Patient-reported wellbeing and clinical disease measures over time captured by multivariate trajectories of disease activity in individuals with juvenile idiopathic arthritis in the UK: a multicentre prospective longitudinal study

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Summary
Background Juvenile idiopathic arthritis (JIA) is a heterogeneous disease, the signs and symptoms of which can be summarised with use of composite disease activity measures, including the clinical Juvenile Arthritis Disease Activity Score (cJADAS). However, clusters of children and young people might experience different global patterns in their signs and symptoms of disease, which might run in parallel or diverge over time. We aimed to identify such clusters in the 3 years after a diagnosis of JIA. The identification of these clusters would allow for a greater understanding of disease progression in JIA, including how physician-reported and patient-reported outcomes relate to each other over the JIA disease course.

Methods In this multicentre prospective longitudinal study, we included children and young people recruited before Jan 1, 2015, to the Childhood Arthritis Prospective Study (CAPS), a UK multicentre inception cohort. Participants without a cJADAS score were excluded. To assess groups of children and young people with similar disease patterns in active joint count, physician’s global assessment, and patient or parental global evaluation, we used latent profile analysis at initial presentation to paediatric rheumatology and multivariate group-based trajectory models for the following 3 years. Optimal models were selected on the basis of a combination of model fit, clinical plausibility, and model parsimony.

Findings Between Jan 1, 2001, and Dec 31, 2014, 1423 children and young people with JIA were recruited to CAPS, 239 of whom were excluded, resulting in a final study population of 1184 children and young people. We identified five clusters at baseline and six trajectory groups using longitudinal follow-up data. Disease course was not well predicted from clusters at baseline; however, in both cross-sectional and longitudinal analyses, substantial proportions of children and young people had high patient or parent global scores despite low or improving active joint counts and physician global scores. Participants in these groups were older, and a higher proportion of them had enthesis-related JIA and lower socioeconomic status, compared with those in other groups.

Interpretation Almost one in four children and young people with JIA in our study reported persistent, high patient or parent global scores despite having low or improving active joint counts and physician’s global scores. Distinct patient subgroups defined by disease manifestation or trajectories of progression could help to better personalise health-care services and treatment plans for individuals with JIA.

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Introduction Juvenile idiopathic arthritis (JIA) is a heterogeneous condition with onset in childhood or early adolescence and common disease features that include joint swelling and pain.1 If not controlled, persistent joint inflammation can lead to cartilage damage and the potential need for joint-replacement surgery, with persistent pain and fatigue associated with functional limitations and lower health-related quality of life.2,3 Key outcomes for individuals with JIA are included in a core outcome set and are incorporated into the juvenile arthritis disease activity score (JADAS) and clinical JADAS (cJADAS),4,5 two composite outcome measures of JIA. Although JADAS allows for a single measure of disease activity in individuals with JIA, the individual components of the score do not always correlate.6 This is particularly evident for components measured by the physician (active joint count or the physician's global assessment) versus those reported by the patient (such as parent or patient global evaluation). Approximately a quarter of children and young people (aged younger than 16 years) with clinically inactive disease (a disease state defined by clinician-only measured markers of disease activity) have ongoing symptoms,7 including disability, in

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Evidence before this study

Traditionally, outcomes in chronic disease research, such as those used in juvenile idiopathic arthritis (JIA), have focused on changes either in single disease measures or in composite outcomes over time. This does not allow an understanding of how individual measures change in relation to each other. Because most measures represent unique aspects of disease, one cannot assume that they change in parallel. Novel unsupervised machine learning methods offer the opportunity to find so-called latent clusters of outcomes over time, facilitating a greater understanding of disease progression than is possible with a traditional dichotomy of improved or not improved. We searched MEDLINE and Embase from April 1, 1974, to Jan 1, 2019, for studies published in English of JIA (MeSH “juvenile arthritis”) using the search strings (MeSH “machine learning” or “artificial intelligence” or key word “trajectory”). Published studies have identified clusters of children and young people that differ in single aspects of disease over time. We did not find studies that used longitudinal multivariate approaches to understand how core clinical outcomes in patients with JIA progress in relation to each other after diagnosis.

Added value of this study

Our work reports global longitudinal patterns of disease in children and young people with JIA, extending knowledge of the heterogeneity in disease course beyond the existing International League of Associations for Rheumatology paradigm. Additionally, studies have repeatedly shown that patient-reported outcomes do not correlate well with physician-reported outcomes. Our study shows that there are multiple clusters among children and young people with JIA who have different patterns in these outcomes over time, and that these patterns sometimes diverge. In doing so, we provide a foundation for reassessment of how JIA disease measures are used to capture disease course and clinical outcomes.

Methods

Study population

The study population was comprised of children and young people recruited for the Childhood Arthritis Prospective Study (CAPS), a UK multicentre inception cohort of...
patients with childhood-onset arthritis. CAPS began recruitment in 2001 and had recruited over 1700 participants by Jan 1, 2019. Ethical approval for the cohort was gained from the Northwest Multicentre Ethics Committee (REC/02/8/104, IRAS 184042); written informed consent was provided by the parents or guardians, and assent was provided from children and young people, where appropriate.

Children and young people with a physician’s diagnosis of JIA were selected for analysis if they were recruited before Jan 1, 2015, to allow for at least 3 years of follow-up. If no cJADAS score could be calculated at any point, they were excluded.

Data collection
Data were collected at initial presentation to paediatric rheumatology (baseline) and annually thereafter. Between 2001 and 2010, data were also collected 6 months after baseline. Data at each timepoint included demographics, disease features including International League of Associations for Rheumatology (ILAR) category, disease activity, and medication data; these were extracted from medical records by study nurses. For this analysis, ILAR categories were assigned using data recorded 1 year after baseline; if this was missing, the closest ILAR category recorded on either side of 1 year was used, with preference given for the baseline value. Additionally, participants were asked to complete the Childhood Health Assessment Questionnaire (CHAQ), which incorporates components of the physician’s global assessment of disease activity, and patient or parent global evaluation of wellbeing. Parents or guardians of participants younger than 11 years completed these questionnaires; the option to self-complete was available for young people aged 11 years or older.

An index of multiple deprivation ranking was assigned to all children and young people on the basis of their residence (postcode) at the time of study registration; these rankings were based on the English indices of deprivation, the Welsh index of multiple deprivation, and the Scottish index of multiple deprivation.20–24 Within each country (England, Scotland, and Wales), deprivation is ranked on the basis of a combination of seven (eight in Wales) domains of deprivation (income, employment, health, education, crime and community safety, housing, living environment, and access to services) and then split into quintiles. Each child and young person was mapped to the relevant quintile within their country on the basis of their rank, and then the quintiles for all three countries were combined into a single variable ( quintiles) for analysis.

Modelled disease outcomes
The outcome measures used for the primary analysis were the components of the cJADAS with an active joint count up to ten (cJADAS 10): active joint count, physician’s global assessment of disease activity, and patient or parent global evaluation of wellbeing. Components of cJADAS 10 were chosen in preference to JADAS because the cJADAS 10 does not require erythrocyte sedimentation rate, which is often not measured routinely in children with JIA in the UK.6,7 VAS scores were converted from mm to cm, in a range of 0–10 cm. As part of cJADAS 10, an active joint count up to ten was used. This score was used because of high correlation with cJADAS 27 and 71.5

| Participants (n=1184) | Data available, n (%) |
|----------------------|-----------------------|
| **Demographic features** | | |
| Gender               | 1184 (100%)           |
| Female               | 773 (65%)             |
| Male                 | 411 (35%)             |
| Race or ethnicity    | 1166 (98%)            |
| White                | 1044 (90%)            |
| Other race or ethnicity | 122 (10%)          |
| Age at initial presentation, years | 7.4 (3.4–11.7) | 1174 (99%) |
| Symptom duration to initial presentation, months | 4.5 (2.2–8.6) | 1156 (98%) |
| Socioeconomic status (IMD) | 1107 (93%) |
| 20% most deprived    | 295 (27%)             |
| Middle 60%           | 592 (53%)             |
| 20% least deprived   | 220 (20%)             |
| ILAR category        | 1177 (99%)*           |
| Systemic             | 71 (6%)               |
| Oligoarthritis       |                       |
| Persistent           | 528 (45%)             |
| Extended             | 66 (6%)               |
| RF-negative polyarticular | 265 (23%) |
| RF-positive polyarticular | 45 (4%)               |
| Enthesitis-related    | 69 (6%)               |
| Psoriatic            | 85 (7%)               |
| Undifferentiated     | 50 (4%)               |
| **cJADAS 10 components** | | |
| Active joint count   | 2 (1–5) | 1092 (92%) |
| Physician’s global assessment, cm | 2 (1.6–5.1) | 855 (72%) |
| Patient or parent global evaluation, cm | 2.3 (0.6–5.0) | 867 (73%) |
| Overall cJADAS 10 score | 9.0 (4.8–14.3) | 672 (57%) |
| **Other disease-related variables** | | |
| Limited joint count  | 1 (1–4) | 1092 (92%) |
| ESR                  | 21 (8–49)             | 831 (70%) |
| CHAQ                 | 0.8 (0.1–2.0) | 868 (73%) |
| Pain evaluation, cm  | 3.0 (0.9–5.8) | 869 (73%) |
| Uveitis (at presentation) | 36 (4%) | 858 (72%) |
| **Treatment** | | |
| Time to first definitive treatment, days† | 18 (2–56) | 1184 (100%) |
| **Psychosocial factors** | | |
| CHQ psychosocial score (subset n=468) | 50 (39–56) | |
| GHQ score (subset n=613) | 29 (22–38) | |

Data are n (%) or median (IQR), unless otherwise specified. CHAQ=Child Health Assessment Questionnaire. cJADAS 10=Clinical Juvenile Arthritis Disease Activity Score with an active joint count up to ten. ESR=erythrocyte sedimentation rate. GHQ-General Health Questionnaire. ILAR=International League of Associations for Rheumatology. IMD=index of multiple deprivation. RF=rheumatoid factor. *84% taken from 1-year follow-up. †Intra-articular steroids in oligoarthritis and methotrexate in other ILAR categories.

Table 1: Baseline characteristics
Clustering and subgroup discovery

We used two clustering approaches to explore latent classes in patients with JIA: a cross-sectional analysis at baseline and a longitudinal analysis from baseline to 3 years of follow-up. Longitudinal clustering was undertaken independently of baseline clustering, with no inheritance of classes between the two methods. Class assignment at baseline versus in trajectories over 3 years were then compared graphically by use of a chord diagram, which illustrates the mapping between the two resulting sets of classes or clusters.

Latent profile analysis (a form of generalised structural equation modelling that fits categorical latent variables based on continuous observed variables) identified subgroups of children and young people on the basis of shared cJADAS 10 components at baseline. Latent profile analysis was applied with STATA 15 package traj. Each individual was exclusively assigned to a cluster for which the highest posterior probability of group membership was obtained. Models used Poisson (for active joint count) and normal (for global scores) distributions. We selected the optimal number of groups (out of ten) on the basis of the Bayesian information criteria (BIC), selecting that which resulted in the lowest BIC.

Group-based trajectory models (specialised longitudinal finite mixture models within latent class growth analyses, with model-estimated parameters based on maximum likelihood estimation) were then used to group children and young people on the basis of shared trajectories of cJADAS 10 components during the 3 years after initial presentation to paediatric rheumatology. These models were constructed with STATA package traj. The model was specified with the three cJADAS 10 components as the dependant or outcome variables, using censored-normal distributions for both global assessments and zero-inflated Poisson distribution for active joint count. We tested linear, quadratic, and cubic polynomials for the trajectory shape, with one to ten trajectory groups tested within each polynomial form.

We selected an optimal model through a combination of statistical fit, clinical plausibility, and parsimony. Initially, models were excluded if they had a group representing less than 1% of the cohort, a mean posterior probability for any group membership lower than 70%, or relative entropy lower than 0.5. The top models for each polynomial form were then selected on the basis of BIC. In cases where similar model fit and adequacy were evident between competing models, we selected between similarly fit models by assessing “clinical characterisation and plausibility”, as recommended by Lennon and colleagues.

Characteristics of clusters

We examined characteristics of children and young people such as demographic, clinical, and psychosocial factors at initial presentation for clusters within the latent classes at baseline and the trajectory groups using descriptive and univariable statistics. Additionally, pain (10 cm VAS) and functional ability (CHAQ scores) were compared with component trajectories in the optimal model, as these variables have previously been found to explain variation in wellbeing scores in both individuals with JIA and those with rheumatoid arthritis. We assessed differences in categorical variables with χ² and Fisher’s exact test and continuous variables with Kruskal-Wallis statistics for longitudinal models.

Missing data

We undertook no imputation of missing data. As a maximum-likelihood-based technique, group-based trajectory modelling is somewhat robust to potential bias caused by missing data, as long as they are missing at random. This assumption of data missing at random was explored in additional analyses detailed in the appendix (pp 9–11). All analyses were done with Stata version 14, except for latent profile analyses, done with Stata version 15. Data visualisation was completed in R, version 3.6.1, using RStudio, version 1.2.5001.

Sensitivity to noise

We did a secondary analysis to evaluate the sensitivity of the longitudinal trajectory model to random noise added to the dataset. Random noise was taken from a zero-inflated Poisson distribution (λ=2, p₀=0.4) for active joint count and from a censored normal distribution with

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**Figure 1: Median cJADAS 10 components for each latent class at baseline**

| Class Description | Median Score (IQR) |
|-------------------|--------------------|
| All low           | 1 (0.5–2.5)        |
| All high          | 7.5 (5–10)         |
| High AJC          | 7.5 (5–10)         |
| High PGA          | 5 (3–7.5)          |
| High PGE          | 7.5 (5–10)         |

AJC=active joint count. cJADAS=clinical Juvenile Arthritis Disease Activity Score with an active joint count up to 10. PGA=physician’s global assessment. PGE=patient or parent global evaluation.
bounds at 0 and 10 by use of the STATA gentrun package for physician and parental global scores. Trajectories were evaluated after adding 1%, 2.5%, 5%, 10%, and 25% additional noise to the dataset.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or preparation of this manuscript. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results
Between Jan 1, 2001, and Dec 31, 2014, 1423 children and young people with JIA were recruited to CAPS. 238 participants without a record of cJADAS 10 were excluded, and one participant died during the study, therefore the final analysis included 1184 children and young people. Compared with those excluded, the study cohort was younger (by a median 1.7 years), had a higher proportion of white participants (1044 [90%] of 1166 vs 178 [79%] of 225), and a higher proportion of participants with rheumatoid factor-negative polyarthritis (265 [23%] of 1179 vs 27 [12%] of 222; appendix pp 1–2).

773 (65%) of 1184 participants were female and 411 (35%) were male, and 594 (50%) of 1179 with available ILAR category data had oligoarthritis (table 1). Median age at initial presentation was 7.4 years (IQR 3.4–11.7). Over the course of 3 years, 205 children and young people were discharged from paediatric rheumatology, with reasons including being “well” (80 [39%]), repeat non-attendance (26 [13%]), and transfer to adult service (59 [29%]; appendix p 1). Overall, cJADAS 10 data were available for 1140 (96%) of children and young people at baseline and for 912 (77%) at 6-month, 1116 (94%) at 1-year, 1030 (87%) at 2-year, and 949 (80%) at 3-year follow-ups.

The optimal model identified five distinct classes of children and young people at baseline (figure 1, average posterior probability for assigned group 0.78). The largest group (comprising 554 [47%] of 1184 participants) had lower values than those of other groups for all cJADAS 10 components (termed all-low group). A second group included 182 (15%) participants and had raised values in all three outcomes (termed all-high group). Three other groups were characterised by low to moderate disease activity, with higher values in a single cJADAS 10 component than in the other two components: high active joint count (189 [16%] participants), high physician global assessment (98 [8%]), and high patient or parent global evaluation (161 [14%]). Clinical and demographic characteristics of these groups are presented in the appendix (pp 2–4).
The optimal multivariate model classified six cubic trajectory groups (figure 2; appendix pp 5–7). In four groups, the three outcomes followed approximately similar trajectory patterns and values, defined according to their relative patterns of severity across the outcomes from baseline to 3-year follow-up: low-remission group (380 [32%] of 1184 participants), low-low group (242 [20%]), high-low group (191 [16%]), and high-low-high group (113 [10%]). In the two remaining groups (low-persistent group and high-persistent group), the different components followed divergent trajectories. Children and young people in these groups either had lower initial joint counts and physician global scores that improved over time (low-persistent group, 162 [14%] participants) or higher initial joint counts and physician global scores that improved over time (high-persistent group, 96 [8%] participants). In both these groups, however, participants had an initially higher patient or

| Group population (n=1184) | Low-remission | Low-low | High-low | High-low-high | Low-persistent | High-persistent | p value* |
|--------------------------|---------------|---------|----------|---------------|----------------|----------------|---------|
| Demographic features     |               |         |          |               |                |                |         |
| Gender                   |               |         |          |               |                |                |         |
| Female                   | 237 (62%)     | 164 (68%) | 129 (68%) | 81 (72%)      | 95 (59%)       | 67 (70%)       | 0·14    |
| Male                     | 143 (38%)     | 78 (32%) | 62 (32%) | 32 (28%)      | 67 (41%)       | 29 (30%)       |         |
| Race or ethnicity        |               |         |          |               |                |                |         |
| White                    | 339 (91%)     | 211 (89%) | 170 (90%) | 96 (88%)      | 140 (87%)      | 88 (93%)       | 0·63    |
| Other race or ethnicity  | 35 (9%)       | 27 (11%) | 19 (10%) | 13 (12%)      | 21 (13%)       | 7 (7%)         |         |
| Patients with available data | 374 (98%)  | 228 (98%) | 189 (99%) | 109 (96%)     | 161 (99%)      | 95 (99%)        |         |
| Age, years†             | 6·5 (2·9–11·0) | 6·8 (3·1–11·0) | 6·9 (3·4–11·0) | 8·5 (4·5–12·0) | 8·7 (7·7–13·0) | 11·0 (7·2–14·0) | <0·0001 |
| Disease duration, months | 4·2 (2·0–7·2) | 4·0 (2·1–8·9) | 3·8 (2·1–7·6) | 5·9 (1·0–13·0) | 5·2 (2·1–9·6) | 7·0 (3·5–15·0) | <0·0001 |
| Socioeconomic status     |               |         |          |               |                |                |         |
| 20% most deprived        | 81 (22%)      | 50 (22%) | 40 (24%) | 32 (30%)      | 62 (42%)       | 30 (34%)        |         |
| Middle 60%               | 200 (55%)     | 121 (52%) | 94 (55%) | 55 (52%)      | 71 (48%)       | 50 (57%)        |         |
| 20% least deprived       | 83 (23%)      | 60 (26%) | 36 (21%) | 19 (18%)      | 15 (10%)       | 7 (8%)          |         |
| Patients with available data | 364 (96%)  | 231 (95%) | 170 (89%) | 106 (94%)     | 148 (91%)      | 88 (92%)        |         |
| ILAR category            |               |         |          |               |                |                |         |
| Systemic                | 21 (6%)       | 10 (4%)  | 19 (10%) | 10 (9%)       | 7 (4%)         | 4 (4%)          | <0·0001 |
| Oligoarthritis          |               |         |          |               |                |                |         |
| Persistent               | 274 (72%)     | 145 (60%) | 22 (12%) | 14 (13%)      | 70 (44%)       | 3 (3%)          |         |
| Extended                 | 8 (2%)        | 18 (7%)  | 10 (5%)  | 11 (10%)      | 14 (9%)        | 5 (5%)          |         |
| RF-negative polyarthritis | 25 (7%)   | 32 (13%) | 99 (52%) | 46 (41%)      | 19 (12%)       | 44 (46%)        |         |
| RF-positive polyarthritis | 3 (1%)    | 5 (2%)   | 10 (5%)  | 8 (7%)        | 7 (4%)         | 10 (10%)        |         |
| Enthesitis-related       | 15 (4%)       | 9 (4%)   | 8 (4%)   | 7 (6%)        | 18 (11%)       | 12 (13%)        |         |
| Psoriatic                | 20 (5%)       | 16 (7%)  | 10 (5%)  | 11 (10%)      | 19 (12%)       | 9 (9%)          |         |
| Undifferentiated         | 12 (3%)       | 6 (2%)   | 13 (7%)  | 5 (4%)        | 5 (3%)         | 9 (9%)          |         |
| Patients with available data | 378 (99%)  | 241 (99%) | 191 (100%) | 112 (99%)     | 159 (98%)      | 96 (100%)       |         |
| Disease-related features |               |         |          |               |                |                |         |
| cJADAS 10                | 4·9 (3·0–8·2) | 6·2 (3·7–8·3) | 16·5 (13·1–19·8) | 17·0 (12·5–19·9) | 10·5 (7·7–12·7) | 17·3 (12·8–20·5) | <0·0001 |
| Active joint count       | 1 (1–2)       | 1 (1–2)  | 9 (6–14) | 5 (3–10)      | 1 (1–3)        | 9 (4–21)        | <0·0001 |
| Limited joint count      | 1 (0–2)       | 1 (1–2)  | 5 (2–10) | 4 (1–8)       | 1 (1–2)        | 6 (2–13)        | <0·0001 |
| Physician’s global assessment, cm | 2·0 (1·0–3·1) | 2·4 (1·2–3·8) | 5·2 (3·2–7·0) | 5·6 (3·7–7·0) | 2·8 (1·8–4·7) | 4·6 (2·8–6·4) | <0·0001 |
| Patient or parental global evaluation, cm | 1·2 (0·2–3·0) | 1·2 (0·3–2·6) | 3·4 (1·1–6·0) | 4·7 (1·8–6·5) | 5·1 (3·1–7·0) | 4·7 (2·2–6·5) | <0·0001 |
| CHAQ score               | 0·4 (0·0–0·9) | 0·4 (0·0–0·9) | 1·0 (0·5–1·8) | 1·3 (0·8–2·0) | 1·1 (0·5–1·6) | 1·3 (0·8–1·9) | <0·0001 |
| ESR, mm/h                | 14 (6–35)     | 19 (7–40) | 30 (14–60) | 32 (13–60) | 21 (8–41) | 25 (8–79) | <0·0001 |
| Pain, cm                 | 1·6 (0·2–4·6) | 2·0 (0·5–4·5) | 3·9 (1·0–6·0) | 5·0 (2·2–7·0) | 5·0 (3·5–6·6) | 5·1 (3·1–7·1) | <0·0001 |
| Specific joint activity (right or left) |         |         |          |               |                |                |         |
| Ankle                    | 57 (16%)      | 56 (25%) | 138 (76%) | 55 (54%)      | 37 (26%)       | 57 (66%)        | <0·0001 |
| Cervical spine           | 1 (<1%)       | 2 (1%)   | 15 (8%)  | 4 (4%)        | 0 (0%)         | 10 (12%)        | <0·0001 |
| Hip                      | 9 (3%)        | 3 (1%)   | 25 (14%) | 8 (8%)        | 3 (2%)         | 16 (19%)        | <0·0001 |
| Wrist                    | 30 (8%)       | 19 (8%)  | 109 (60%) | 38 (40%)      | 14 (10%)       | 43 (50%)        | <0·0001 |
| Patients with available data | 353 (93%)  | 227 (94%) | 181 (95%) | 101 (89%) | 140 (86%) | 86 (90%) | <0·0001 |

(Table 2 continues on next page)
Articles

The signs and symptoms of JIA are diverse and can change over the course of disease, due to treatment effects and evolution of the underlying condition. Our study identified six clusters of children and young people with JIA who had different patterns across three core outcome variables in the 3 years after initial presentation to paediatric rheumatology. In four of these groups, the three components of cJADAS followed similar patterns to each other. In the two other groups, slow improvements in active joint counts and physician’s global scores were coupled with persistent poor patient or parent wellbeing scores. When using information from baseline alone, five clusters of children and young people with JIA were identified; these overlapped to some degree, but not completely, with the

| Table 2: Demographic and clinical characteristics measured at initial presentation to paediatric rheumatology across multivariate trajectory groups |
|---------------------------------------------------------------|
| **Low-remission** | **Low-low** | **High-low** | **High-low-high** | **Low-persistent** | **High-persistent** | **p value** |
| Systemic features in systemic JIA (n=71) | 19 (90%, n=21) | 9 (90%, n=10) | 17 (89%, n=19) | 9 (90%, n=10) | 7 (100%, n=7) | 4 (100%, n=4) |
| Enthesitis in enthesitis-related JIA (n=56) | 3 (27%, n=11) | 2 (22%, n=9) | 3 (38%, n=8) | 1 (17%, n=6) | 4 (33%, n=12) | 5 (50%, n=10) |
| Psoriasis in psoriatic JIA (n=73) | 6 (32%, n=9) | 3 (21%, n=14) | 3 (30%, n=10) | 3 (30%, n=10) | 4 (33%, n=12) | 5 (63%, n=8) |
| Uveitis (n=854) | 16 (6%, n=256) | 6 (3%, n=181) | 4 (3%, n=138) | 2 (2%, n=87) | 5 (4%, n=116) | 3 (4%, n=76) |
| **Psychosocial features** | | | | | | |
| CHQ psychosocial score (n=468) | 51 (0 (43 8–56 8) | 52.5 (45 0–57 8) | 48.8 (37 3–54 0) | 42.3 (30 8–54 1) | 46.8 (32 7–54 6) | 45.4 (38 5–51 1) |
| GHQ score (n=613) | 28 (20–34) | 28 (22–36) | 30 (24–41) | 32 (24–41) | 31 (24–44) | 33 (22–44) |
| **Treatment within 3-year follow-up** | | | | | | |
| Time to first definitive treatment, days | 18 (7–49) | 25 (7–82) | 10 (0–35) | 14 (0–57) | 28 (7–103) | 6 (0–59) |
| Ever biological use between initial presentation and 3-year follow-up | 26 (7%) | 47 (19%) | 51 (27%) | 53 (47%) | 51 (31%) | 54 (56%) |

Data are n (%) or median (IQR). Percentages are out of available data for each variable (table 1). CHAQ=Childhood Health Assessment Questionnaire. CHQ=Child Health Questionnaire. cJADAS=clinical Juvenile Arthritis Disease Activity Score with a ten active joint count. ESR=erythrocyte sedimentation rate. GHQ=General Health Questionnaire. ILAR=International League of Associations for Rheumatology. JIA=juvenile idiopathic arthritis. RF=rheumatoid factor. *Kruskal-Wallis, χ², or Fisher’s exact test. †Age at initial presentation to paediatric rheumatology. ‡Intra-articular steroids in oligoarthritis, synthetic disease-modifying anti-rheumatic drugs in all other categories.
六轨迹基线分群通过随访确定。因此，疾病严重度在初次发作时是重要的，但不完全预测未来的疾病状态，这也将受到干预措施的影响。

疾病严重度分类标准对JIA有共识性，并且主要关注于关节计数和额外体征在早期疾病阶段。14–17 ILAR分类标准是未来缓解的最强预测因子。30,31 在这项研究中，我们没有尝试重新分类JIA；相反，通过数据驱动的方法，我们试图理解早期疾病的特征。我们在基线时报告了五个JIA集群，在随后的三年内报告了六个集群，基于医生和患者的疾病评估。虽然几个ILAR分类在某些疾病集群中具有极大的代表率（如所有低基线集群中64%的寡关节炎，以及低-缓解轨迹群中的47%），但是ILAR分类无法在每个时间点上完全识别JIA的结局。同样，基线时的集群无法识别三种JIA结局是否会分歧或保持平行。

纵向数据驱动的集群能够可靠地捕捉基线集群模式，同时捕捉到多个疾病测量的改变模式。这些纵向方法是为JIA提供分层管理计划的有希望的途径，因为它们提供了疾病活动和影响的更精细的图景。

我们的研究报告了六个独特的疾病结局集群。多名研究者在多中心、回顾性队列中对659名儿童和年轻人的JIA进行量化研究。18 该研究报道了高比例的孩子和年轻人低缓解（20%的参与者）或低低（45%）活动计数，这几乎与我们研究中66%的个体在每个时间点上具有最少活动关节数的集群相一致。在我们的研究中，这些低疾病和缓解集群被特征为较高比例的参与者的寡关节炎和较年轻年龄，而非其他组。然而，14%的群集存在长期持续性差的患者或家长全球幸福感评分，尽管平均来说至少在三个集群中的一个集群（58%的研究人口）的活动计数为零，这表明在每种情况下JIA不一定达到完全缓解。

注：无症状、迅速下降的症状或持续较高的症状。

我们的研究中没有一个分群达到了平均幸福感为0 cm的水平，尽管平均来说至少在三个分组中的一个分组（58%的群体）的活动计数为零，这表明在每种情况下JIA不一定达到完全缓解。
even within these low-activity groups, at least some children and young people did not rate their wellbeing score as zero.

To our knowledge, this was the first study to examine how the cJADAS 10 components track in relation to each other over time. The modelling of multiple measures of disease allowed for the identification of groups in which these scores diverged over time, which might have been less obvious if only the composite score had been used. Groups that had persistent poor wellbeing scores, despite improving joint counts and physician global scores, were difficult to distinguish from groups in which outcomes progressed in parallel to their initial presentation to paediatric rheumatology. Disease features at initial presentation were similar between groups that had low numbers of active joint counts at baseline and those that had high numbers of active joints, regardless of wellbeing trajectories. The greater representation of participants with enthesitis-related JIA in both persistent groups was a distinguishing disease feature (11% and 13% in persistent groups vs 4–6% in the other groups). Extra-articular features, such as enthesitis, are not captured in active joint counts, and these children and young people might have high related levels of inflammatory pain. Additionally, there might be substantial overlap between painful non-inflammatory conditions, such as fibromyalgia, and enthesitis, which might not be used to inform the physician global assessment. Although similar clinically to participants in groups with improving wellbeing scores, those with persistently poor wellbeing scores tended to be older, have longer disease duration, live in more deprived areas, and have poorer health-related quality of life scores, with wellbeing scores at initial presentation higher in the low-persistent group (5·1 cm) than in the low-remission (1·2 cm) or low-low (1·1 cm) groups. High wellbeing scores at initial presentation coupled with low active joint counts might, therefore, indicate an individual already beginning on this divergent trajectory or with pre-existing health concerns. Using a different subset of patient-prioritised outcomes, Guzman and colleagues also reported a group where joint activity decreased despite persistent pain and impact on quality of life, including several study-defined impact measures. In the Canadian cohort, fewer children and young people were allocated to this disease course (10%) and they had relatively early control of joint activity, compared with the slow improvements observed in our study. Both of these groups of children and young people illustrate the heterogeneity in the signs and symptoms of JIA both over time and in relation to each other. This heterogeneity highlights the future applicability of unsupervised machine learning to inform stratified management approaches in children and young people with JIA, where groups with great unmet needs, such as those with persistent symptoms despite resolution of inflammatory joint activity, can be identified. A single composite score, such as cJADAS 10 score, might be an useful indicator of non-remission, but might not be able to, on its own, explain why a child or young person has not reached remission.

Our study benefitted from being set within one of the largest inception cohorts of children and young people with JIA globally. CAPS collects a wide range of information from both medical records and patient-completed questionnaires over time. This allowed for a detailed, longitudinal analysis of the cJADAS 10 components and the additional exploration of multiple factors, measured at initial presentation to paediatric rheumatology, that characterised group membership, such as demographic, clinical, and psychosocial characteristics. The inception nature of the cohort, together with models that could incorporate missing data, allowed for the inclusion of most of the cohort, minimising selection bias through both left-censorship and drop-out. Additionally, informative drop-out in CAPS allowed for the exploration of bias through data potentially missing not-at-random.

Our study assessed trajectories of disease from the point of initial presentation to paediatric rheumatology. All children and young people were treated within the same health-care system, but individual responses to treatment were not modelled. Some therapies might have been prescribed before initial presentation to paediatric rheumatology. Therefore, these trajectories do not necessarily reflect patterns from disease onset and are useful to understand progression from the point of first contact with paediatric rheumatology. The trajectories presented are means based on an approximately annual follow-up within the first 3 years after initial presentation to paediatric rheumatology. The JIA disease course might have increased variability over time with more frequent capture of disease measures. Additionally, modelling a higher active joint, such as in cJADAS 71, rather than cJADAS 10 would not be expected to produce additional trajectory groups but might have raised the initial mean joint counts for high-low, high-low-high, and high-persistent groups. Finally, the follow-up was limited to 3 years in this study, on the basis of the observation of greatest changes in disease over the first year after diagnosis, to limit bias from patients transferred to adult clinics and to maximise sample size. However, Berard highlighted the potential for disease worsening after 5–10 years of stable disease. Therefore, additional modelling would be valuable into adulthood, with effort needed in the research community to plan for the retention of individuals who have transferred to adult clinics.

Using the components of cJADAS, six distinct trajectories were observed for children and young people with JIA in the 3 years after initial presentation to paediatric rheumatology, with low disease activity and remission being common but not universal. Disease trajectories were not predicted entirely by ILAR category or disease manifestations at diagnosis. Importantly, in a fifth of children and young people, a divergence was observed between improving joint counts but persistently high scores for wellbeing, whose pain and function scores
mirrored those of wellbeing over time. Understanding the biological and sociological mechanisms underpinning groups of children and young people within different clusters has the potential to improve disease management plans for a more personalised approach to treatment for individuals with JIA.

Contributors
SJWS-W did the analyses. SJWS-W, KLH, LRW, WT, and NG all contributed to the design of the study, interpretation of the results, and drafting and revision of the manuscript. KLH, LRW, and WT were involved in data acquisition. All authors read and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data sharing
Information regarding applying for access to CAPS data can be found online.

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