Enthesitis-related Arthritis Is Associated with Higher Pain Intensity and Poorer Health Status in Comparison with Other Categories of Juvenile Idiopathic Arthritis: The Childhood Arthritis and Rheumatology Research Alliance Registry

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ABSTRACT. ***Objective.*** To assess the relative effect of clinical factors and medications on pain intensity, physical function, and health status in juvenile idiopathic arthritis (JIA).

Methods. We conducted a retrospective cross-sectional study of data from children with JIA enrolled in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry. We tested whether clinical characteristics of JIA were associated with pain intensity, physical function, and health status using multivariable linear and ordinal logistic regression.

Results. During the study period, 2571 subjects with JIA enrolled in the CARRA Registry. Ratings of pain intensity, physical function, and health status differed significantly between JIA categories. In comparison to other categories of JIA, subjects with enthesitis-related arthritis (ERA) reported worse pain and function. In multivariable analyses, higher active joint count and current use of nonsteroidal antiinflammatory drugs (NSAID), biologics, or corticosteroids were associated with worse scores on all patient-reported measures. ERA and older age were significantly associated with higher pain intensity and poorer health status. Systemic JIA and uveitis were significantly associated with worse health status. Enthesitis, sacroiliac tenderness, and NSAID use were independently associated with increased pain intensity in ERA. The correlation was low between physician global assessment of disease activity and patient-reported pain intensity, physical function, and health status.

Conclusion. Significant differences in pain intensity, physical function, and health status exist among JIA categories. These results suggest that current treatments may not be equally effective for particular disease characteristics more common in specific JIA categories, such as enthesitis or sacroiliac tenderness in ERA. (First Release Oct 15 2012; J Rheumatol 2012;39:2341–51; doi:10.3899/jrheum.120642)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS PEDIATRIC RHEUMATIC DISEASES
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Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatologic condition in childhood, affecting 1 to 4 per 1000 children[1,2]. The term JIA describes a clinically heterogeneous group of diseases characterized by arthritis that begins before age 16 years, involves 1 or more joints, and lasts at least 6 weeks. Distinct clinical features characterize each of the JIA categories during the first 6 months of disease. The goal of treatment in JIA is to control inflammation and prevent morbidities such as vision loss, growth disturbances, joint contractures, joint destruction, and functional limitations. An increasing body of literature suggests that clinical examination and physician assessment

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of disease activity are insufficient for a complete understanding of the effect of disease on children with JIA. Therefore, a thorough assessment of treatment response includes not only physical examination components such as active joint count (AJC), but also patient-reported measures of pain, physical function, and health status. Differences in pain intensity, physical function, and health status in children across JIA categories have not been well described.

Several studies suggest that pain is highly prevalent in JIA, often persisting into adulthood[3,4,5]. Results using various methodologies have shown that children with JIA have pain on most days in the mild to moderate range and that the amount of pain predicts activity limitations[6,7,8]. Studies have demonstrated that pain in children with JIA is significantly associated with increased disease activity[9,10] and reduced participation in school and social activities[8]. Disease severity, however, accounts for only a small proportion of the variance in pain reported by children with JIA[6,11,12,13]. These reports suggest that there are many factors other than those identified by physical examination, physician global assessment (PGA), and disease activity scores that contribute to self-reported pain intensity in the JIA population.

Decreased physical function, like pain, is prevalent in JIA and is not fully accounted for by physical examination findings. Previous studies show that only half of patients with JIA have a Juvenile Arthritis Functionality Score of 0, indicating no disability[14], and that children with JIA have decreased physical function even in the absence of physical examination findings indicative of disease activity, including synovitis and joint contractures[15]. Additionally, self-reported depression, anxiety, and behavioral problems are significantly associated with decreased physical function but not disease activity in children with polyarticular disease[16].

Health-related quality of life (HRQOL) and health status are also important components of the overall assessment of children with JIA[17]. Several studies have reported that children with JIA have poorer HRQOL in comparison to healthy children as well as children with other chronic diseases[7,18,19,20]. Significant predictors of HRQOL include pain, physical function, disease activity, school absences, and subjective burden of medication use[17,20,21].

We used a retrospective cross-sectional design to analyze data from the large Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry, which contains clinical and medication data from children with JIA enrolled at participating US sites, as well as several patient-reported outcomes. In our study, we aimed (1) to characterize pain intensity, physical function, and health status in a large cross-sectional multicenter sample of children with JIA; (2) to compare pain intensity, physical function, and health status across JIA categories; and (3) to evaluate the relationship between PGA and pain intensity, physical function, and health status in JIA.

MATERIALS AND METHODS

Our study was reviewed by The Children's Hospital of Philadelphia institutional review board and was deemed "not human subjects research" because the data are retrospective and identification was removed.

Patients. The source population was subjects with JIA enrolled in the CARRA Registry between May 2010 and June 2011. The CARRA Registry is a multicenter observational database of US children with rheumatic diseases. Sixty centers representing all major geographic regions of the country contribute data to the registry. Subjects are a convenience sample enrolled without regard to disease duration, disease severity, current disease activity, or therapy. All subjects met International League Against Rheumatism (ILAR) criteria[22] for JIA according to the treating physician. The registry includes self- and physician-reported measures.

Measures of pain intensity. At enrollment the subject or parent was asked, "How much pain have you [or your child] had because of your [his/her] rheumatic condition in the past week?" Pain intensity was reported using integers from 0 to 10, anchored by the words "No Pain" and "Very Severe Pain." High correlation between the traditional 10-cm visual analog scale (VAS) and the integer-based scale has been reported for the measurement of pain intensity[23,24,25].

Measures of physical function. Subjects or parents rated the subject's disease-related functional status during the past week using the Childhood Health Assessment Questionnaire (CHAQ)[26]. The CHAQ is widely used in pediatric rheumatology research and clinical practice among children with JIA[27,28]. It comprises 30 questions, covering 8 functional ability domains related to daily living during the past week: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities. A disability index (DI) is calculated based on the mean of the 8 domains; the DI ranges from 0 to 3, with higher scores indicating worse disability[27].

Health status. Health status measures the parent/subject's perception of his/her health, taking into account personal values, cultural beliefs, goals, and concerns. At enrollment, subjects or parents were asked, "How do you rate your [child's] health?" Subjects and parents were given a 5-choice response scale with the following options: very poor, poor, good, very good, and excellent.

Disease characteristics and activity. Disease characteristics and activity were assessed at enrollment using a variety of sources including subject/parent report, physician assessment and physical examination, and chart abstraction. The duration of symptoms in years was reported by the subject/parent. The treating physician was responsible for determination of the following: (1) JIA ILAR category; (2) AJC; (3) presence of enthesitis; (4) presence of sacroiliac tenderness; and (5) PGA of disease severity. The AJC was defined as the number of joints with active arthritis; active arthritis was defined as a joint with swelling or tenderness with limited range of motion. The PGA of disease severity used integers from 0 to 10, anchored by the words "not active" and "very active". The number of joints ever affected (< 5 or ≥ 5), history of uveitis, and radiographic evidence of joint damage defined as joint narrowing, erosion, or ankylosis (present/absent) were abstracted from the subject's medical record.

Medications. Past and current use of medications including daily nonsteroidal antiinflammatory drugs (NSAID), nonbiologic disease-modifying antirheumatic drugs (DMARD), biologics, and systemic corticosteroids were abstracted from the subject's medical records. Medications in the nonbiologic DMARD category include sulfasalazine, methotrexate, leflunomide, cyclosporine, mycophenolate mofetil, cyclophosphamide, and azathioprine. Medications in the biologics category include etanercept, adalimumab, abatacept, infliximab, rituximab, tocilizumab, rilonacept, golimumab, canakinumab, and anakinra.

Statistical analysis. Differences in demographics and clinical characteristics between JIA categories were compared using the Kruskal-Wallis or chi-squared test, as appropriate. We tested whether demographics and clinical characteristics of JIA were associated with pain intensity, physical function, and health status using multivariable linear (pain and function)

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and ordinal logistic (health status) regression. Predictor variables for pain intensity, physical function, and health status included age at enrollment, sex, insurance status (uninsured or insured), physician-reported JIA ILAR category, duration of symptoms (years), AJC, number of joints ever affected (< 5 or ≥ 5), radiographic evidence of joint damage (present/absent), current daily NSAID use (yes/no), current nonbiologic DMARD use (yes/no), current biologic use (yes/no), and current systemic corticosteroid use (yes/no). Uveitis (history, active, none) was also included as a variable in the model for health status. For all analyses, the reference JIA category was oligoarticular-persistent. In the restricted analysis of subjects with enthesitis-related arthritis (ERA), additional variables included current enthesitis, current sacroiliac tenderness, HLA-B27 positivity, and inflammatory bowel disease (IBD). Because of collinearity with AJC (correlation > 0.5), PGA of disease was not used in any of the multivariable analyses.

Significant predictors in univariate analysis ($p < 0.05$) were included in the initial multivariable models. The final multivariable models were built using a backward elimination, eliminating attributes with p values > 0.2 when the full and nested models were compared and found to have similar likelihood ratios. Standardized regression coefficients (betas) are reported for each analysis. For binary variables, regression coefficients of 0.2, 0.5, and 0.8 are considered small, medium, and large associations, respectively[20,29]. For continuous predictors, regression coefficients of 0.1, 0.3, and 0.5 are considered small, medium, and large associations, respectively[20,29]. For each regression, the explained variance (R-square) was determined.

To test the association between PGA of disease activity and self-reported outcomes we performed pairwise correlation tests between PGA of disease activity and self-reported arthritis-specific pain intensity, CHAQ, and health status. All analyses were performed using Stata 12 (StataCorp).

RESULTS

Subjects. During the 14-month study period there were 2571 children with JIA enrolled in the CARRA Registry. The most common JIA categories were polyarticular rheumatoid factor-negative (n = 761, 30%), oligoarticular-persistent (n = 697, 27%), and ERA (n = 268, 10%; Table 1). The median disease duration across JIA categories was 3.9 years [interquartile range (IQR) 1.9, 7.3]. Seventy-three percent of subjects with JIA were female and 59% had a polyarticular course of disease (≥ 5 joints ever affected). Forty-seven percent had active arthritis and 4% had active enthesitis at the time of enrollment.

Twenty-four percent and 42% of patients with ERA had active enthesitis or a history of enthesitis, respectively. Enthesitis was most common in these types of JIA: ERA, psoriatic arthritis (PsA), undifferentiated, and oligoarticular-extended (Table 1); however, enthesitis was reported in all JIA categories. Three percent of subjects had active sacroiliac tenderness. Sacroiliac tenderness was most

Table 1. Patient characteristics by juvenile idiopathic arthritis category.

	All	Systemic	Poly RF+	Poly RF–	Oligo persistent	Oligo extended	ERA	Undiff	PsA	p*
N (%)	2571	232 (9)	190 (7)	761 (30)	697 (27)	210 (8)	268 (10)	52 (2)	161 (6)	
Age at onset, yrs, median (IQR)	5.4 (2.3, 9.9)	4.4 (2.4, 8.5)	11.1 (7.7, 13.7)	5.2 (2.3, 9.4)	3.6 (2.0, 6.9)	2.8 (1.6, 6.0)	10.4 (7.3, 12.8)	6.6 (2.0, 11.0)	8.2 (2.8, 11.8)	< 0.01
Female, n (%)	1879 (73)	133 (57)	167 (88)	606 (80)	536 (77)	182 (87)	111 (41)	34 (65)	110 (68)	< 0.01
Uninsured, n (%)	40 (2)	7 (3)	12 (2)	12 (2)	7 (1)	3 (1)	5 (2)	1 (2)	1 (1)	0.51
Disease duration, yrs	3.9 (1.9, 7.3)	4.2 (1.5, 8)	3.5 (1.7, 5.8)	4.5 (2.1, 7.9)	3.2 (1.4, 6.2)	5.8 (2.9, 9.5)	3.3 (1.8, 6.0)	3.3 (1.7, 6.7)	4.0 (2.3, 7.7)	< 0.01
≥ 5 joints ever affected, median, n (%)	1499 (59)	158 (69)	727 (96)	177 (93)	9 (1)	182 (87)	120 (45)	27 (52)	99 (62)	< 0.01
Radiographic evidence of joint damage, n (%)	527 (21)	62 (32)	66 (40)	151 (23)	86 (15)	52 (28)	65 (27)	9 (20)	36 (26)	< 0.01
Active joint count, median (IQR)	0 (0, 2)	0 (0, 2)	1 (0, 4)	0 (0, 2)	0 (0, 1)	1 (0, 2)	1 (0, 2)	0 (0, 1)	0 (0, 2)	< 0.01
PGA	1 (0, 2)	1 (0, 3)	1 (0, 2)	2 (0, 3)	1 (0, 2)	1 (0, 3)	1 (0, 2)	1 (0, 2)	1 (0, 2)	< 0.01
DMARD, current n (%)	1318 (51)	134 (58)	133 (70)	423 (56)	263 (38)	130 (62)	122 (46)	21 (40)	92 (57)	< 0.01
Biologics, current n (%)	974 (38)	122 (53)	115 (61)	345 (45)	113 (16)	83 (40)	111 (41)	14 (26)	71 (44)	< 0.01
Corticosteroids, current n (%)	216 (13)	54 (27)	42 (29)	74 (16)	14 (3)	5 (3)	18 (13)	1 (4)	8 (9)	< 0.01
Enthesitis, n (%)	98 (4)	2 (1)	2 (1)	10 (1)	2 (0.5)	6 (3)	62 (24)	3 (6)	11 (7)	< 0.01
Sacroiliac tenderness, n (%)	73 (3)	1 (< 1)	1 (1)	12 (2)	1 (1)	2 (1)	47 (18)	0 (0)	6 (4)	< 0.01
Uveitis,										
Active, n (%)	110 (4)	0 (0)	0 (0)	26 (3)	59 (9)	12 (6)	4 (2)	2 (4)	7 (4)	< 0.01
History, n (%)	175 (7)	4 (2)	2 (1)	46 (6)	67 (10)	33 (16)	12 (5)	3 (6)	8 (5)	

* Differences in demographics and clinical characteristics between the JIA categories were compared using the Kruskal-Wallis or chi-squared test, as appropriate. RF: rheumatoid factor; ERA: enthesitis-related arthritis; PsA: psoriatic arthritis; IQR: interquartile range; PGA: physician global assessment; DMARD: disease-modifying antirheumatic drug; Poly: polyarticular; Oligo: oligoarticular; Undiff: undifferentiated.

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common in the ERA category. Eighteen percent and 39% of patients with ERA had current or a history of sacroiliac tenderness on examination, respectively.

Pain intensity. Sixty-nine percent of JIA subjects reported pain within the past week, defined as pain intensity > 0 on the numeric VAS scale. Figure 1A shows the proportion of children reporting pain within the past week by JIA category. The median pain intensity within the past week for all JIA subjects was 2 (IQR 0, 4). This pain intensity is in accord with previous studies of children with JIA[6,8,30,31]. Pain intensity scores differed significantly between JIA categories ($p < 0.001$; Figure 1B). In comparison with other

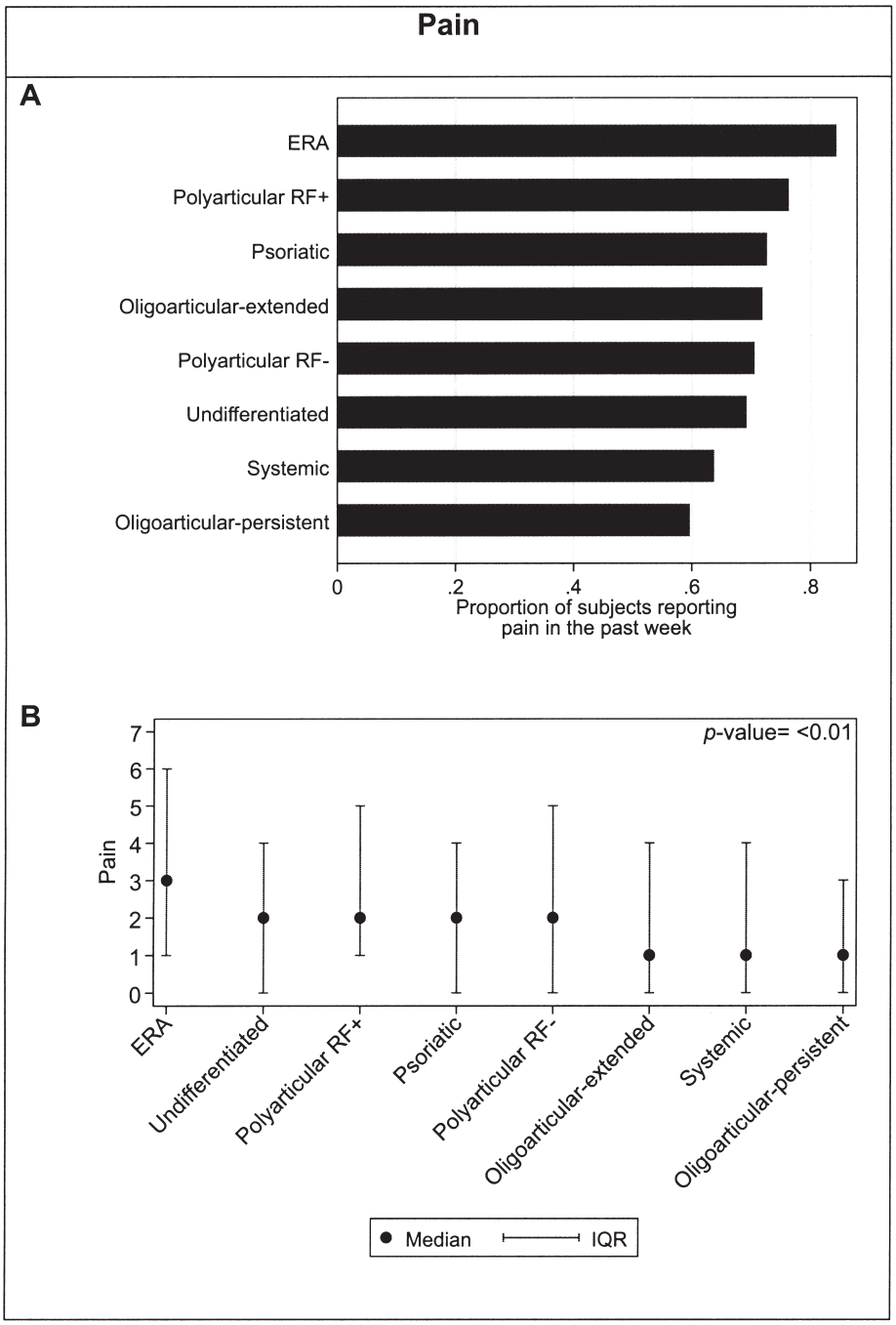

Figure 1. Pain and function by JIA category. A. Proportion of subjects reporting any pain within the past week. Pain was defined as VAS > 0. B. Median and IQR of pain reported by VAS. Significant differences of pain existed across JIA categories ($p < 0.01$). IQR: interquartile range; ERA: enthesitis-related arthritis; RF: rheumatoid factor.

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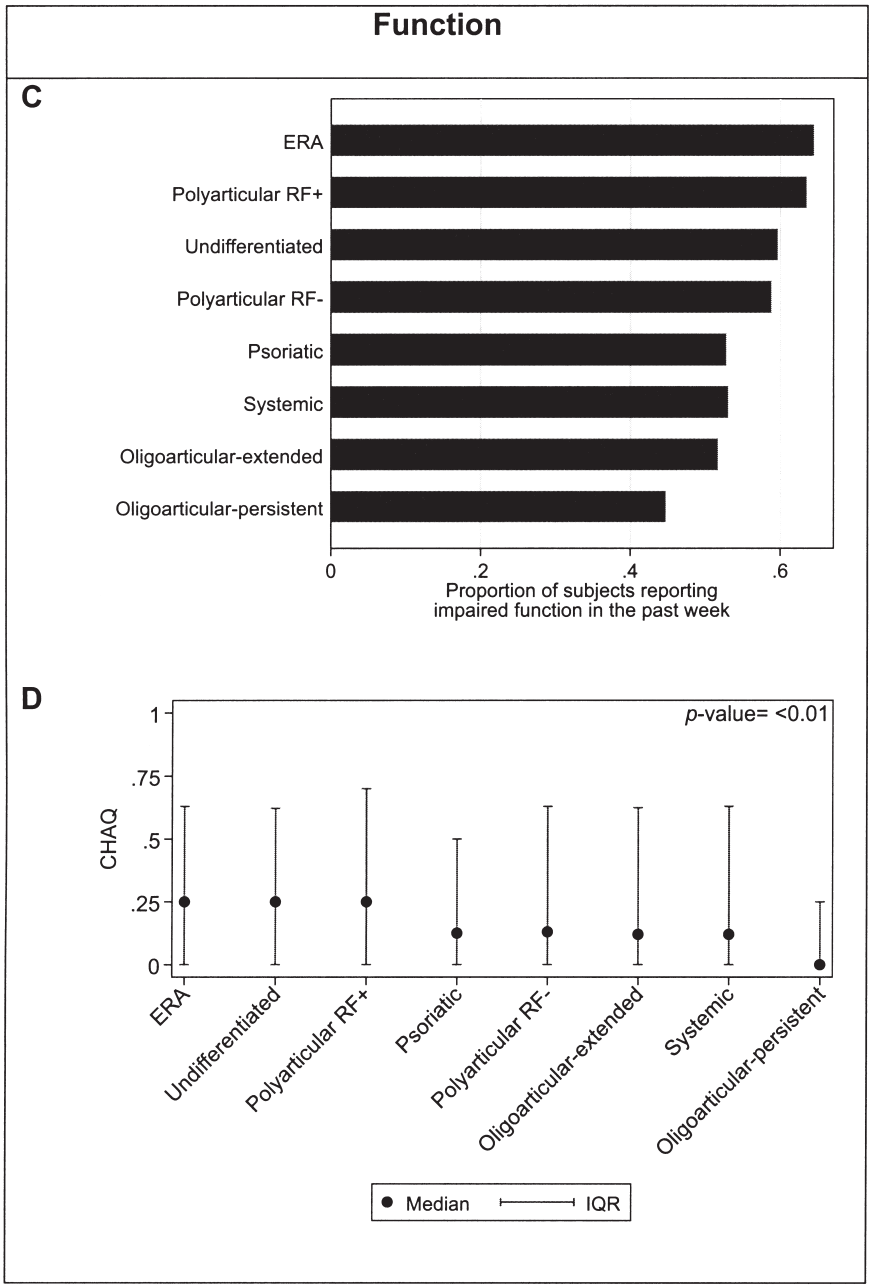

Figure 1. C. Proportion of subjects reporting impaired function within the past week. Scores of 0.13, 0.63, and 1.75 represent mild, mild to moderate, and moderate disability, respectively[32]. D. Median and IQR of parent/child function as reported by Childhood Health Assessment Questionnaire (CHAQ). Significant differences of function exist across JIA categories using the Kruskal-Wallis test ($p < 0.01$). Scores were not adjusted for subject characteristics or disease activity. IQR: interquartile range; ERA: enthesitis-related arthritis; RF: rheumatoid factor.

categories of JIA, subjects with ERA reported pain most frequently (n = 226, 84%) and had the highest pain intensity (Figures 1A and 1B).

The results of univariate and multivariable analyses are shown in Table 2. After multivariable regression modeling, significant clinical predictors of higher pain intensity were ERA disease category, older age, higher AJC, and current daily NSAID, biologic, and corticosteroid use. ERA had a medium strength association and current NSAID and corticosteroid use had a large association with increased pain intensity, whereby medium and large associations are defined by beta coefficients > 0.5 and 0.8, respectively[20,29].

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Table 2. Clinical variables associated with pain, function, and health status. For all analyses the reference JIA category is oligoarticular-persistent JIA. Significant predictors in univariate analysis ($p < 0.05$) were included in initial multivariable models. The final multivariable models were built using a backward elimination, eliminating attributes with $p > 0.2$ when the full and nested models were compared. Only results for variables included in the final models are listed in the multivariable analyses columns. For binary variables, regression coefficients of 0.2, 0.5, and 0.8 are considered small, medium, and large associations, respectively[20,29]. For continuous predictors, regression coefficients of 0.1, 0.3, and 0.5 are considered small, medium, and large associations[20,29].

	Pain Coefficient (95% CI)		Function Coefficient (95% CI)		Health Status Coefficient (95% CI)	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
ERA	1.53 (1.17, 1.90)***	0.68 (0.21, 1.15)**	0.18 (0.11, 0.25)***	0.09 (–0.01, 0.19)	0.93 (0.66, 1.19)***	0.41 (0.02, 0.79)*
Undifferentiated	0.75 (0.02, 1.49)*	0.06 (–0.89, 1.02)	0.18 (0.04, 0.32)*	0.09 (–0.10, 0.28)	0.35 (–0.17, 0.87)	0.24 (–0.48, 0.96)
Polyarticular RF+	1.13 (0.71, 1.55)***	0.11 (–0.38, 0.59)	0.24 (0.16, 0.32)***	0.00 (–0.12, 0.11)	0.99 (0.69, 1.29)***	0.13 (–0.27, 0.54)
Psoriatic	0.51 (0.06, 0.95)*	0.42 (–0.14, 0.98)	0.10 (0.01, 0.19)*	0.05 (–0.07, 0.17)	0.50 (0.19, 0.82)**	0.10 (–0.35, 0.55)
Polyarticular RF–	0.66 (0.39, 0.93)***	–0.02 (–0.35, 0.30)	0.21 (0.15, 0.26)***	0.02 (–0.08, 0.11)	0.61 (0.42, 0.80)***	0.24 (–0.02, 0.51)
Systemic	0.54 (0.15, 0.93)**	0.11 (–0.30, 0.53)	0.17 (0.10, 0.25)***	0.03 (–0.06, 0.13)	0.72 (0.44, 1.00)***	0.46 (0.12, 0.80)**
Oligoarticular-extended	0.27 (–0.13, 0.67)	0.15 (–0.28, 0.59)	0.13 (0.05, 0.21)**	0.04 (–0.06, 0.15)	0.21 (–0.07, 0.50)	0.12 (–0.22, 0.47)
Older age (each additional yr)	0.10 (0.08, 0.12)***	0.04 (0.02, 0.07)***	0.01 (–0.00, 0.01)	—	0.07 (0.05, 0.08)***	0.05 (0.03, 0.07)***
Symptom duration	0.03 (0.01, 0.06)**	—	–0.01 (–0.01, 0.00)	—	0.02 (0.00, 0.04)	—
Sex	0.05 (–0.18, 0.28)	—	0.04 (–0.00, 0.09)	—	0.09 (–0.07, 0.25)	—
Active joint count	0.18 (0.15, 0.20)***	0.11 (0.08, 0.14)***	0.04 (0.04, 0.05)***	0.03 (0.03, 0.04)***	0.11 (0.09, 0.13)***	0.07 (0.05, 0.10)***
≥ 5 joints ever affected	0.41 (0.20, 0.62)***	—	0.17 (0.13, 0.21)***	0.06 (–0.01, 0.14)	0.48 (0.33, 0.63)***	—
Imaging evidence of joint damage	0.23 (–0.03, 0.49)	—	0.06 (0.01, 0.11)*	—	0.45 (0.27, 0.63)***	—
NSAID	1.63 (1.44, 1.83)***	1.28 (1.04, 1.51)***	0.24 (0.20, 0.28)***	0.17 (0.13, 0.22)***	0.81 (0.66, 0.95)***	0.71 (0.52, 0.90)***
DMARD	0.03 (–0.17, 0.24)	—	0.06 (0.02, 0.10)**	0.09 (0.04, 0.14)***	0.30 (0.15, 0.44)***	0.45 (0.25, 0.65)***
Biologics	0.23 (0.02, 0.44)*	0.39 (0.15, 0.64)**	0.08 (0.04, 0.12)***	0.22 (0.15, 0.30)***	0.48 (0.33, 0.63)***	0.70 (0.39, 1.01)***
Corticosteroids	1.71 (1.35, 2.08)***	0.94 (0.57, 1.31)***	0.40 (0.33, 0.48)***	0.03 (–0.01, 0.08)	1.23 (0.94, 1.51)***	0.14 (–0.05, 0.33)
Insured	–0.29 (–1.11, 0.53)	—	–0.06 (–0.23, 0.10)	—	0.01 (–0.57, 0.60)	—
Uveitis						
Current	—	—	—	—	0.01 (–0.34, 0.37)	0.53 (0.09, 0.97)*
Past	—	—	—	—	–0.44 (–0.72, –0.15)**	–0.09 (–0.44, 0.27)

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. ERA: enthesitis-related arthritis; RF: rheumatoid factor; NSAID: nonsteroidal antiinflammatory drugs; DMARD: disease-modifying antirheumatic drugs.

However, the multivariate model accounted for only 18% (R-square) of the variance in pain, in accord with previous studies demonstrating that measurable clinical attributes such as disease activity and arthritis category only partially explain the distribution of self-reported pain intensity in JIA[6,11].

Treating physicians likely have made some errors with ILAR JIA category assignment. This is demonstrated in Table 1, noting that enthesitis was present across all subtypes, which would suggest that some subjects might belong in the ERA, PsA, or undifferentiated arthritis categories. In a sensitivity analysis, the point estimates and significance of pain intensity did not change when we excluded children with enthesitis who were not classified by the treating physician as PsA, ERA, or undifferentiated categories.

Because ERA was associated with increased pain intensity in comparison with other JIA categories, we investigated whether particular disease characteristics more common in ERA, such as enthesitis, sacroiliac tenderness, HLA-B27 positivity, and concurrent IBD contributed to this association. Results of univariate and multivariable analyses are shown in Table 3. Active enthesitis, active sacroiliac tenderness, and current daily NSAID use were significantly and independently associated with increased pain intensity in subjects with ERA. Of these associations, enthesitis and sacroiliac tenderness were the strongest.

Physical function. Fifty-four percent of JIA subjects reported impaired function within the past week, defined as CHAQ > 0. Scores of 0.13, 0.63, and 1.75 represent mild, mild to moderate, and moderate disability, respectively[32]. Figure 1C shows the proportion of children reporting impaired function by JIA category. The median CHAQ score for all patients with JIA was 0.125 (IQR 0, 0.75), but it differed significantly between JIA categories (Figure 1D). The JIA category with the largest proportion of children reporting impaired function was ERA (n = 172, 64%).

The results of univariate and multivariable analyses are shown in Table 2. After multivariable regression modeling and controlling for disease severity, significant clinical predictors of higher CHAQ scores (more impaired physical function) were a higher AJC and current NSAID, biologic, and corticosteroid use. The multivariate model accounted for 19% (R-square) of the variance in function.

Health status. The median health status for all patients with

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Table 3. Clinical variables associated with pain in enthesitis-related arthritis. Significant predictors in univariate analysis ($p < 0.05$) were analyzed further in multivariable analyses. The final multivariable model was built using a backward elimination, eliminating attributes with $p > 0.2$ when the full and nested models were compared. Only results for variables included in the final model are listed in the multivariable analysis column.

	Pain VAS Coefficient (95% CI)	
	Univariate	Multivariate
Older age (yrs)	0.11 (0.01, 0.21)*	0.06 (–0.07, 0.20)
Symptom duration	0.08 (–0.03, 0.18)	—
Sex	0.55 (–0.14, 1.23)	—
Active joint count	0.21 (0.07, 0.36)**	0.18 (–0.04, 0.40)
≥ 5 joints ever affected	–0.19 (–0.87, 0.50)	—
Imaging evidence of joint damage	–0.41 (–1.22, 0.40)	—
NSAID	1.27 (0.60, 1.93)***	1.77 (0.86, 2.69)***
DMARD	0.23 (–0.45, 0.91)	—
Biologics	0.11 (–0.58, 0.80)	—
Corticosteroids	1.43 (0.06, 2.81)*	0.60 (–0.83, 2.03)
Insured	2.97 (0.50, 5.44)*	2.54 (–0.16, 5.23)
Enthesitis	1.72 (0.93, 2.50)***	1.49 (0.18, 2.79)*
Sacroiliac tenderness	2.15 (1.30, 3.00)***	1.77 (0.39, 3.15)*
HLA-B27 positivity	–0.77 (–1.48, –0.06)*	0.32 (–0.63, 1.26)
Inflammatory bowel disease	–0.57 (–1.56, 0.42)	—

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. VAS: visual analog scale; NSAID: nonsteroidal antiinflammatory drugs; DMARD: disease-modifying antirheumatic drugs.

JIA was 2 or "very good" (IQR 2, 3; Figure 2). Scores for health status differed significantly between JIA categories ($p < 0.01$; Figure 2). The results of univariate and multivariable analyses are shown in Table 2. After multivariable regression modeling, significant clinical predictors of a higher (worse) health status score were ERA or systemic categories of JIA, older age, higher AJC, current uveitis, and current NSAID, biologic, or corticosteroid use. However, the multivariate model accounted for only 7% (R-square) of the variance in health status.

Association of PGA of disease activity and parent/patient-reported outcomes. The median PGA for all JIA categories was 1 (IQR 0, 2). The pairwise correlations between PGA of disease activity and pain, function, and health status scores were low (0.43, 0.37, and 0.30, respectively; p values for all < 0.001). The relationships between the PGA and pain, function, and health status are shown in Figure 3.

DISCUSSION

This retrospective cross-sectional study of enrollment data for children with JIA from a large national registry demonstrates significant differences in pain intensity, physical function, and health status across JIA categories. Despite low disease activity as measured by PGA, the majority of JIA subjects had pain and decreased function within the past week. A higher proportion of subjects with ERA reported

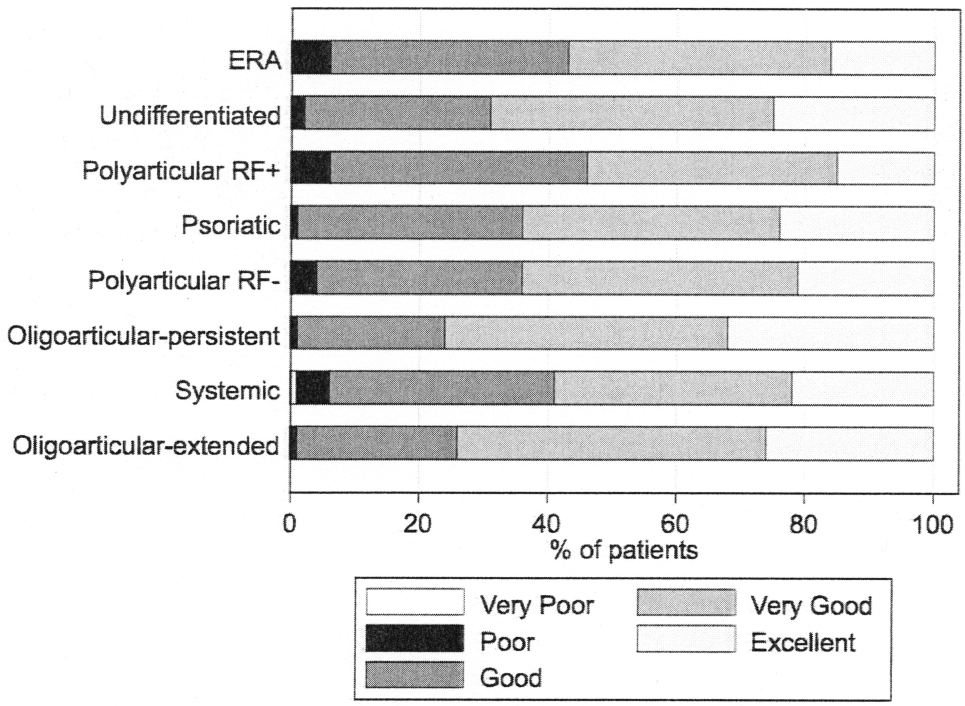

Figure 2. Health status by juvenile idiopathic arthritis (JIA) category. The health status questionnaire uses a 5-choice response scale: very poor, poor, good, very good, and excellent. Percentage based on total number of patients in each JIA category.

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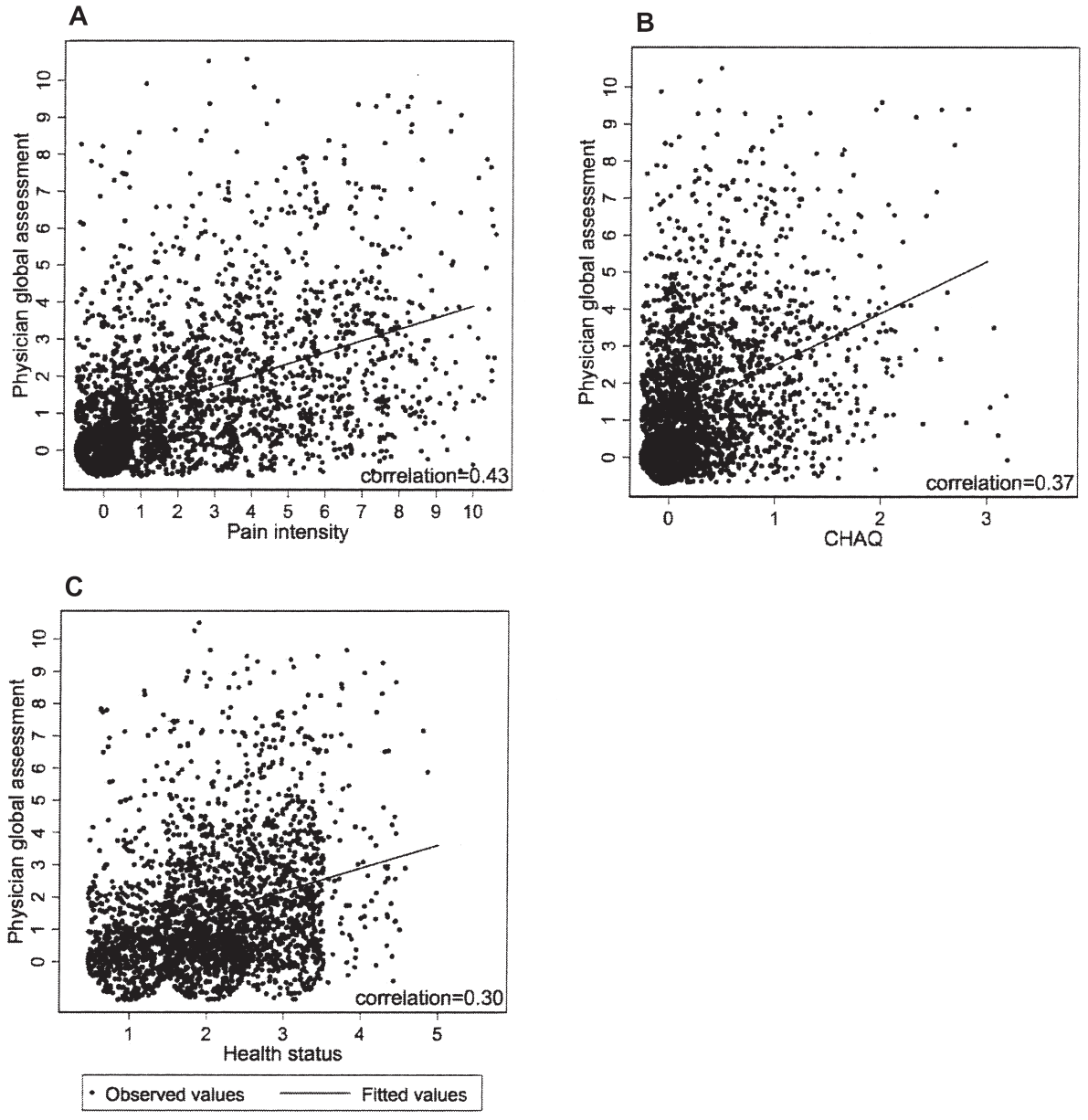

Figure 3. Correlation of physician global assessment (PGA) with self-reported outcomes. Pairwise correlation between PGA of disease activity and (A) pain intensity; (B) physical function as measured by the Childhood Health Assessment Questionnaire (CHAQ); and (C) health status. The jitter function was used to randomly place observed values around their true value to avoid overlap with identical values, thus depicting the amount of data at a given value.

pain and decreased function than did subjects in other JIA categories. Additionally, subjects with ERA reported higher levels of pain intensity than did subjects in other JIA categories. Multivariable regression modeling identified higher AJC and current NSAID, biologic, or corticosteroid use as predictors of worse scores on all 3 self-reported measures — pain intensity, physical function, and health status. ERA and older age were significantly associated with increased pain intensity and decreased health status. Systemic JIA and current uveitis were significantly associated with decreased health status. Active enthesitis, sacroiliac tenderness, and current NSAID use were significantly and independently associated with pain intensity in subjects with ERA.

The correlations between PGA of disease activity and self-reported measurements of pain intensity, physical function, and health status were low. This finding highlights the importance of collecting patient-reported outcomes both in clinical practice and in registries because they provide different qualitative information from the PGA. Additionally, our models accounted for 18%, 19%, and 7% of the variance in pain, function, and health status, respectively,

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suggesting that clinical examination, PGA, and disease attributes are insufficient for a complete understanding of the effect of disease on children with JIA. Other factors that might affect these self-reported outcomes that were not studied include stress, mood, and emotion regulation.

Our findings should be interpreted in the context of several limitations. First, the CARRA Registry consists of a convenience sample of patients with JIA; however, subjects are recruited without regard to disease duration, disease severity, current disease activity, or therapy. However, it is unknown whether disease severity or treatments differed in children who were and children who were not enrolled in the registry at the same clinical site. However, selection bias was likely center-specific and diminished by the large number of contributing clinical centers. Second, treating physicians likely have made some errors with ILAR JIA category assignment. This is demonstrated in Table 1, particularly noting that not all patients with polyarticular disease have 5 or more joints ever involved, and that enthesitis was present across all subtypes. Future studies should assess the validity of physician-assigned JIA categories in the CARRA registry. In a sensitivity analysis, the point estimates and significance did not change when we excluded children with enthesitis who were not classified by the treating physician as the ERA, PsA, or undifferentiated categories. If the diagnosis of ERA relies on having tender entheses (and the child is actually tender everywhere because of pain amplification and not true ERA by ILAR criteria), there may be differential misclassification. Third, the treating pediatric rheumatologist ascertained AJC and presence of enthesitis during routine clinical care. All pediatric rheumatologists contributing data to the CARRA Registry perform a standard joint examination to assess for arthritis and use standard measures to define active arthritis[22]. However, currently there are no standardized methods of assessing or defining pediatric enthesitis. Therefore, the interpretation of enthesitis likely varies among physicians. Future development of a standardized enthesitis assessment either by physical examination or imaging is vital. Lastly, the presence of fibromyalgia tender points and diagnoses of amplified pain or fibromyalgia are not currently recorded in the CARRA registry.

Despite these caveats, our study indicates that significant differences exist across JIA categories in the patient-reported outcomes of pain intensity, physical function, and health status. Further, a higher proportion of subjects with ERA reported increased pain and decreased function than did subjects in the other JIA categories. These differences suggest that (1) our current treatments may not be equally effective for each of the JIA categories; (2) our current treatments may not be as effective for particular disease characteristics more common in specific JIA categories, such as enthesitis or limited back mobility in ERA[33]; or (3) we are treating certain JIA categories more aggressively and earlier than others, resulting in improved self-reported outcomes. Therefore, future comparative effectiveness and clinical trials should be powered to perform subgroup analyses rather than grouping all categories of JIA together.

Our study also demonstrates that the ERA category of JIA is a significant predictor of increased pain intensity and poorer health status. Interestingly, the ERA subjects in our cohort reported poorer patient-reported outcomes but did not have significantly higher PGA or active joint counts than did subjects in the other JIA categories. Active enthesitis, sacroiliac tenderness, and current NSAID use were significantly and independently associated with pain intensity in subjects with ERA. This finding is expected, because enthesitis has a major effect on function and quality of life in adults with ankylosing spondylitis (AS)[34]. In comparison to adults with AS who do not have enthesitis, those with enthesitis show significantly worse scores on the Bath Ankylosing Spondylitis Functional Index and the AS-specific quality of life index[34]. A small study (n = 95) of patients with JIA also reported impaired well-being and increased pain in ERA compared with other JIA categories[35]. Our results confirm these findings in children and demonstrate the compelling need for a standardized assessment of enthesitis as part of the routine evaluation of children with JIA.

We also found a low correlation between standardized scores of PGA of disease activity and self-reported measurements of pain intensity, physical function, and health status, as reported in rheumatoid arthritis[36] and JIA[37]. One issue considered in previous studies that have examined the correlation of PGA and pain (or other characteristics) is how PGA is assessed in patients with variable features. For example, does an oligoarthritis patient with minimal active arthritis and severe uveitis have a high or low PGA? Does a patient with minimal arthritis and marked enthesitis have a high or low PGA? These types of issues may be contributing to the lack of associations observed in this database and the literature, and should be explored further in future studies. Other studies have found better[35,38,39] and poorer correlations[37] between function (as measured by the CHAQ) and PGA. Regardless, our findings underscore the importance of collecting self-reported outcomes in clinical practice, registries such as the CARRA registry, and clinical trials as they provide different qualitative information from the PGA.

Our study demonstrates significant differences in self-reported outcomes between JIA categories. Subjects with ERA reported more frequent and more intense pain as well as more frequent decreased physical function than did subjects in other JIA categories. Enthesitis and sacroiliac tenderness were significantly and independently associated with pain in subjects with ERA. Our findings suggest that current treatment strategies may not be equally aggressive or effective across JIA categories. Future comparative effectiveness studies and clinical trials should carefully account

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for JIA categorization and test therapeutic strategies to improve self-reported outcomes in JIA and ERA, in particular to optimize the health status of children with JIA.

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