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ORIGINAL RESEARCH

Disease activity trajectories from childhood to adulthood in the population-based Nordic juvenile idiopathic arthritis cohort

Veronika Rypdal ,[1,2] Mia Glerup ,[3] Martin Rypdal,[4] Ellen Arnstad,[5,6] Kristiina Aalto,[7] Lillemor Berntson,[8] Anders Fasth,[9] Troels Herlin,[3] Charlotte Myrup,[10] Suvi Peltoniemi,[11] Marite Rygg,[5,12] Ellen Berit Nordal[13,14]

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For numbered affiliations see end of article.

Correspondence to
Dr Veronika Rypdal;
veronika.g.rypdal@uit.no

ABSTRACT

Objectives To identify long-term disease activity trajectories from childhood to adulthood by using the clinical Juvenile Arthritis Disease Activity Score (cJADAS10) in juvenile idiopathic arthritis (JIA). Second, to evaluate the contribution of the cJADAS10 components and explore characteristics associated with active disease at the 18-year follow-up.

Methods Patients with onset of JIA in 1997–2000 were followed for 18 years in the population-based Nordic JIA cohort. We used a discrete mixture model for longitudinal clustering of the cJADAS10 and its components. We assessed factors potentially associated with higher scores on the patient's global assessment of well-being (PaGA) by hierarchical clustering and correlation analysis.

Results Four disease activity trajectories were identified based on the cJADAS10 components among 427 patients. In trajectory-group 2, the PaGA and the physician's global assessment of disease activity (PhGA) increased significantly during the course, but not the active joint count. The increase in the PaGA was significantly higher than the increases in the PhGA and the active joint count ($p<0.0001$). A similar pattern was found among all the patients with active disease in the total cohort. Patients with higher PaGA scores had unfavourable scores on several other patient-reported outcomes.

Conclusions We have identified groups of patients based on long-term disease activity trajectories. In our study the PaGA was the most important driver of disease activity into adulthood assessed by cJADAS10. We need to better understand how our patients interpret global well-being and implement strategies to achieve inactive disease perceived both by the patient and the physician.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with juvenile idiopathic arthritis (JIA) may have a considerable disease burden despite low or no clinical evidence of inflammatory active arthritis.

WHAT THIS STUDY ADDS

⇒ This study is the first reporting long-term disease activity trajectories that characterise young adults with JIA having reduced global well-being despite no or low level of active joints.

⇒ A significant proportion of patients had active disease according to the clinical Juvenile Arthritis Disease Activity Score (cJADAS10) despite few or no active joints at the 18-year follow-up. These patients had a higher score mainly due to the patient-reported outcome, patient's global assessment of well-being (PaGA). Altogether, 104/176 (59%) had active disease (cJADAS10>1) despite having no active joints, and 59/176 (33%) had active disease despite no active joints and a physician's global assessment of disease activity equal to zero.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our results imply that the patient-reported disease experience is often not adequately met. Clinicians must assess not only the total JADAS score, but rather what is the main component driving the active disease. If the main driver is PaGA, despite no active joints, therapeutic strategies in addition to disease modifying anti-rheumatic drugs and biologics may be relevant. Additional treatment approaches such as physical and sport therapy, pain management and coping strategies and family counselling should be considered for implementation as a part of broader treat-to-target strategy in JIA.

⇒ Based on the identified long-term disease activity trajectories prediction of patients that will benefit from an early multidisciplinary treatment approach to achieve long-term inactive disease may be feasible.

INTRODUCTION

The treatment target in juvenile idiopathic arthritis (JIA) is clinically inactive disease or lowest possible disease activity.[1] To pursue this goal, we must assess our patients frequently and intensify treatment when required. The clinical Juvenile Arthritis Disease Activity

Score (cJADAS10) is one of several validated JIA-specific composite indices and integrates information from the number of active joints (up to 10), the physician's global assessment of disease activity (PhGA), and the patient or parental global assessment of well-being (PaGA).[2–4] It is a valuable tool to monitor changes in disease activity and treatment decision-making and response to treatment in clinical trials. However, it includes an overall subjective evaluation from both the patient and the physician that may be influenced by non-inflammatory factors, and this should be kept in mind when using composite scores in for instance escalation of treatment strategies and response to treatment.[5]

Given the heterogeneity and fluctuating nature of JIA, the relative importance of the different clinical features and their appropriate management may change throughout the disease course.[6] Identifying clusters of disease-activity trajectories may give us valuable information useful for tailoring treatment strategies. Shoop-Worrall *et al* applied unsupervised learning in a cohort study to identify clusters of patients with similar disease activity based on the cJADAS10 components during the first 3 years of the disease.[7] They state a need for long-term studies assessing disease activity trajectories into adulthood.[7] There are no prospective population-based studies assessing clusters of long-term disease activity from childhood into adulthood. Therefore, our study aims to identify different disease activity trajectories in a population-based cohort with a follow-up of 18 years using the cJADAS10 components. By exploring the disease activity trajectories, we aim to identify characteristics that should prompt individually tailored treatment strategies[1] to achieve long-term inactive disease, perceived by the physician and, most importantly, by the patient.

METHODS

Study population

The Nordic multicentre population-based prospective JIA cohort recruited 510 children with onset of JIA between January 1997 and June 2000 and followed them until November 2017. Twelve centres from specific geographical areas in Denmark, Finland, Norway and Sweden participated. During the inclusion period, letters were repeatedly sent to primary healthcare, child health centres and orthopaedic, paediatric and rheumatology specialists in the catchment areas to ensure the referral of all eligible patients.[8] Cohort details have previously been described.[8 9]

Approvals from medical research ethical committees and data protection authorities were granted according to the regulations of each participating country. Written informed consent was obtained from children older than 15 years, and from the parents of younger children.

Data collection

We collected data prospectively every 6 months during the first year and then at 1–3-year intervals up to the 8-year follow-up. The last visit was the 18-year follow-up. The study visits with extra extensive data collection were the baseline, 8-year and 18-year follow-up. Data registered at each study visit included the International League of Associations for Rheumatology (ILAR) category according to the 2004 criteria.[10] The ILAR category was registered at baseline, and updated from the 8-year and the 18-year visit.[6 8] During the study period there was a significant decrease in the overall oligoarthritis group because of the shift to the oligoarthritis extended category and a significant increase in the psoriatic arthritis category mostly due to development of psoriasis. These are previously published data.[6 8] Demographics, complete active joint count (active joint defined as a joint with swelling or limitation of movement with pain or tenderness), disease activity variables, patient-reported variables, treatment history and laboratory tests were also collected.

Patient inclusion criteria for clustering of disease trajectories

We included patients with JIA, according to the ILAR criteria,[10] with a minimum of two study visits during the observation period. One visit had to be a visit before the 8-year follow-up and the last visit had to be the 18-year follow-up. At each visit, information on at least one variable included in the cJADAS10 was required. For patients that met the inclusion criteria, all available data on the three components of the JADAS10 were used to estimate trajectory groups and trajectories. When the model is fitted to the data, it uses all the available information and there is no need for imputation of missing data. Each patient is assigned a probability for belonging to each of the four groups based on available data.

Patient-reported outcomes

Self-reported pain (pain Visual Analogue Scale (VAS)) and PaGA was denoted on a 10 cm VAS (0: No pain or best well-being, 10: Maximum pain or worst well-being). Childhood Health Assessment Questionnaire[11] or the corresponding Health Assessment Questionnaires[12] was filled in (0: No physical disability, 3: Maximum physical disability). Self-reported fatigue was assessed with the Fatigue Severity Scale (FSS). The FSS includes items covering the physical, social and cognitive effects of fatigue, yielding a score between 1 and 7 (higher score indicating more fatigue).[13] The Pittsburgh Sleep Quality Index (PSQI)[14] was used to assess sleep quality with scores from 0 to 21 (highest scores indicating the worst sleep). Health-related quality of life (HRQoL) was assessed with the generic 36-Item Short-Form Health Survey (SF-36)[15] yielding physical and mental summary scores (lower scores indicating poorer HRQoL). Information regarding if the patient was receiving social security benefits due to not being able to work at the 18-year visit was registered.

Physician-reported outcomes

The PhGA was denoted on a 10 cm VAS (0: No disease activity, 10: Maximum disease activity). Damage was

assessed using the Juvenile Arthritis Damage Index of articular damage (JADI-A) and extra-articular damage (JADI-E). The JADI aims to capture long standing damage. A score of 0 implies no damage, with a maximum score of 72 for JADI-A and 17 for JADI-E.[16]

Statistical analysis

Descriptive statistics for demographics and clinical characteristics

Fisher's exact test or χ^2 was used for differences between the disease activity trajectory groups for dichotomised variables, and the Kruskal-Wallis test for continuous variables. For assessment of changes in cJADAS10 scores and the components included in the cJADAS10 from baseline to the 8-year, and from the 8-year to the 18-year follow-up, the Wilcoxon signed-rank test was used. Statistical analyses were performed with Stata/MP V.16 and Wolfram Mathematica V.13.3.0.

Clustering of disease activity trajectories

We chose to study the cJADAS10 since it correlates strongly with the more complex JADAS versions that include inflammatory markers and/or higher joint counts.[2 17] Active disease was defined as cJADAS10>1 according to the 2012–2014 cut-offs for inactive disease (≤1); the same cut-off for oligoarthritis and polyarthritis.[4 18] Clinical meaningful names were given to the four disease activity trajectory groups, according to the median cJADAS10 scores at baseline and at the 18-year visit. Group 1: Minimal disease activity to minimal/inactive disease (MiDA-ID); group 2: Minimal disease activity to moderate disease activity (MiDA-MDA); group 3: High disease activity to minimal disease activity (HDA-MiDA); group 4: High disease activity to high disease activity (HDA-HDA). These names were chosen because the median cJADAS10 scores roughly corresponded to the standard cut-offs of inactive, minimal, moderate and high disease activity from the 2012 to 2014 cut-offs.[2] However, it is important to clarify that this does not represent a clear disease activity state, but rather a clinical meaningful name for the most common disease activity state in each trajectory group and the development throughout the course up until the 18-year follow-up.

We applied a longitudinal clustering algorithm to group patients according to the time evolution of disease activity over two decades.[19] We used the algorithm implemented by the Stata-package traj,[20 21] which is based on a discrete mixture model. It grouped patients with similar trajectories from the baseline visit to the 18-year follow-up. Patients were clustered according to the time series of the cJADAS10 components: The active joint count, the PhGA and the PaGA. For each patient, we constructed a multivariate time series based on these three components. We analysed data from all available study visits for each participant throughout the disease course.

We wanted to keep the number of groups as small as possible to prevent spurious results yet high enough to distinguish trajectories with apparent clinical differences. Based on the assumption that patients' disease activities states could be partitioned into at least two groups at early stages of the disease ('minimal/moderate' and 'moderate/high' disease activity) and at least two groups when entering adulthood ('minimal/inactive' and 'moderate/high' disease activity), we chose to start with four groups. We tried to increase the number of groups and explored the stability of the partitioning by repeated experiments where we randomly removed 10% of the included patients and constructed new groups. We subsequently computed how often two patients that were in the same group when all patients were included in the analysis were also in the same group when 10% of the patients were removed before the construction of the groups. This was repeated 10 times for each group number and the estimated probability that two patients who were in the same group would still be in the same group after perturbing the data set was taken as a measure of stability. This stability measure is presented in online supplemental table 1 and in online supplemental figure 1. The results show a decline as the number of groups increases, but there is a notable drop (from 0.89 to 0.67) when going from four to five groups. The unstable results observed when using more than four groups led us to proceed with four groups.

Following the approach of Shoop-Worrall *et al*,[22] we modelled the active joint count using a zero-inflated Poisson distribution and PhGA and PaGA using normal distributions. We explored polynomials of order 1–3 in the trajectory model and made assessments based on inspection of trajectory plots (online supplemental figure 2A–C). Bayesian information criteria are presented in online supplemental table 2. We decided to proceed with second-order (quadratic) polynomials since we wanted to keep the polynomial order as small as possible to avoid overfitting, and linear models were not able to model observed differences in trends between early stages and late stages of the disease course (online supplemental figure 2A,B). The constructed groups were very similar using first-order (linear) and second-order (quadratic) polynomials (online supplemental table 3). For the cJADAS10 and the components, we computed the median values and IQR for each month after the onset of JIA. We smoothened the resulting curves using a low-pass filter to obtain better visualisations of the results.

Heat-map construction of factors explored for associations with the PaGA

We constructed a heat-map plot by hierarchical clustering to explore factors associated with the PaGA. The purpose of the hierarchical clustering is to group patients that have similar factors together. Each row in the heat-map matrix corresponds to one of the assessed factors collected at the 18-year follow-up, and each column corresponds to a patient. The colour of the matrix cell corresponds to the value of the normalised variable. The sign of some of the variables was changed before normalisation so that low values (blue colour) are favourable results (low PhGA scores, low/zero active joint

count, low scores on pain VAS or fatigue VAS, good physical and mental HRQoL, good sleep quality, low levels of self-reported fatigue, good quality of sleep or no need for social security benefits) and high values (red colour) are unfavourable results on the above mentioned factors. The patients' and variables' orders were randomly shuffled before we used a hierarchical clustering algorithm to order rows (factors) and columns (patients) so that similar factors and patients appeared next to each other. We computed the Pearson correlation between the assessed factors in the heat-map and illustrated the results in a correlation-matrix plot. We performed imputation for missing data in constructing the heat-map and correlation matrix, using an algorithm for multiple imputations (Mathematica V.13.1.0 software). The algorithm tested five methods (normal imputation, kernel density estimates, the contingency table method, decision trees and the Gaussian mixture) for synthesising missing data in the three cJADAS10 components. For our data, the contingency table method performed best in internal cross-validations and therefore this method was used to impute the missing variables. We only imputed data after clustering the trajectories since the clustering method handles missing data and makes probabilistic assignments to groups even based on the available data. The variables included in the imputation models were the same as those included in the constructions of the heat-map and the correlation matrix: Self-reported pain (VAS), self-reported fatigue on the FSS, sleep quality assessed by the PSQI, physical and mental HRQoL assessed with the generic SF-36, if the patient was receiving social security benefit support at the 18-year visit (yes/no), information on active joint count and the PhGA score.

RESULTS

JIA cohort characteristics

A total of 427 patients with JIA according to the ILAR criteria fulfilled the inclusion criteria having a minimum of two study visits, one before the 8-year follow-up and the other had to be the 18-year visit. Information on at least one variable included in the cJADAS10 was required at each visit. The original Nordic cohort constituted of 510 patients. 83 patients were excluded because they were not fulfilling criteria. For 79 of the 83, the reason was lost to follow-up at the 18-year visit. There were four patients without an early visit with data on at least one component of the cJADAS10. Among the 427 included patients, 290 (68%) were women. The patients were followed from a median age of 6.4–23.4 years. Characteristics of the Nordic JIA cohort at baseline and at the 18-year follow-up are shown in table 1.

When comparing gender, age at onset of JIA, age at the visit and follow-up time between patients fulfilling the inclusion criteria versus those not included in this study, there were no significant differences (data not shown). The median number of study visits for each patient was 5 (IQR 2–5). There were three major visits. The baseline visit occurred at a median 7 months (IQR 6–8 months) after disease onset, the 8-year follow-up at a median 8 years (IQR of 7.8–8.5 years) with a range of up to 12 years and the 18-year follow-up at a median of 17.6 years (IQR 16.8–18.4 years) with a range of up to 20 years after disease onset.

In addition to the three major study visits there were several in-between study visits. Figure 1 presents all the computed median cJADAS10 scores during the 18-year observation period. There was a decrease in the median cJADAS10 scores from baseline and up until the period for the 8-year follow-up ($p<0.0001$), and then a slight increase in the scores towards the 18-year follow-up ($p<0.0001$).

The contribution of the cJADAS10 components to active disease according to cJADAS10

Among all the patients participating at the 18-year follow-up 139/415 (33.5%) had active disease according to the American College of Rheumatology (ACR) 2011 criteria,[23] this proportion was 130/323 (40.2%) for the patients examined at the outpatient clinic (without the patients undergoing the standardised telephone interview). For active disease according to cJADAS10>1, this proportion was 176/389 (45.2%) for all the included patients and 157/308 (51.0%) excluding patients participating through the standardised telephone interview. Of the 176 patients with active disease according to cJADAS10>1, 104 (59.1%) did not have any active joints and 59 (33.5%) had active disease despite no active joints and no active disease according to the physician (PhGA=0). For the 176 patients with active disease at the 18-year follow-up the median cJADAS10 score was 4.5 (IQR 2.5–9.5). For each component included in the cJADAS10, the values were as follows: median number of active joints 0, median PhGA 1.0 and median PaGA 3.0 (table 2).

There was a significant decrease in the median cJADAS10 scores from baseline to the 8-year visit and a significant increase from the 8-year to the 18-year visit. Both the PhGA and the PaGA increased significantly from the 8-year to the 18-year visit. The increase in the PaGA was significantly higher than the increase in the PhGA ($p<0.0001$) from the 8-year to the 18-year visit, contributing more to the total cJADAS10 score (table 2). The active joint count did not increase significantly during the observation period. The contribution of the PaGA to the cJADAS10 score at the 18-year visit was significantly higher than the PhGA and the active joint count ($p<0.0001$). Among the 396 patients where we had a PaGA score at the 18-year follow-up, 91 (23.0%) had a PaGA score >1 and no active joints, 62 (15.7%) had a PaGA score >2 and 47 (11.9%) a PaGA score >3, despite no active joints.

Disease activity trajectory groups

Four disease trajectory groups were constructed based on longitudinal cluster analysis using all the available

Table 1 Characteristics of the Nordic juvenile idiopathic arthritis cohort at the baseline visit and the 18-year follow-up

Demographics	n	Baseline	n	18-year follow-up*
Gender female n (%)	427	290 (67.9)	427	290 (67.9)
Age at onset of symptoms (years), median IQR	427	5.7 (2.7–9.7)		
Time to study visit (years), median IQR	427	0.6 (0.5–0.7)	427	17.6 (16.8–18.4)
Full-time employed or student, n (%)			424	306 (72.2)
Transferred directly to adult rheum. care, n (%)†			427	163 (38.2)
Transferred later to adult rheum. care, n (%)†			427	60 (14.1)
ILAR category, n (%)				
Oligoarthritis persistent	427	232 (54.3)	427	115 (26.9)
Oligoarthritis extended			427	85 (19.9)
RF-negative polyarthritis	427	90 (21.1)	427	75 (17.6)
RF-positive polyarthritis	427	7 (1.6)	427	6 (1.4)
Enthesitis-related arthritis	427	31 (7.3)	427	41 (9.6)
Psoriatic arthritis	427	8 (1.9)	427	28 (6.6)
Undifferentiated	427	45 (10.5)	427	63 (14.7)
Systemic	427	14 (3.3)	427	14 (3.3)
ANA positive‡	382	140 (36.6)		
HLA-B27 positive	410	89 (21.7)		
Treatment at the visit, n (%)				
NSAID	417	224 (53.7)	267	77 (28.8)
sDMARD	427	78 (18.3)	427	84 (19.7)
bDMARD	422	7 (1.7)	427	83 (19.4)
Disease activity measures				
Number of active joints, median IQR	427	1 (0–3)	427	0 (0–0)
PhGA, median IQR	229	1.0 (0.5–2.9)	416	0 (0–1.0)
PaGA, median IQR	251	1.0 (0.1–2.9)	396	0.5 (0–2.5)
ESR (mm/h), median IQR	344	14 (8–28)	277	5 (2-9)
cJADAS10 score, median IQR	222	4.4 (1.7–8.5)	389	1.0 (0–4.0)
CHAQ/HAQ score, median IQR	260	1.0 (0–3.0)	396	0 (0–0.4)
Pain VAS, median IQR	247	0.3 (0–1.1)	396	0.5 (0–3.0)
Morning stiffness ≥15 min, n (%)	418	223 (53.3)	379	67 (17.7)
Uveitis, n (%)	424	19 (4.5)	427	95 (22.3)
Damage, n (%)				
JADI-A>0	258	0	427	69 (16.2)
JADI-E>0	258	0	427	43 (10.1)

*104 participated through a standardised telephone interview at the 18-year visit. For the 323 patients attending the visit, PaGA was available for 308 and PhGA for 321 participants.
†After the regular follow-up at the paediatric rheumatologist was finished due to age limit, the patient was transferred directly or not to adult care.
‡ANA measured by immunofluorescence on Hep-2 cells, performed at least twice with a minimum of 3 months apart.
A, articular damage (0-72); ANA, antinuclear antibodies; bDMARD, biologic disease-modifying antirheumatic drug; CHAQ/HAQ, Child Health Assessment Questionnaire/Health assessment questionnaire (0–3); cJADAS10, clinical Juvenile Arthritis Disease Activity score (0–30); E, extra-articular damage (0–17); ESR, erythrocyte sedimentation rate; HLA-B27, human leucocyte antigen B27; ILAR, International League of Associations for rheumatology; JADI, Juvenile Arthritis Damage Index; NSAID, non-steroidal anti-inflammatory drug; PaGA, patient or parental global assessment of disease impact on well-being; PhGA, physician's global assessment of disease activity; RF, rheumatoid factor; sDMARD, synthetic disease-modifying antirheumatic drug; VAS, Visual Analogue Scale (0–10).

cJADAS10 components throughout the 18 years observation period. Figure 2 shows the four disease activity trajectories from baseline to the 18-year follow-up. The total number of assessable study visits were 2517, with the total number of the cJADAS10 components as follows: joint count, n=2516, 0.1% missing, PhGA, n=1865, 26% missing

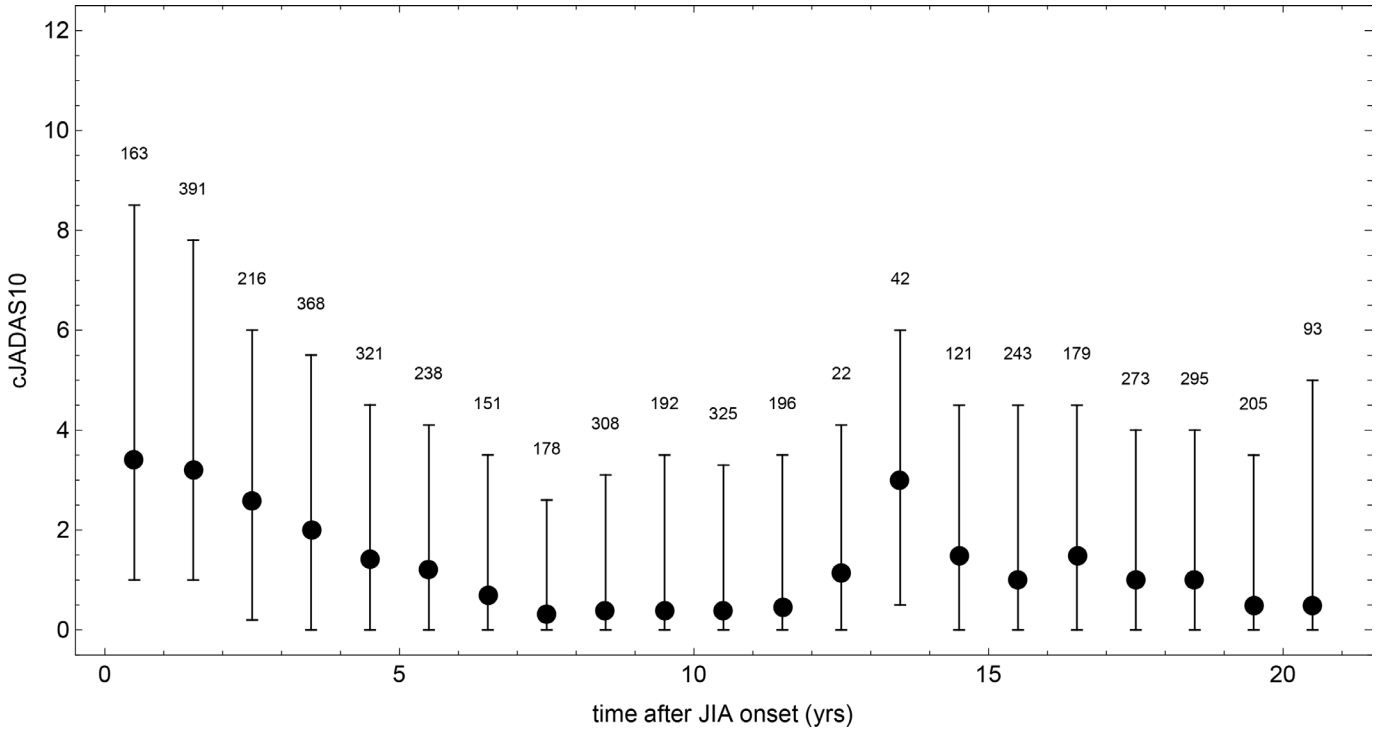

Figure 1 The median cJADAS10 scores for the total cohort from time after JIA onset to the 18-year follow-up. Median cJADAS10 (clinical Juvenile Arthritis Disease Activity score, with evaluation of up to 10 active joints) with IQR and the number of assessed cJADAS10 values at each point. JIA, juvenile idiopathic arthritis.

and PaGA, n=1904, 24% missing. Figure 2 shows the four disease activity trajectories of the individual components of the cJADAS10 and the composite cJADAS10 scores. These numbers also include the values obtained through the standardised telephone interview.

Group 1 (MiDA-ID), consisted of 168 patients (39.3%) with minimal disease activity at baseline (median cJADAS10: 1.7, IQR 0–3.9), throughout the observation period and MiDA-ID at the 18-year-follow-up. Group 2 (MiDA-MDA), with 104 patients (24.4%), had minimal disease activity at baseline (median cJADAS10: 2.2, IQR 1.5–4.5), but with increased disease activity towards the 18-year visit. Group 3 (HDA-MiDA), contained 119 patients (27.9%) with high disease activity at baseline (median cJADAS10: 8.4, IQR 5.0–12.7) and with decreasing disease activity throughout the observation period. Group 4 (HDA-HDA), with 36 patients (8.4%) had high disease activity at baseline (cJADAS10: 13.8, IQR 6.6–19.0), throughout the observation period and at the 18-year follow-up. The clinical characteristics of each trajectory group is shown in table 3.

Table 4 shows the changes in median cJADAS10 and components from baseline to the 18-year follow-up for the four disease activity trajectory groups, and the online supplemental table 4A,B presents pairwise comparisons of the trajectory groups that have similar disease activity at baseline. Online supplemental table 5 shows the patients with active disease in the four disease activity trajectory groups excluding the patients participating through the standardised telephone interview. The proportion of active disease according to the ACR criteria and a cJADAS10>1 was slightly higher when excluding these

Table 2 cJADAS10 scores and components at the three major visits for the patients with active disease* at the 18-year follow-up

	n	Baseline	n	8-year follow-up	n	18-year follow-up	P value†	
cJADAS10 score	114	5.0 (2.0–11.3)	131	2.0 (0–5.8)	176	4.5 (2.5–9.5)	<0.0001	<0.0001
Active joint count	176	1.0 (0–3.0)	172	0 (0–1.0)	176	0 (0–1.0)	<0.0001	0.42
PaGA	125	1.0 (0.2–3.4)	140	0.4 (0–2.5)	176	3.0 (1.5–5.0)	0.002	<0.0001
PhGA	117	1.7 (0.8–3.8)	135	0.5 (0–1.8)	176	1.0 (0–2.5)	<0.0001	<0.0001

Values are median (IQR) and total numbers.
*Active disease defined as cJADAS10>1; cJADAS10, clinical Juvenile Arthritis Disease Activity score with active joint count to 10 joints (0–30); PaGA, patient or parental global assessment of well-being (0–10); PhGA, physician's global assessment of disease activity (0–10).
†P value in the first column is for the difference between baseline and 8-year follow-up. P value in the second column is for the difference between 8-year and 18-year follow-up.

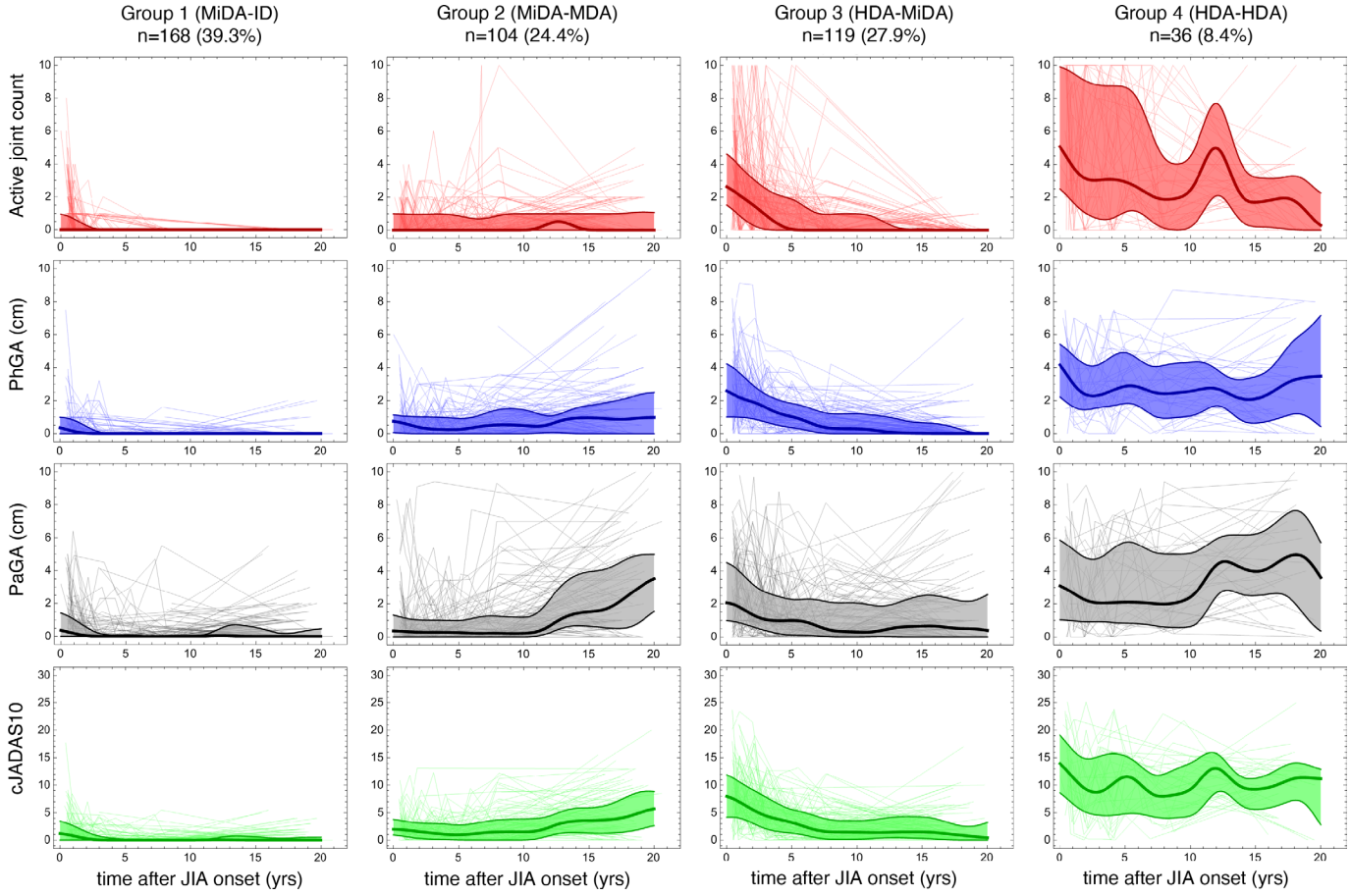

Figure 2 The four disease activity trajectories from childhood to adulthood over an 18-year follow-up period in the Nordic JIA cohort. Median active joint count (thick red line) with IQR (upper and lower lighter red lines) and active joint count for each patient with the available data (thin red lines). Median PhGA (thick blue line) with IQR (upper and lower lighter blue lines) and the PhGA for each patient with the available data (thin blue lines). Median PaGA (thick black line) with IQR (upper and lower lighter black lines) and the PaGA for each patient with the available data (thin black lines). Median cJADAS10 (thick green line) with IQR (upper and lower lighter green lines) and the cJADAS10 for each patient with the available data (thin green lines). cJADAS10, The clinical Juvenile Arthritis Disease Activity Score with evaluation of up to 10 active joints; HDA-HDA, high disease activity to high disease activity; HDA-MiDA, high disease activity to minimal disease activity; JIA, juvenile idiopathic arthritis; MiDA-ID, minimal disease activity to minimal/inactive disease; MiDA-MDA, minimal disease activity to moderate disease activity; PaGA, patient or parental global assessment of well-being; PhGA, physician's global assessment of disease activity.

patients compared with the four groups when all the patients were included (table 3).

Most of the patients in group 1 (MiDA-ID) belonged to the persistent oligoarthritis category, with 12.2% having active disease defined as cJADAS10>1 at the last study visit (table 3). Compared with the other groups, disease-modifying antirheumatic drug (DMARDs) was used less frequently, most of the patients and the physicians perceived the disease to be inactive, with median PhGA and PaGA of 0 (table 3, table 4 and online supplemental table 4A).

Group 3 (HDA-MiDA) had the second lowest percentage of active disease at the 18-year follow-up (46.9%). In contrast to group 1, these patients had a more severe disease at baseline (table 4). The extended oligoarticular and rheumatoid factor (RF)-negative polyarticular categories were the most common categories in group 3 (table 3). Compared with group 4 (HDA-HDA) with similar high disease activity at baseline, group 3 had significantly lower scores on physician and patient-reported outcomes at the 18-year follow-up (online supplemental table 4B).

In group 2 (MiDA-MDA), 77.7% had active disease with cJADAS10>1 at the last visit. However, the median active joint count was 0, as was also found for both groups 1 and 3, where the majority had minimal/inactive disease at the final visit. Group 2 mainly contained patients with oligoarthritis, with a higher proportion of extended oligoarthritis and significantly more use of DMARDs during the disease course compared with group 1 (table 3 and online supplemental table 4A). The cJADAS10 score significantly increased from 8-year to 18-year follow-up, with a significant increase in the PaGA and the PhGA, but not in the number of active joints (table 4). The increase in the PaGA was significantly higher than the increase in the PhGA ($p<0.0001$) for group 2.

Table 3 Comparisons of characteristics between the four disease activity trajectory groups identified in the Nordic JIA cohort

Characteristics	Group 1 (MiDA-ID)	Group 2 (MiDA-MDA)	Group 3 (HDA-MiDA)	Group 4 (HDA-HDA)	P value
Total n=427, n (%)	168 (39.3)	104 (24.4)	119 (27.9)	36 (8.4)	
Gender female, n (%)	101 (60.1)	76 (73.1)	82 (68.9)	31 (86.1)	0.009
Age at onset of symptoms (years), median (IQR)	5.4 (2.7–9.2)	5.2 (2.5–9.9)	6.4 (2.3–9.6)	8.7 (3.8–11.5)	0.17
Age at last study visit (years), median (IQR)	23.4 (20.5–26.5)	22.6 (20.0–27.0)	23.6 (20.2–27.3)	26.4 (20.9–29.4)	0.24
Time to first study visit (months), median (IQR)	7 (6–8)	6 (6–7.5)	7 (6–11)	7 (6–12)	0.24
Time to last study visit (years), median (IQR)	17.8 (17.1–18.7)	17.4 (16.5–18.5)	17.5 (16.7–18.2)	17.4 (16.3–18.2)	0.01
Full-time employed or student, n (%)	132 (78.5)	68 (65.4)	84 (70.6)	22 (61.1)	0.001
Transferred directly to adult rheum. care, n (%)	26 (15.5)	55 (52.9)	56 (47.1)	26 (72.2)	<0.0001
Transferred later to adult rheum. care, n (%)	20/156 (12.8)	23/80 (28.8)	12/100 (12.0)	5/29 (17.2)	0.008
ANA positive, n (%) *	39/150 (26.0)	43/94 (45.7)	44/108 (40.7)	14/30 (46.6)	0.005
HLA-B27 positive, n (%)	26/157 (16.5)	29/101 (28.7)	27/118 (22.9)	7/36 (19.4)	0.06
ILAR category at 18-year follow-up, n (%)					<0.0001
Oligoarthritis persistent	81 (48.2)	23 (22.1)	11 (9.2)	0	<0.0001
Oligoarthritis extended	17 (10.1)	35 (33.6)	30 (25.2)	3 (8.3)	<0.0001
RF-negative polyarthritis	22 (13.1)	14 (13.5)	28 (23.5)	11 (30.6)	0.02
RF-positive polyarthritis	0	2 (1.9)	3 (2.5)	1 (2.8)	0.10
Enthesitis-related arthritis	11 (6.5)	13 (12.5)	10 (8.4)	7 (19.4)	0.07
Psoriatic arthritis	8 (4.8)	8 (7.7)	9 (7.6)	3 (8.3)	0.62
Undifferentiated	21 (12.5)	7 (6.7)	24 (20.2)	11 (30.6)	0.001
Systemic JIA	8 (4.8)	2 (1.9)	4 (3.4)	0	0.51
Treatment history, n (%)					
sDMARD at baseline	22 (13.1)	15 (14.4)	29 (24.4)	12 (33.3)	<0.0001
bDMARD at baseline	2 (1.2)	5 (4.8)	0	0	0.05
sDMARD, baseline to 8-year follow-up	61 (36.3)	56 (53.8)	93 (78.2)	35 (97.2)	<0.0001
bDMARD, baseline to 8-year follow-up	9 (5.4)	17 (16.3)	38 (31.9)	25 (69.4)	<0.0001
No medication from 8-year to18-year follow-up	122 (72.6)	24 (23.1)	37 (31.1)	3 (8.3)	<0.0001
sDMARD at 18-year follow-up	9 (5.4)	30 (28.8)	28 (23.5)	16 (44.4)	<0.0001
bDMARD at 18-year follow-up	8 (4.8)	25 (24.0)	31 (26.1)	19 (52.8)	<0.0001
sDMARD, baseline to 18-year follow-up	63 (37.5)	61 (58.7)	95 (79.8)	35 (97.2)	<0.0001
bDMARD, baseline to 18-year follow-up	15 (8.9)	38 (36.5)	46 (38.7)	28 (77.8)	<0.0001
Disease activity measures at 18-year follow-up					
Number of active joints, median (IQR)	0 (0–0)	0 (0–1)	0 (0–0)	2 (0–4)	0.0001
One or more active joint, n (%)	0	39/104 (37.5)	12/119 (10.1)	23/36 (63.9)	0.0001

Continued

Table 3 Continued

Characteristics	Group 1 (MiDA-ID)	Group 2 (MiDA-MDA)	Group 3 (HDA-MiDA)	Group 4 (HDA-HDA)	P value
PhGA, median (IQR)	0 (0–0), n=163	1.0 (0–2.0), n=101	0 (0–0.5), n=116	3.0 (1.0–4.5), n=36	0.0001
PaGA, median (IQR)	0 (0–0.5), n=151	2.0 (0.5–4.5), n=95	0.5 (0–2.0), n=115	4.0 (2.0–7.5), n=35	0.0001
Active disease ACR 2011 criteria, n (%)†	11/162 (6.8)	62/102 (60.8)	36/115 (31.3)	30/36 (83.3)	0.0001
cJADAS10>1, n (%)	18/147 (12.2)	73/94 (77.7)	53/113 (46.9)	32/35 (91.4)	0.0001
cJADAS10 score, median (IQR)	0 (0–0.5)	4.0 (1.5–8.5)	1.0 (0–3.0)	10 (6.5–14.0)	0.0001
Pain VAS, median (IQR)	0 (0–1.0), n=151	2.0 (0.5–4.0), n=95	1.0 (0–3.5), n=115	4.5 (1.5–7.0), n=35	0.0001
Morning stiffness of any duration, n (%)	26/140 (18.6)	48/93 (51.6)	39/111 (35.1)	23/35 (65.7)	<0.0001
Morning stiffness ≥15 min, n (%)	9/140 (6.4)	19/93 (20.4)	25/111 (22.5)	14/35 (40.0)	0.03
Uveitis diagnose, n (%)	27 (16.1)	29 (27.9)	32 (26.9)	7 (19.4)	0.06
Damage, n (%)					
JADI-A>0	8 (4.7)	20 (19.2)	23 (19.3)	18 (50.0)	<0.0001
JADI-E>0	9 (5.3)	21 (20.2)	9 (7.6)	4 (11.1)	0.07
Surgery related to JIA sequel	6 (3.6)	7 (6.7)	10 (8.4)	7 (19.4)	0.01

Disease activity trajectory groups from baseline to 18-year follow-up.
*ANA measured by immunofluorescence on Hep-2 cells, performed at least twice with a minimum of 3 months apart.
†ACR 2011 criteria, American College of Rheumatology 2011 criteria.
A, articular damage (0–72); ANA, antinuclear antibodies; bDMARD, biologic disease-modifying antirheumatic drug; cJADAS10, clinical Juvenile Arthritis Disease Activity score (0–30); E, extra-articular damage (0–17); HDA, high disease activity; HLA-B27, human leukocyte antigen B27; ID, inactive disease; ILAR, International League of Associations for Rheumatology; JADI, Juvenile Arthritis Damage Index; JIA, juvenile idiopathic arthritis; MDA, moderate disease activity; MiDA, minimal disease activity; PaGA, patient global assessment of disease impact on well-being; PhGA, physician's global assessment of disease activity; RF, rheumatoid factor; sDMARD, synthetic disease-modifying antirheumatic drug; VAS, Visual Analogue Scale (0–10).

Group 4 (HDA-HDA) also had a high proportion of patients with cJADAS10>1 (91.4%) at the last study visit. This group had the highest proportion of the RF negative polyarticular, enthesitis-related arthritis and undifferentiated JIA categories, and the highest proportion of DMARDs use during the 18 years observation period and at the last visit (table 3, table 4 and online supplemental table 4B).

Both group 2 (MiDA-MDA) and group 4 (HDA-HDA), had higher proportions of patients with JADI-A>0 indicating some form of articular damage, and group 2 had also significantly higher JADI-E>0, compared with the groups with similar cJADAS10 starting point at baseline (online supplemental table 4A,B).

Exploring factors that may influence the scoring of the PaGA

Based on the finding that the PaGA was the main driver for a cJADAS10 score above 1 at the 18-year visit, we sought to explore other patient-reported outcomes that could be influencing the PaGA scoring. We explored seven patient-reported outcomes: Mental-related quality of life, physical-related quality of life, sleep quality, self-reported fatigue, fatigue VAS, pain VAS and social security benefits. We postulated that having unfavourable scores on these factors would be associated with a tendency towards scoring higher on the PaGA. In addition, we assessed the two physician-assessed outcomes included in the cJADAS10: Active joint count and PhGA. To explore if there were any subgrouping of patients with similarities in the factors and patterns of PaGA scoring we performed cluster analysis as described in the method section. Figure 3 shows in a heat-map the results of the clustering analyses. Patients with similarities on the assessed factors are placed near each other, but the clustering did not show a natural splitting of the patients into distinct groups but rather showed a continuum where the patients with unfavourable scores on several of the assessed variables had higher PaGA scores. To quantify the degree of relationship between the assessed factors and the PaGA we performed correlation analysis illustrated in the correlation matrix of the assessed variables and PaGA. Self-reported fatigue (r=0.76) and pain (r=0.77) correlated strongly with the PaGA (figure 4). As expected, we found moderate to strong correlations between the different patient-reported variables (figure 4).

DISCUSSION

This is the first long-term prospective study to use unsupervised learning to identify clusters of disease activity trajectories covering the transition from childhood to adulthood. Based on the cJADAS10 components, four different disease activity trajectories were identified. Trajectory group 2 (MiDA-MDA) and group 4

Table 4 cJADAS10 and components at the three major visits for each trajectory group in the Nordic juvenile idiopathic arthritis cohort

	n	Baseline	n	8-year follow-up	N	18-year follow-up	P value*	
Group 1 (MiDA-ID)								
cJADAS10	70	1.7 (0–3.9)	101	0 (0–0.1)	147	0 (0–0.5)	<0.0001	0.40
Active joint count	168	0 (0–1.0)	168	0 (0–0)	167	0 (0–0)	<0.0001	0.03
PaGA	84	0.5 (0–1.5)	123	0 (0–0)	151	0 (0–0.5)	<0.0001	0.01
PhGA	73	0.5 (0–1.0)	103	0 (0–0)	163	0 (0–0)	<0.0001	0.45
Group 2 (MiDA-MDA)								
cJADAS10	55	2.2 (1.5–4.5)	78	1.5 (0–3.7)	94	4.0 (1.5–8.5)	0.20	0.008
Active joint count	104	0 (0–1.0)	101	0 (0–1.0)	104	0 (0–1.0)	0.36	0.50
PaGA	65	0.5 (0–1.5)	83	0.2 (0–1.2)	95	2.0 (0.5–4.5)	0.28	<0.0001
PhGA	57	0.9 (0.3–1.2)	81	0.5 (0–1.5)	101	1.0 (0–2.0)	0.29	<0.0001
Group 3 (HDA-MiDA)								
cJADAS10	71	8.4 (5.0–12.7)	85	1.5 (0.2–4.0)	113	1.0 (0–3.0)	<0.0001	0.33
Active joint count	119	3.0 (2.0–5.0)	115	0 (0–1)	119	0 (0–0)	<0.0001	0.0004
PaGA	76	2.2 (1.0–4.3)	89	0.4 (0–1.9)	115	0.5 (0–2.0)	<0.0001	<0.0001
PhGA	72	2.4 (1.0–4.2)	86	0.3 (0–1.3)	116	0 (0–0.5)	<0.0001	0.58
Group 4 (HDA-HDA)								
cJADAS10	26	13.8 (6.6–19.0)	27	7.8 (2.6–15.5)	35	10.0 (6.5–14.0)	0.08	0.46
Active joint count	36	4.0 (2.5–10.0)	36	2.5 (0–6.0)	36	2.0 (0–3.5)	0.01	0.38
PaGA	26	2.8 (1.0–6.2)	28	1.9 (0.5–5.1)	35	4.0 (2.0–7.5)	0.99	<0.0001
PhGA	27	4.4 (2.0–5.1)	29	2.3 (0.8–5.0)	36	3.0 (1.0–4.5)	0.39	<0.0001

Disease activity trajectory groups from baseline to 18-year follow-up.
Values are median IQR and total numbers.
*P value in the first column is for the difference between baseline and 8-year follow-up. P value in the second column is for the difference between 8-year and 18-year follow-up.
cJADAS10, clinical Juvenile Arthritis Disease Activity score (0–30); HDA, high disease activity; ID, inactive disease; MDA, moderate disease activity; MiDA, minimal disease activity; PaGA, patient global assessment of disease impact on well-being (0–10); PhGA, physician's global assessment of disease activity (0–10).

(HDA-HDA) had the highest rates of active disease at the 18-year follow-up and had a significant increase in the PhGA and the PaGA, but not in the active joint counts. Among the patients with active disease at the 18-year follow-up in the total JIA cohort, we also found a significant increase in the PhGA and the PaGA scores from the 8-year to the 18-year follow-up, with the PaGA increasing significantly more than the PhGA, despite no significant increase in the active joint count.

Persistent disease activity in JIA is associated with long-term sequelae such as joint damage and functional disability.[9] Several studies have shown that severe disease activity at onset, predicts a more severe disease course and that achieving early inactive disease is associated with better long-term outcome.[24 25] The JADAS composite scores are often used as disease activity measures and offers the advantage of capturing a broader aspect of disease consequences by including the PaGA. The PaGA reflects valuable and complex information about the disease state that may not be captured by physician-reported measurements. The patient may incorporate patient-experiences associated with JIA, that may or may not be expression for current active disease, but rather reflects functional disability, joint damage, quality of life, pain, sleep and fatigue. The PhGA captures the examiner's subjective appraisal of the patient's disease activity. Studies have shown that the PhGA is not scored homogeneously.[26 27] Currently there are no guidelines on how to score the PhGA or the PaGA.

The JADAS has been suggested as a possible outcome measure in a treat-to-target (T2T) strategy focusing on tight disease control with intensifying therapeutic intervention when active disease is present.[1 28] However, what if a high score does not reflect inflammatory joint disease activity, but rather poor quality of sleep or pain due to other factors than inflammatory disease activity? A discordance between the active joints count and the parent/patient's perception of disease activity is not an uncommon clinical experience.[29]

There are few comparable studies evaluating disease activity trajectories based on cJADAS10. Shoop-Worrall *et al*[7] published a study identifying six disease activity trajectory groups over a follow-up period of 3 years exploring each component of the cJADAS10. Although we have

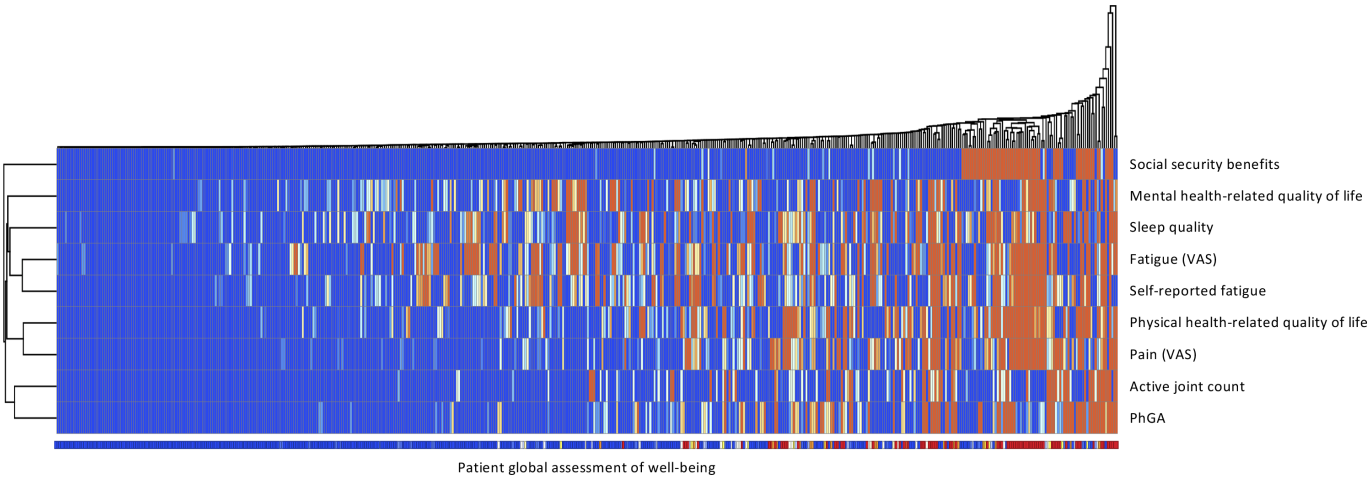

Figure 3 Heat-map and dendogram visualisation of explored factors hypothesised to be associated with higher PaGA scores at the 18-year follow-up. Each column corresponds to a patient. Explored factors hypothesised to be associated with higher PaGA scores at the 18-year follow-up are rows. An hierarchical clustering algorithm was used to group patients with similar patterns for the factors together to form the heat-map, and this heat-map was annotated (the lower panel) with the PaGA. The PaGA scores are low (blue colour) to the left, and high (red colour) to the right. The included factors were: Social security benefits (patient reported), mental health-related quality of life (HRQoL), sleep quality assessed by the Pittsburgh Sleep Quality Index, fatigue VAS (Visual Analogue Scale, 0–10 cm), self-reported fatigue assessed by the Fatigue Severity Scale, physical HRQoL, pain VAS, active joints and the physician's global assessment of disease activity (PhGA) on a VAS scale. PaGA, patient global assessment of disease impact on well-being.

fewer clusters of disease activity trajectories and a longer follow-up period, similar results were obtained in our study. They found approximately 25% of patients having persistent high PaGA scores, despite having a low joint count or no active joints.[7] In our study 23% had PaGA score >1 without having active joints. Also, three of the four trajectories identified in our study had similarities to the trajectories *low-remission group*, *high-low group* and *high-persistent trajectory* from their study.[7] The follow-up time is an important difference between the two studies, making a direct comparison difficult.

Another trajectory analysis study of disease activity was performed among the patients in the Childhood Arthritis and Rheumatology Research Alliance Registry (CARRA).[30] Shiff *et al* modelled five disease activity trajectories based on the cJADAS10 the first 2 years after the diagnosis of JIA. The individual components of the cJADAS10 were not modelled. There are some similarities when comparing the cJADAS10 trajectory curves in our study with the CARRA study. However, when comparing the active joints, the PaGA, the PhGA and the median cJADAS10 at baseline, the trajectories had higher values in all the disease activity outcome measures than our population-based study. The follow-up time of 2 years and the numbers of patients in the CARRA study differs from ours, and we can therefore not directly compare the studies. The authors stated that their results supported a T2T-strategy of early aggressive treatment. Based on the findings in our study, increasing therapeutic strategies may not be the correct measure in patients with long-standing JIA. However, a higher proportion of damage assessed by JADI among our patients in trajectory group 2 (MiDA-MDA) and group 4 (HDA-HDA) suggest that therapeutic strategies may not have been optimal early in the disease course. Previous studies have shown that the PaGA may be a proxy for functional disability and damage.[31] In our study there was a significantly higher proportion of patients with JADI-A and JADI-E>0, indicating some kind of articular or extra-articular damage in the groups with higher PaGA scores. This may be an important factor to consider when evaluating the cJADAS10 in patients with long-standing JIA.

A recent study by Trachtman *et al* investigated resilience among patients with JIA and systemic lupus erythematosus. They found that resilience was lower among children with JIA compared with the general population and inversely associated with fatigue, and positively correlated with mobility and peer relationships.[32] These results are in concordance with our findings of higher fatigue scores among factors influencing PaGA scoring.

A strength of our study is the population-based approach made possible by the uniform and mostly free of charge healthcare system for children and young persons in the Nordic countries. The Nordic JIA cohort is also one of the most recent prospective JIA cohorts providing information on long-term disease activity trajectories. Even though the follow-up period was as long as 18 years, the rate of patients lost to follow-up was rather low. The use of standardised disease activity measures at several study visits during the 18-year disease course is also a strength, including patient-reported and physician-reported outcomes.

Limitations of the study are missing data for some of the variables in cJADAS10, and that some of the patients did not attend physically the visit but participated through the standardised telephone interview at

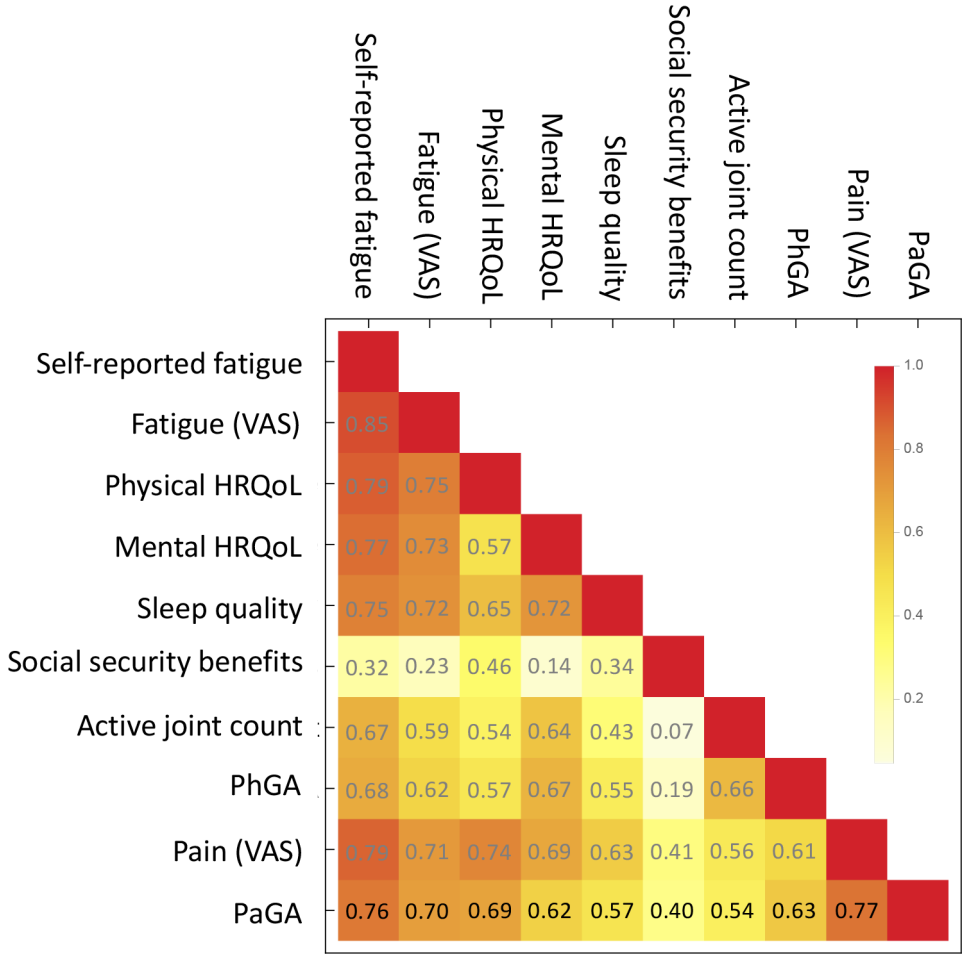

Figure 4 Correlation matrix plot of factors evaluated for association with PaGA at the 18-year follow-up. Pearson correlations between variables assessed in the heat-map. Strong correlations (r>0.70). Moderate correlations (r=0.50–0.70). Variables: Social security benefits (patient reported), mental health-related quality of life (HRQoL), sleep quality assessed by the Pittsburgh Sleep Quality Index, fatigue VAS (Visual Analogue Scale, 0–10 cm), self-reported fatigue assessed by the fatigue Severity Scale, physical HRQoL, pain VAS and the physician's global assessment of disease activity (PhGA) on a VAS scale. PaGA, patient global assessment of disease impact on well-being.

the 18-year follow-up. However, we performed analysis excluding these patients and the number of patients achieving active disease at the 18-year visit increased. Since this is a population-based study we decided to keep these patients to not bias the results towards a direction of more severe disease if we do not report these patients that constitute a considerable proportion of the patients with inactive disease. Also, the first study visit occurred at approximately 6 months, and treatment may have been started before this visit. The disease-activity trajectories start from the first study visit and not the first start of symptoms and there is a low number of participants in one of the clusters. Ideally, we wished we had more registered visits to capture more episodes of flares. Also, the gap of time between the 8-year follow-up and the 18-year follow-up where we did not have any regular study visits, may have at the 18-year visit assigned a patient as having active disease/a flare up when it may have been in inactive disease for several years, and in this way assigned as having high disease activity. However, this is less likely because when looking at the overall patterns in the disease activity trajectory groups this happening in a few cases would most likely not influence the whole group/trajectory result.

Our study shows that the PaGA reflects diverse information about the disease state, not captured by the physician-assessed outcomes. Clinicians must assess not only the total JADAS score, but rather what is the main component driving the active disease. If the main driver is PaGA, despite no active joints, therapeutic strategies other than intensifying DMARDs/biologics may be relevant. Information from the patient should be sought to explore the individual situation and guide interventions. Validated instruments on fatigue, sleep quality, psychosocial and physical functioning and HRQoL should be used. Implementing a multidisciplinary approach in the T2T-strategies for children with JIA is essential, because in addition to treating joint inflammation, treating perceived disease activity may be equally as important. After all, how the perception of disease burden experienced by the patient is what really matters because this is what most impacts their everyday life. Future work will

focus on guidelines for a homogenous scoring of the PaGA and the PhGA, to facilitate for optimal information both from the patient and the physician for describing the disease activity. Information on disease activity trajectories into adulthood may be used to develop prediction models for prediction of complex trajectories, to enable early targeted interventions improving the long-term outcomes in JIA.

Author affiliations
[1]Department of Clinical Medicine, UiT The Arctic University of Norway, Tromso, Troms, Norway
[2]Department of Pediatrics, University Hospital of North Norway, Tromsø, Troms, Norway
[3]Department of Pediatrics, Aarhus University Hospital, Aarhus, Denmark
[4]Department of Mathematics and Statistics, UiT The Arctic University of Norway, Tromsø, Troms, Norway
[5]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway
[6]Department of Pediatrics, Levanger Hospital, Levanger, Norway
[7]Pediatric Research Center, New Children's Hospital, Helsinki University Hospital, Helsinki, Finland
[8]Department of Woman's and Children's Health, Uppsala University, Uppsala, Sweden
[9]Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Göteborg, Sweden
[10]Department of Paediatrics, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[11]Clinic of Rheumatology, Helsinki University Central Hospital, Helsinki, Uusimaa, Finland
[12]Department of Pediatrics, St. Olavs Hospital, Trondheim, Norway
[13]Department of Pediatrics, University Hospital of North Norway, Tromsø, Norway
[14]Institute of Clinical Medicine, UiT The Arctic University of Norway, Tromsø, Norway

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Contributors VR, MR, EBN, AF, TH, LB and MR were involved in the conception and design of the study. VR performed basic analysis and interpretation of data and drafted the manuscript. MR performed the cluster analysis, trajectory analysis and the development of the heat map. VR, MG, MR, EA, KA, LB, AF, TH, CM, SP, MR and EBN were involved in interpretation of data, drafting of the manuscript and revising it critically for important intellectual content. VR, MG, MR, EA, KA, LB, AF, TH, SP, MR and EBN were involved in the acquisition of data. All authors read and approved the final manuscript. VR is responsible for the overall content as the guarantor. The guarantor accepts full responsibility for the work and/or conduct of the study, had access to the data, and controlled the decision to publish.

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ORCID iDs
Veronika Rypdal http://orcid.org/0000-0003-3476-305X
Mia Glerup http://orcid.org/0000-0002-9128-9908

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