measures. The novelty in looking at associations between early pain report and long-term remission status, medication, and development into more unfavorable disease categories is also a major strength. Some limitations must be recognized. The exclusion of all the Finnish participants reduced the number

of study participants but did not change the population-based design of the study. The missing early pain scores from the other countries might have skewed the remaining cohort, but the distribution of JIA categories and the remission status were comparable among those with or without early pain scores. Even though the VAS pain instrument is disease-specific, we cannot rule out that other musculoskeletal co-conditions, such as generalized joint hypermobility, specific onset symptoms, or differences in timing of diagnosis, might have influenced the child's/parent's pain rating. However, these possibilities are a challenge to all pain research. Since pain is a subjective descriptor, our cohort is close to population-based, and because trained pediatric rheumatologists ascertained the JIA diagnosis, we do not think that these possibilities will seriously disturb the interpretation of our results. Similarly, we cannot ascertain the nature of bodily pain that the participants scored when filling out this question in the CHQ questionnaire. However, we only used this question in accordance with the CHQ instructions, as one of many items describing a summary of physical function, and not as a pain measure. Parents reporting their child's pain for children age <9 years constituted a majority of pain reports at the baseline visit, but a small minority at the 8-year follow-up. We cannot rule out some element of parent/child discordance, although the subanalyses on pain reports according to age at baseline seem to indicate that discordance was not a major problem. This result is in accordance with a study from 2006 showing moderate agreement between parent's and child's pain rating (17). Our results are not directly comparable, because the parent/child pain reports are not from the same visit. The early pain scores from the baseline study visit 7 months after disease onset were given by participants both while taking and not taking medication, but only a few had started DMARDs.

Consistent with previous research, we found pain as a frequent symptom among the participants in our study cohort (14,16,36). We found a reduction in the number of participants reporting pain from baseline (76%) to the 8-year follow-up (57%). A quite similar reduction was found by Lovell and Walco (37) in 1989, demonstrating pain frequency of 60% at baseline, 50% at 1-year follow-up, and 40% at 5-year follow-up. In a recent 30-year follow-up study of JIA in Norway, 66% of the participants reported pain of some degree (24).

In accordance with other studies, the intensity of pain was mainly in the mild-to-moderate range (19,37,38). Our results on early pain intensity with a mean VAS pain score of 3.0 are consistent with a recent cross-sectional study in children and adolescents with JIA from the southeastern region of the US, showing a mean VAS pain score of 2.6 (13). Our results on pain intensity at the 8-year follow-up appear to be lower compared to other studies (14,39). Those studies are, however, skewed to the severe end of the JIA spectrum, whereas our population-based study included the full disease spectrum. Also, to compare studies on pain, age and disease duration must be taken into account.

Even in the biologic era with generally good disease control, persistent pain during the course of the disease remains a concern (26,40,41). Half of our participants reporting pain at 7 months after disease onset also reported pain at the 8-year follow-up, indicating high pain persistency. This finding is in agreement with results from other studies showing that a significant number of children and adolescents with JIA continue to report pain during the course of disease and into adulthood (14,24,42). Notably, the proportion of pain persistence is fairly similar, whether the parents report their child's pain, or whether the pain is self-reported at baseline. Pain persistence despite a seemingly good treatment response supports theories that the causes of pain are multifactorial (41,43). Both psychosocial and biologic factors contribute to these children's subjective experience of pain (38,44,45).

Pain as a predictor of unfavorable health-related quality of life in children with JIA is widely studied (21,23,46,47). In a multinational quality-of-life study from the Pediatric Rheumatology International Trials Organization, pain was found to be a predictor of psychosocial well-being (21). In agreement with our study, previous studies have shown that pain at presentation was a strong predictor of persistent pain (42,48). In accordance with our results, pain as a predictor of functional disability was also found in a small cross-sectional study from the US (49). Except for health-related quality-of-life outcomes and functional disability, studies that specifically address pain as a predictor of other long-term outcomes, such as remission, damage, medication, and changing of JIA categories, are lacking. Our results demonstrate for the first time that early pain is associated with not achieving remission without medication in a long-term perspective. We also demonstrate, for the first time, that early pain reports predict a higher risk of development into extended oligoarticular or other unfavorable JIA categories during the course of the disease. This finding suggests that early pain may be an indicator of subclinical disease activity or a marker of a more severe disease category. This possibility is also supported by the fact that a higher proportion of participants with an early pain report used DMARDs/biologics during the course of the disease.

Even though pain assessment has been highlighted as a quality measure of pediatric arthritis care (50), pain scores are infrequently used as guiding tools in daily care of these patients (41). Our results demonstrate that pain in children with JIA at an early stage in their disease should be taken seriously, not just to relieve ongoing discomfort, but probably also as a sign of ongoing clinical or subclinical disease activity. This necessity emphasizes the importance of pain assessment in routine care of children and adolescents with JIA. In a Canadian study where patients, parents, and clinicians were asked what matters most in the care of JIA, pain was 1 of the 5 most important factors (11). The active joint count was the only 1 of these 5 factors that is included in the pediatric version of the ACR core variables for clinical care in

children with JIA (12). The association between early pain reports and long-term unfavorable outcome adds to the discussion on the validity of the ACR core variables, and on whether pain should be included in these variables. In conclusion, early self-reported pain in JIA is common, tends to persist, and seems to predict unfavorable long-term disease outcome in several outcome dimensions.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Arnstad had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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