

Description of Active Joint Count Trajectories in Juvenile Idiopathic Arthritis

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ABSTRACT. Objective. To describe the trajectories of longitudinal joint disease activity in juvenile idiopathic arthritis (JIA), and to examine associations of clinical and laboratory characteristics with the identified trajectories.

Methods. A retrospective cohort study at 2 Canadian centers was performed. The longitudinal trajectories of active joint counts were described in a proof-of-concept study using a latent growth curve analysis. Baseline patient characteristics were compared across trajectory groups.

Results. Data were analyzed on 659 children diagnosed with JIA between March 1980 and September 2009. The median age at diagnosis was 10.0 years (interquartile range 3.7–13.4) and 61% (402/659) were female. The International League of Associations for Rheumatology (ILAR) diagnoses were as follows: oligoarthritis (36%), enthesitis-related arthritis (20%), rheumatoid factor (RF)-negative polyarthritis (13%), undifferentiated arthritis (12%), psoriatic arthritis (8%), systemic arthritis (7%), and RF-positive polyarthritis (4%). Based on the trajectories of their active joint counts, the 659 patients were each classified in 1 of 5 latent classes (which can be described as high decreasing, moderate increasing, persistent moderate, persistent low, and minimal joint activity). These latent classes were clinically and statistically distinct from the ILAR categories.

Conclusion. In this proof-of-concept study, in which we used an analytic methodology in a novel way, we identified 5 clinically and statistically distinct trajectories of disease course. The subsets of patients within each class were different from those described by the ILAR classification criteria. This successful application of this method supports its use in a chronic disease with a fluctuating course such as JIA. These methods should be expanded for the purposes of predictive modeling. (First Release Oct 1 2014; J Rheumatol 2014;41:2466–73; doi:10.3899/jrheum.130835)

Key Indexing Terms:

JUVENILE IDIOPATHIC ARTHRITIS

LONGITUDINAL STUDY

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Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease of childhood. JIA is not a single disease, but rather a diagnosis that applies to arthritis of unknown

etiology, persisting for more than 6 weeks, and with an onset before age 16 years¹. The most recent proposed classification criteria, by the International League of Associations

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for Rheumatology (ILAR; second revision 2001), is an expert, consensus-based system developed to delineate relatively homogeneous, mutually exclusive categories of idiopathic childhood arthritis to aid in the conduct of research¹.

There is a paucity of reliable indicators of prognosis and outcome in JIA^{2,3}. Specific information regarding expected disease course within the categories of JIA is lacking, and for individual patients, there is a limited ability to advise or predict the expected disease course⁴. This may be partly attributable to suboptimal initial classification, but more importantly, may be related to inferior statistical techniques used in predicting outcomes.

Traditional indicators of outcomes in JIA include persistent disease activity, loss of function, effects on quality of life, and joint damage on radiographs^{2,3,5,6,7,8,9}. Generally, outcomes have been evaluated at a fixed timepoint and modeled as continuous or dichotomous variables (e.g., joints damaged or number of swollen joints at given timepoints), or have been analyzed as time to a defined event (e.g., remission, disability). These descriptions of the patient status at fixed points in time do not adequately reflect the patient's course in a chronic, relapsing, and remitting disease such as JIA. We propose that a more appropriate outcome may be the disease course itself. To characterize patients' disease courses, we used a latent growth curve analysis (LGCA) to examine longitudinal joint disease activity in a unique dataset of clinical data from 2 centers, each with a single pediatric rheumatologist.

MATERIALS AND METHODS

Study design. Using clinical data from a retrospective cohort study of children with JIA, we performed a proof-of-concept study using a statistical modeling technique (latent growth curve analysis) to identify distinct longitudinal active joint count trajectories. Clinical data were extracted from 2 Canadian pediatric rheumatology centers (Royal University Hospital, Saskatoon, and Health Sciences Centre, Winnipeg), each of which have had the same pediatric rheumatologist in practice over the entire span of data collection. Research Ethics Board approval for our study was obtained from the University of Toronto, the Hospital for Sick Children (Toronto), University of Saskatchewan (Saskatoon), and the University of Manitoba (Winnipeg).

Inclusion and exclusion criteria. Eligible patients required the onset of symptoms before age 16 and a diagnosis of juvenile rheumatoid arthritis¹⁰ or JIA¹ confirmed by a pediatric rheumatologist no more than 90 days before the first clinic visit (the date of study entry). A cutoff of 90 days was chosen to limit the time of potential medication exposure prior to the first visit. Patients were excluded from the cohort for any of the following reasons: fewer than 3 visits with the rheumatologist, no first visit documented in the medical record, or an incorrect original diagnosis. Data items for our study were extracted from pediatric rheumatology clinic records that had occurred at 6-monthly (± 2 mos) intervals from first to last visit with the rheumatologist or end of data collection period (April 2009 in Saskatoon, July 2009 in Winnipeg).

For our study, JIA subtypes were retrospectively assigned by the principal investigator (RB) according to ILAR¹ criteria using abstracted data.

Trajectory descriptor variable: "outcome variable". The active joint count

(AJC) was used as the main outcome variable. An active joint was defined as either a swollen joint or a joint with loss of range of motion with joint pain or tenderness. The AJC was chosen as the trajectory descriptor variable because it is a marker of disease activity¹¹, 1 of the core set variables used in the assessment of outcomes in clinical trials in juvenile arthritis¹².

Further, AJC is a reliably recorded measure of disease activity present in the medical records that could be abstracted for a retrospective study. We recognize that JIA is a multidimensional disease and there are other important patient- and disease-related factors that are determinants of disease activity. In this proof of concept study, using the LGCA method, we focused on 1 of the most important outcomes over time (AJC) to test the hypothesis that disease course over time could be characterized by the use of an LGCA.

Statistical analysis. The longitudinal trajectories of active joint counts were described using an LGCA. This method is ideally suited to a population for which the underlying hypothesis is that the population comprises unobserved subpopulations¹³. LGCA aims to classify individuals into statistically distinct groups based on individual response patterns so that individuals within a group are more similar than individuals in different groups.

LGCA measures and explains differences across subjects in their trajectories over time. While a conventional growth curve modeling approach attributes all heterogeneity among subjects to random variation around a common mean growth curve for the population, the defining characteristic of the latent variable growth curve model is that it identifies groups of subjects with different mean growth curves.

Model building and selection. Model fit characteristics were evaluated by statistical fit indices, classification quality, and clinical usefulness¹⁴. The 0-inflated, negative-binomial distribution that fitted to the AJC data has 2 key properties: (1) some proportion of the values are equal to 0, and (2) the rest follow a negative-binomial distribution that can be thought of as a Poisson distribution with additional variability. To find the optimal model, a series of quadratic LGCA and growth mixture models were fit sequentially. All models were run with intercept, linear, and quadratic terms to allow for more flexibility in estimating the shape of the trajectories.

Models were compared using the Bayesian information criterion (BIC), a measure of model fit that has a penalty for model complexity (i.e., number of variables). A low BIC was 1 criterion used in the choice of the number of classes and the best-fitting distribution.

Using LGCA, it is not possible to determine definitively which group an individual belongs to, but the model does generate the probability of an individual's membership in each group. Each individual was classified to the group with the largest probability. The quality of classification to the latent classes was determined by examining these probabilities, with values of < 0.7 indicating a poor fit and values > 0.9 indicating excellent classification¹⁵. Entropy, an index used to quantify the uncertainty of classification of subjects into groups, was also used to assess classification. Entropy values range from 0 to 1, with 0 corresponding to randomness and 1 to perfect classification¹⁶.

Statistical software. Univariate analyses were conducted to describe the study population with SAS version 9.2 for Windows (SAS Institute Inc.). Trajectories of AJC were investigated using LGCA with Mplus version 6.0 (Muthén and Muthén, 1998–2010)^{17,18}. The associations between baseline patient characteristics and their latent class were tested by an ANOVA or Fisher's exact test. Statistical significance was defined as a $p < 0.05$.

RESULTS

Data were collected on 1074 subjects, of which 68 were not eligible because their age at onset of symptoms was > 16 years (14) or their diagnosis was made > 90 days before the first visit with the rheumatologist (54). A total of 347 eligible subjects were excluded for the following reasons:

no documented first visit (2), incorrect diagnosis (1), and < 3 visits with the rheumatologist (344). Because no information was extracted for the excluded patients, they could not be compared to study subjects. Data from the remaining 659 subjects (361 from Saskatoon, 298 from Winnipeg) were used for analysis. The study participants had a variable length of followup with a median of 4.5 years and a minimum of 18 months, as specified by the inclusion criteria. A cutoff of 20 visits (9.5 years) was chosen as the maximum to be used in the growth curve modeling because patient numbers were small after this.

Table 1 shows the demographics and clinical characteristics of the 659 study participants at first visit. Of the 35.7% of participants with the oligoarthritis subtype, 12.8% (30/235) had a polyarticular course (extended oligoarthritis)¹. Medications started before or at the first visit included nonsteroidal antiinflammatory drugs (NSAID) for 394 patients (60%), disease-modifying antirheumatic drugs (DMARD) for 20 (3%), oral corticosteroids for 18 (3%), and intraarticular steroid injections for 70 (11%). No patient was using a biologic therapy at the first visit. During the followup period, 615 patients (93%) were treated with NSAID, 223 (34%) with intraarticular injections, 94 (14%)

Table 1. Demographic and clinical characteristics of the cohort. Values are n (%) unless otherwise specified.

Characteristics	n = 659
Female sex	402 (61.0)
ANA-positive, n = 628	286 (45.5)
Age at diagnosis, yrs, mean (SD)	8.9 (4.9)
Active joint count, mean (SD)	2.7 (6.0)
ILAR diagnosis	
Systemic arthritis	45 (6.8)
Oligoarthritis	235 (35.7)
Polyarthritis, RF-negative	87 (13.2)
Polyarthritis, RF-positive	23 (3.5)
Psoriatic arthritis	54 (8.2)
Enthesitis-related arthritis	134 (20.3)
Undifferentiated	81 (12.3)
Individual ILAR criteria	
Systemic fever	45 (6.7)
Psoriasis	46 (8.9)
Dactylitis	33 (7.9)
RF-positive	23 (3.5)
Lumbosacral back pain	147 (28.0)
Enthesitis	148 (31.8)
HLA-B27 positive	93 (16.6)
First degree family history of psoriasis	99 (17.6)
Family history of HLA-B27 associated disease	91 (16.3)
ESR, mm/h, at first visit, median (25%–75%), n = 554	21.0 (9.0–40.5)
CRP, mg/l, at first visit, median (25th%–75th%), n = 178	4.00 (0.0–12.0)

ANA: antinuclear antibody; RF: rheumatoid factor; ILAR: International League of Associations for Rheumatology; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

with oral corticosteroids, 208 (32%) with 1 or more DMARD, and 34 (5%) with biologic therapies.

Model building and selection. Three-, 4-, 5-, and 6-class solutions were fit to the data. The final 2 best-fitting models we considered had 4 and 5 groups (Table 2). The 5-class model had a better fit, with lower BIC (20193.8 vs 20276.9) and Akaike information criterion (20005.2 vs 20106.2), but slightly worse performance on the classification indices. The mean posterior probability of group membership for the 5-class model was 0.817 (0.758–0.896) and for the 4-class LGCA was 0.849 (0.751–0.959). The 4-class model also had the higher entropy values (0.734 vs 0.730). However, the 5-class model included a clinically distinct group (moderate increasing) that was missing from the 4-class model (Figure 1). With the sixth version of the Mplus software, determination of CI around the estimated curves was not possible.

The 5-class LGCA was chosen as the final model and retained for further analysis. The 5 classes were (1) high decreasing (8.8% of study population): initial severe polyarthritis (mean AJC 14.1) followed by a gradual decrease in mean AJC over years; (2) moderate increasing (10% of study population): initial mean AJC of 5.5 followed by an increasing AJC after 5 years (mean AJC 9.7); (3) persistent moderate (16.4% of study population): initial mean AJC 3.2 followed by persistent moderate AJC; (4) persistent low (44.8% of study population): mild joint disease activity (initial mean AJC 0.9) followed by improvement; and (5) minimal joint activity (20.2% of study population): minimal to no active joint disease throughout the course (initial mean AJC 0.3).

Association of characteristics at first visit with identified trajectories. The baseline characteristics are presented for each class in Table 3. Enthesitis, dactylitis, ethnicity, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were not considered in this analysis because > 25% of the values for these variables were missing. There was a statistically significant difference between the classes for all variables considered (p values for Scheffe's F test or chi-square/Fisher's exact test all < 0.05), except for psoriasis (p = 0.26).

The persistent low class contained the highest proportion of the ILAR category oligoarthritis-persistent. The proportion of antinuclear antibody (ANA)-positive subjects was higher in the persistent low, moderate increasing, and persistent moderate classes than in the high decreasing or minimal joint activity classes. Polyarthritis rheumatoid factor (RF)-negative and positive patients were mostly in the moderate increasing and high decreasing classes. The minimal joint activity class subjects were more likely to have lumbosacral back pain, be HLA-B27-positive, and have a family history of HLA-B27-associated diseases, but were less likely to be ANA-positive.

The most striking finding when examining characteristics of subjects in each class was that ILAR categories

Table 2. Fit statistics for the LGCA model building*.

Characteristics	2-class LGCA	3-class LGCA	4-class LGCA	5-class LGCA	6-class LGCA
Class size (%)					
1	73	57	44	44	42
2	26	25	20	20	18
3	—	18	18	16	17
4	—	—	18	10	10
5	—	—	—	10	9
6	—	—	—	—	3
Fit statistics					
AIC	20530.5	20206.3	20106.2	20005.2	19941.5
BIC	20665.3	20359.0	20276.9	20193.8	20148.0
Entropy	0.889	0.789	0.734	0.730	0.744

*Based on the fit indices (smaller AIC and BIC) and class size, the 4-class and 5-class solutions were superior. The 5-class LGCA model was selected based on clinical relevance and usefulness. It provides 1 further clinically meaningful class that represented 10% of the total population. Given our clinical knowledge of the disease course, this class represented a subset of patients who present with moderate active joint disease, but progress to involve more joints. A 6-class LGCA model did have smaller AIC and BIC values, however, the additional class was small (3%) and did not represent a clinically distinct group. LGCA: latent growth curve analysis; AIC: Akaike information criterion; BIC: Bayesian information criterion.

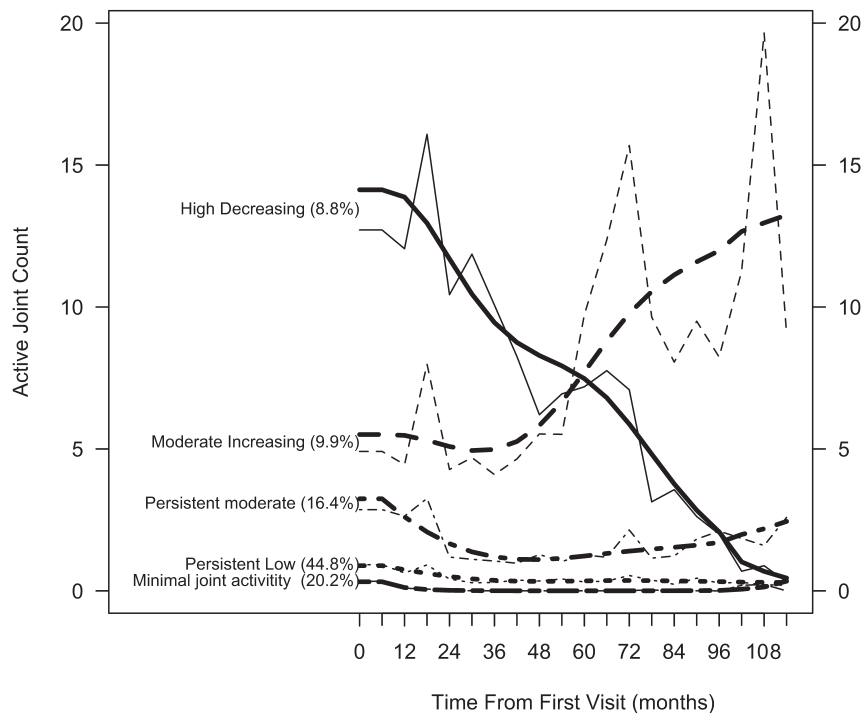


Figure 1. Observed and fitted trajectories from the 5-class latent growth curve analysis. Bold lines are the fitted trajectories and fine lines are the observed values at each time point for subjects in that latent class.

were dispersed among the classes (Figure 2), supporting the notion that variability in disease course is not adequately explained by ILAR criteria. Most patients were in the persistent low class and patients with oligoarthritis were found primarily in this group. However, patients with systemic arthritis and polyarthritis were dispersed among classes.

There were 15.8% (1318/8324) missing visits. However, for the visits that were recorded, the outcome variable (AJC)

was missing in only 33. There were significant percentages (> 25%) of missing data for some baseline characteristics (ESR, CRP, enthesitis, and dactylitis) and this precluded their evaluation in the univariate analysis.

DISCUSSION

In this retrospective cohort study, encompassing 10 years of data, we explored the use of a longitudinal statistical approach to characterize disease course in JIA in a novel

Table 3. Characteristics of the study participants stratified by trajectory (n = 659). Except for p values and where otherwise specified, data are n (%) or n/N (%).

Characteristics	Minimal Joint Activity	Persistent Low	Moderate Increasing	Persistent Moderate	High Decreasing	Univariate Analysis p
Subjects in class	133 (20.2)	295 (44.8)	65 (9.9)	108 (16.4)	58 (8.8)	
Variable*						
Female sex	61 (45.9)	175 (59.3)	46 (70.8)	79 (73.2)	41 (70.7)	< 0.0001
Age at diagnosis, yrs, mean (SD)	10.0 (4.7)	8.5 (4.8)	10.7 (4.7)	7.7 (5.3)	8.8 (4.7)	< 0.0001
ANA-positive	32/130 (24.6)	137/277 (49.5)	32/61 (52.5)	59/103 (57.3)	26/58 (44.8)	< 0.0001
ILAR diagnosis						< 0.0001
Systemic arthritis	12 (9.0)	14 (4.8)	4 (6.2)	6 (5.6)	9 (15.5)	
Oligoarthritis	27 (20.3)	166 (56.3)	4 (6.2)	35 (32.4)	3 (5.2)	
RF-negative polyarthritis	1 (0.8)	12 (4.1)	27 (41.5)	26 (24.1)	21 (36.2)	
RF-positive polyarthritis	0	1 (0.3)	8 (12.3)	4 (3.7)	10 (17.2)	
Psoriatic arthritis	9 (6.8)	16 (5.4)	6 (9.2)	19 (17.6)	4 (6.9)	
Enthesitis-related arthritis	70 (52.6)	49 (16.6)	5 (7.7)	8 (7.4)	2 (3.5)	
Undifferentiated	14 (10.5)	37 (12.5)	11 (16.9)	10 (9.3)	9 (15.5)	
Individual ILAR criteria*						
Systemic fever	12/133 (9.0)	11/292 (3.8)	4/65 (6.2)	7/108 (6.5)	11/57 (19.3)	0.0084
Psoriasis	12/124 (9.7)	15/220 (6.8)	3/43 (7.0)	13/89 (14.6)	3/43 (7.0)	0.2622
RF-positive	0	6/267 (2.2)	10/60 (16.7)	5/98 (5.1)	13/58 (22.4)	< 0.0001
Inflammatory back pain	65/127 (51.2)	52/232 (22.4)	6/49 (12.2)	16/77 (20.8)	8/41 (19.5)	< 0.0001
HLA-B27-positive	23/125 (18.4)	47/242 (19.4)	2/50 (4.0)	18/93 (19.4)	3/49 (6.1)	0.0190
First degree family hx psoriasis	17/126 (13.5)	34/251 (13.5)	15/52 (28.8)	25/86 (29.1)	8/49 (16.3)	0.0022
Family hx HLA-B27-associated disease	39/129 (30.2)	35/248 (14.1)	7/50 (14.0)	9/81 (11.1)	1/50 (2.0)	< 0.0001
Treatment during followup						
DMARD	4 (3.0)	65 (22.0)	35 (53.9)	58 (53.7)	46 (79.3)	< 0.0001
Biologic therapy	2 (1.5)	9 (3.1)	6 (9.2)	7 (6.5)	10 (17.2)	< 0.0001
Intraarticular steroid injection	17 (12.8)	129 (43.7)	15 (23.1)	49 (45.4)	13 (22.4)	< 0.0001
Oral corticosteroid therapy	11 (8.3)	33 (11.2)	13 (20.0)	14 (13.0)	23 (39.7)	< 0.0001

*Data for enthesitis and dactylitis were not presented as there was > 25% missing data. + Percentages are expressed as % of class. n/N: number positive/number tested; when N is not specified, there was no missing data for the variable and N = class size. ANA: antinuclear antibody; ILAR: International League of Associations for Rheumatology; DMARD: disease-modifying antirheumatic drug; RF: rheumatoid factor.

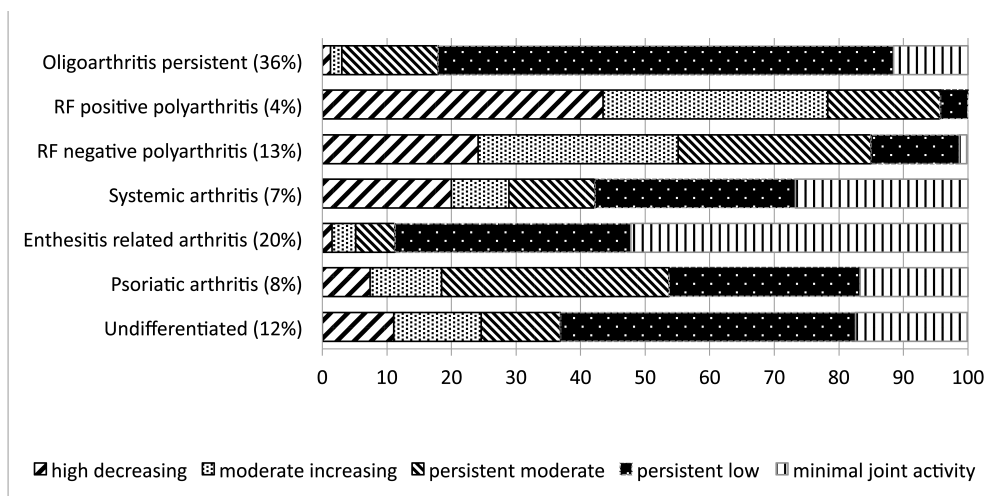


Figure 2. ILAR subtype, stratified by trajectory. ILAR: International League of Associations for Rheumatology. RF: rheumatoid factor.

way. To the best of our knowledge, this proof-of-concept study is the first in JIA to use an LGCA to identify homogeneous subsets of patients that follow a similar pattern of joint disease activity over time.

The final model adopted in our study was a 5-class LGCA model based on statistical fit indices, classification quality, and clinical sensibility. The persistent low and minimal joint activity classes may represent those subjects

whose joint disease was relatively easy to control with therapy. It is likely that other aspects of the disease (enthesitis, fever, uveitis, rash, lumbosacral back pain) are important for the minimal joint activity group, but not identified by AJC as a marker of disease activity. The persistent moderate, moderate increasing, and high decreasing groups were characterized by a more refractory disease. These 3 groups had the highest rates of DMARD use and may have required ongoing or intensified therapy.

If we consider the distribution of the ILAR criteria, certain subtypes are primarily found in 1 class (oligoarthritis) whereas others are dispersed among several classes (systemic and polyarthritis; Figure 2). Our findings are consistent with reports regarding the heterogeneity of the disease course of patients within an ILAR category. For example, a small observational study (n = 45) reported the courses of patients with systemic arthritis as monophasic (1 episode of active disease not lasting more than 24 mos), polycyclic (≥ 1 active and inactive disease episodes), or persistent (active disease for more than 24 mos). In that study, active disease was any of joint disease, systemic features, or inflammatory blood work¹⁹. The patients with systemic arthritis in our study were essentially distributed between high decreasing, persistent low, and minimal joint activity groups.

Among RF-negative patients with polyarthritis, at least 2 subtypes are recognized. The first is a form similar to adult-onset RF-negative RA and is characterized by symmetric synovitis of large and small joints, onset at school age, and ANA negativity. The second resembles oligoarthritis (asymmetric arthritis, early age at onset, female predominance, ANA positivity), except for the number of joints affected in the first 6 months^{4,20}. This is consistent with our results because the patients with RF-negative polyarthritis were distributed among the high decreasing, resembling adult RA and moderate increasing/persistent moderate, suggesting a more oligoarthritis-type course.

The patients with oligoarthritis were primarily in the persistent low class. A longterm outcome study reporting on 207 patients with onset oligoarticular found that at the end of 6 years of followup, the probability of a polyarticular course was 50%²¹. Our cohort had 12.8% (30/235) of the patients with oligoarthritis who followed a polyarticular course. There were only 4 patients (6.2%) with oligoarthritis in the moderately increasing group. There are a few potential reasons why this occurred. First, if the polyarticular extension was mild (low total AJC at extension), this may not have been detected by the LGCA that identifies average change over time within a group. Second, if the patient were treated and quickly returned to low AJC, this rapid transition may not have been detected with the 6-month study visits because the effect of medication was not accounted for in our study.

A few groups have proposed that psoriatic arthritis

should not be a separate JIA category because the course of patients with oligoarticular and polyarticular onset psoriatic arthritis may not be clinically different from patients with oligoarthritis and polyarthritis (non-psoriatic) subtype^{20,22}. We found that the proportion of patients with psoriasis in each class was not significantly different among the classes, supporting the view that the presence of psoriasis is not sufficient to determine a homogeneous group of patients.

To the best of our knowledge, ours is the first study to use LGCA to identify trajectories of disease course in JIA. The aim of this method — to identify and characterize population members with differences in their trajectories — seems ideally suited to a heterogeneous disease process such as JIA. Historically, this method has been used in social and psychological sciences, particularly to examine how social behaviors unfold over time and to study personality development. There is growing interest in LGCA in medicine, because this method may be extended to identify heterogeneity in treatment responses and to further our understanding of growth and development of illness. These methods have been used successfully to describe diverse outcomes in clinical and observational trials, including identifying trajectories of joint space narrowing in knee osteoarthritis²³, disability in the last year of life²⁴, postconcussive symptoms in children with mild traumatic brain injury²⁵, and characterization of responders to treatment in chronic obstructive pulmonary disease²⁶.

Limitations of our study were the retrospective design, including the retrospective ILAR categorization, lack of account for effect of medication on trajectories, and the use of AJC alone without other indicators to describe the disease course. Missing data for the outcome variable was relatively small given this large cohort (15.8%, 1315/8324).

Another limitation was the lack of sociodemographic information regarding the patients who were excluded for having fewer than 3 visits with the rheumatologist, or who were lost to followup. To address this limitation, we compared the joint count (surrogate for disease activity) of patients who go on to have another visit versus those who drop out (Figure 3).

There was a statistically significant difference in the mean AJC at about one-third of the visits. The count for those who dropped out was lower than for those who continued to the next visit. There was marked random variation (large SD) and it is unlikely the differences were clinically significant. There is no obvious trend apart from perhaps early dropouts at visit 3 and the later visits (18–20) where it appears that the mean AJC was higher among those who continued; however, the number of subjects was small.

Overall, at the end of the 20 visits, 51% (321/659) were lost to followup. Censored cases were defined as those subjects whose last visit was within a year of the end of the site-specific study period or after they turned 17; their

Mean AJC at Month n by Follow-up Status at Month n+6

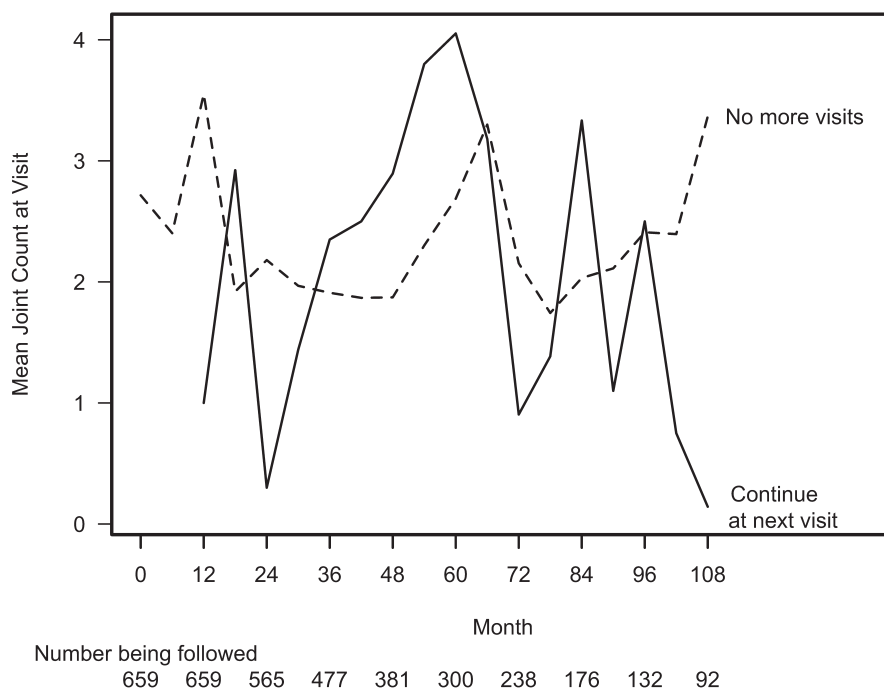


Figure 3. Mean AJC at month n by followup status at month n + 6. AJC: active joint count.

followup ends for reasons that are likely unrelated to their disease status. Someone whose last visit does not match these criteria is called a dropout and it is possible that followup ended because of their disease status.

Medication exposure, clearly an important determinant of the shape of the trajectory as well as an individual's class membership, was not included in the LGCA. To minimize the effect of medications started before study entry, we sought to create an inception cohort that was treatment-naive. However, many patients were receiving treatment at the time of study entry. Despite these limitations, our final model is a reasonable description of a treated population of patients from 2 Canadian centers where practice styles and access to medications are relatively homogeneous. Because this is a historic cohort (data from 1980–2009), a future study may yield different results attributable to better control of the AJC with new and improved therapies.

JIA is a multidimensional disease and the AJC does not represent all important aspects of disease activity. Other important aspects of disease to consider include components of the American College of Rheumatology's JIA disease core set (joints with loss of range of motion, Child Health Assessment Questionnaire, parent/patient global assessment, physician global assessment, ESR)¹². Additional factors that may also be important for disease activity are the size of the

joints involved²⁷. In using the AJC as the disease activity measure, the course of disease in subjects whose primary disease manifestations were enthesitis, uveitis, or systemic features was not adequately characterized.

In this proof-of-concept study, in which we used an analytic method in a novel way, we identified 5 clinically and statistically distinct trajectories of disease course. The subsets of patients within each class were different from those described by the ILAR classification criteria. The results of our study provide important evidence that the clinical course of patients (with either different treatment response or AJC) can be discovered using this methodology. Although LGCA is in its infancy in its application to chronic disease, it does show promise for identifying homogeneous subsets within the heterogeneous JIA population. This successful application of this method supports its use in a chronic disease with a fluctuating course. These methods should be expanded to examine other components of disease activity in addition to replicating these methods in a prospective cohort for the purposes of predictive modeling.

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