# Psoriasis and Temporomandibular Joint Involvement in Juvenile Idiopathic Arthritis (JIA)

A Longitudinal Study of the Nordic JIA Cohort

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Licentiate thesis to be presented at Rudbeckssalen, Rudbecklaboratoriet, Dag Hammarskjölds väg 20, Uppsala, Wednesday, 30 September 2020 at 13:15. The examination will be conducted in Swedish.

**Abstract**

Ekelund, M. 2020: Psoriasis and Temporomandibular Joint Involvement in Juvenile Idiopathic Arthritis (JIA): A Longitudinal Study of the Nordic JIA Cohort. Department of Women's and Children's Health. 42 pp. Uppsala. ISBN 978-91-506-2839-5

Juvenile idiopathic arthritis, JIA, is used as an umbrella term covering a heterogeneous group of chronic arthritis forms in children, many of which have important differences compared to adult arthritis, while others possibly represent similar diseases among children and adults. Classification aims to give a better understanding of the pathogenesis, patterns, disease trajectories and treatment responses. For the juvenile psoriatic arthritis, JPsA, the classification criteria are currently being debated. The distribution of affected joints in JIA differs greatly and it is unknown why some joints appear to be more affected than others. The temporomandibular joint (TMJ) can be affected early in the course of the disease and often the symptoms are mild and without obvious swelling.

This thesis has its origin in the Nordic Study Group of Paediatric Rheumatology and the population-based prospective study of 510 children with newly diagnosed JIA included between 1997 and 1999. Totally 440 children were included in the eight-year follow-up, and in the TMJ study 265 patients were examined and underwent cone-beam computed tomography, CBCT, 17 years after onset.

After eight years a considerable proportion of the children with definite psoriasis were classified as undifferentiated JIA based on the exclusion criteria in the ILAR classification. Our data also presents the heterogenicity of JPsA and the development over time of clinical variables supporting a psoriatic diathesis, as well as the overlap between JPsA and enthesitis-related arthritis in a group of patients. We found that extensive symptoms and dysfunctions of the TMJ are seen in JIA 17 years after disease onset, even in patients registered with inactive disease or remission. Individuals with substantial condylar damage on CBCT were found in all JIA categories. The deeper understanding of a chronic disease over time is crucial for research initiatives to improve care as well as for clinical decisions and planning of the health care.

Our findings suggest a need for a more appropriate classification of JPsA and also that aspects of TMJ involvement should be included in the general health assessment in JIA.

*Keywords*: arthritis, juvenile idiopathic arthritis, juvenile psoriatic arthritis, temporomandibular arthritis, classification.

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Cover photo: Simon Djärf: ”Jag är en människa, inte bara min sjukdom”.

*”Det viktiga är att inte*
*sluta ställa frågor.*

*Nyfikenheten har sina egna*
*skäl att existera.”*

*Albert Einstein*

# List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Ekelund, M., Aalto, K., Fasth, A., Herlin, T., Nielsen, S., Nordal, E., Peltoniemi, S., Rygg, M., Zak, M., Berntson, L.; Nordic Study Group of Paediatric Rheumatology (NoSPeR). Psoriasis and associated variables in classification and outcome of juvenile idiopathic arthritis - an eight-year follow-up study.
*Pediatr Rheumatol Online J,* 2017 Feb 22;15(1):13.

II Glerup, M., Stoustrup, P., Matzen, L.H., Rypdal, V., Nordal, E., Frid, P., Arnstad, E.D., Rygg, M., Thorarensen, O., Ekelund, M., Berntson, L., Fasth, A., Nilsson, H., Peltoniemi, S., Aalto, K., Arte, S., Toftedal, P., Nielsen S., Kreiborg S., Herlin T., Pedersen, T.K. Long-term Outcomes of Temporomandibular Joints in Juvenile Idiopathic Arthritis: 17 Years of Followup of a Nordic Juvenile Idiopathic Arthritis Cohort.
*J Rheumatol*. 2020 May 1;47(5):730-738.

# Contents

# Abbreviations

| | |
|---|---|
| CASPAR | Classification criteria for psoriatic arthritis |
| CBCT | Cone-beam computed tomography |
| CHAQ | Childhood Health Assessment Questionnaire |
| CT | Computed tomography |
| DIP | Distal interphalangeal joint |
| ERA | Enthesitis-related arthritis |
| HAQ | Health Assessment Questionnaire |
| ILAR | International League of Associations for Rheuma |
| JADAS | Juvenile arthritis disease activity score |
| JIA | Juvenile idiopathic arthritis |
| JPsA | Juvenile psoriatic arthritis |
| MIO | Maximal incisal opening |
| PsA | Psoriatic arthritis |
| RA | Rheumatoid arthritis |
| RF | Rheumatoid factor |
| TMJ | Temporomandibular joint |
| VAS | Visual analogue scale |

# Introduction

Juvenile idiopathic arthritis, JIA, is the most common chronic inflammatory joint disease in childhood. The clinical manifestations vary from a mild, self-limiting disease to more severe forms affecting most of the joints, with a major impact on daily life. JIA is used as an umbrella term covering a heterogeneous group of diseases, many of which have important differences compared to adult arthritis, while others possibly represent similar diseases among children and adults. JIA, except for the systemic category, is considered an autoimmune disease, potentially resulting from an abnormal immunological response caused or triggered by environmental factors such as an infection in a genetically predisposed child. The distribution of affected joints differs greatly and it is unknown why some joints appear to be more affected than others.

Scientific breakthroughs in our understanding of how a person's unique molecular and genetic profile makes them susceptible to certain diseases will in the future enable researchers and physicians to tailor the medical treatment to the individual characteristics of each patient, thereby providing personalised medicine. In order to achieve that, we need better understanding of complex chronic diseases like JIA. Possibly, the new knowledge will also lead to a new and better definition and classification of JIA. Long-term follow-up studies based on population-based cohorts are important for this purpose.

## 1. Epidemiology

Several definitions of epidemiology have been suggested. According to the World Health Organization, WHO, epidemiology is the study and analysis of the distribution (who, when, and where), patterns and determinants of health and disease conditions in a defined population. Among other things, this can serve as a basis for health care planning.

In paediatric rheumatology, epidemiological studies describe the incidence, prevalence, natural history and outcome for different disease entities, and they enable the identification of possible etiologic and prognostic factors. A population-based study gives the best possibilities for true figures of incidence but is often time-consuming and costly. In order to obtain reliable numbers it is crucial how the cases are identified and what population is studied. A hospital-based study will recruit more severe cases than an outpatient-based study. Using different classification criteria will also give different figures. Incidence figures for chronic arthritis in European studies vary substantially, (1.3-22.1/100 000) [1]. The large variation can partly be explained by factors such

as different methods for recruiting participants, the genetic background of inflammatory diseases and different infectious panoramas.

## 2. Classification

JIA is a diagnosis of exclusion that encompasses all forms of chronic arthritis of unknown origin, starting before 16 years of age. To describe the manifestations of JIA and to facilitate comparisons of different populations, classification criteria were set up. The classification also aims to give us a better understanding of the pathogenesis, patterns, disease trajectories and treatment responses.

Sets of classification criteria were suggested both in the USA (the ACR-American College of Rheumatology- criteria) and in Europe (the EULAR-The European League Against Rheumatism- criteria) in 1977. Unfortunately, they were not aligned in definitions for inclusion and subgroups, which made studies hard to compare internationally. The current ILAR (International League of Associations for Rheumatology) classification from 1995 was the first attempt to reach international consensus. The criteria were revised in 1997 and are known as the Durban criteria (table 1) [2]. The classification consists of six different, mutually exclusive forms called categories defined in clinical and laboratory measures: systemic arthritis, oligoarthritis (persistent or extended), polyarthritis rheumatoid factor (RF)-positive, polyarthritis RF-negative, enthesitis-related arthritis (ERA), psoriatic arthritis (PsA), and a seventh category, undifferentiated arthritis, which includes those patients who do not fit any criteria or fit more than one. The criteria were originally created to obtain homogenous groups of patients for research purposes but in the absence of diagnostic and clinical criteria they have been used also for clinical purposes.

The onset type of arthritis refers to the number of joints affected in the first six months of disease. The most common subgroup of juvenile arthritis is oligoarticular arthritis. 'Oligo' is Greek and means 'small'. In the oligoarticular group the knee and the ankle are most often affected [3]. In the polyarticular subgroup, arthritis of the finger joints is seen. Dactylitis has a strong association to juvenile psoriatic arthritis, JPsA, where the small joints of the fingers and toes are often affected. The classification of JIA is a continuous work in progress as new knowledge is accumulated regarding aetiology and pathogenesis. The new knowledge has resulted in attempts to reach consensus in identifying more homogeneous clinical groups and to distinguish those forms of chronic arthritis typically seen only in children from the childhood counterpart of adult diseases [4].

The focus of this thesis is the subgroup JPsA and the clinical manifestations of arthritis of the temporomandibular joint, TMJ. The current view on these is presented briefly below.

**Table 1** *The ILAR criteria, definitions and exclusions 1997*

**Systemic arthritis**
*Definition:* Arthritis with or preceded by daily fever of at least two weeks' duration, that is documented to be quotidian for at least three days and accompanied by one or more of the following:
a) Evanescent, non-fixed erythematous rash
b) Generalised lymph node enlargement
c) Hepatomegaly or splenomegaly
d) Serositis
*Exclusions. Exclusions have not been listed.*

**Oligoarthritis**
*Definition:* Arthritis affecting 1-4 joints during the first six months of the disease. Two subcategories are recognised:
a) Persistent oligoarthritis: affects no more than four joints during the disease course
b) Extended oligoarthritis: affects a cumulative total of five joints or more after the first six months of the disease
Polyarthritis (RF-negative)
*Exclusions:*
a) Family history of psoriasis confirmed by a dermatologist in at least one first- or second-degree relative
b) Family history consistent with medically-confirmed, HLA-B27-associated disease in at least one first- or second-degree relative
c) Positive RF-test
d) HLA-B27-positive male with onset of arthritis after eight years of age
e) Presence of systemic arthritis as defined above

**Polyarthritis (RF-negative)**
*Definition:* Arthritis affecting five or more joints during the first six months of the disease, associated with negative RF tests on two occasions at least three months apart.
*Exclusions.*
a) Presence of RF
b) Presence of systemic arthritis as defined above

**Polyarthritis (RF-positive)**
*Definition:* Arthritis affecting five or more joints during the first six months of the disease, associated with positive RF tests on two occasions at least three months apart.
*Exclusions.*
a) Absence of positive tests for RF on two occasions at least three months apart.
b) Presence of systemic arthritis as defined above

**Psoriatic Arthritis**
*Definition.*
1. Arthritis and psoriasis or
2. Arthritis and at least two of:
a) Dactylitis
b) Nail pitting or onycholysis
c) Family history of psoriasis confirmed by a dermatologist in at least one first-degree relative
*Exclusions*
d) Presence of a rheumatoid factor
e) Presence of systemic arthritis as defined above

**Enthesitis-related arthritis**
*Definition.* Arthritis and enthesitis, or arthritis or enthesitis with at least two of:
a) Sacroiliac joint tenderness and/or inflammatory spinal pain
b) Presence of HLA-B27
c) Family history in at least one first- or second-degree relative of a medically-confirmed HLA-B27-associated disease
d) Anterior uveitis that is usually associated with pain, redness or photophobia
e) Onset of arthritis in a boy after the age of eight years
*Exclusions.*
1. Psoriasis confirmed by a dermatologist in at least one first- or second-degree relative
2. Presence of systemic arthritis as defined above

**Other arthritis**
*Definition.* Children with arthritis of unknown origin that persists for at least six weeks but that either
1. Does not fulfil the criteria for any other categories, or
2. Fulfils criteria for more than one of the other categories.
*Exclusions.* Patients who meet the criteria for other categories

## 3. Psoriatic arthritis in children

Of all children with JIA, only around 5% are classified as JPsA in population-based studies [5]. The ILAR criteria for diagnosis JPsA include 1) arthritis and psoriasis 2) arthritis and at least two of the following: dactylitis, nail pitting/onycholysis, or psoriasis in a first-degree relative, in the absence of specified exclusions. The classification of JIA has been regularly criticized, and this is especially true for JPsA [6, 7]. A biphasic age of onset distribution has been noted. Early-onset disease is characterised by female predominance, small joint involvement, dactylitis, and positive antinuclear antibodies. Late-onset JPsA resembles adult-onset psoriatic arthritis (PsA), with male predominance, psoriasis, enthesitis, and axial disease [8]. There are some inconsistencies within the classification itself, particularly with reference to the presence of psoriasis or a family history of psoriasis. A family history of psoriasis in a first or second-degree relative is reason to exclude a patient from the oligoarthritis and ERA categories, but not from polyarthritis RF-positive or negative categories or from the systemic arthritis category. The Vancouver criteria (Table 2) were proposed by Southwood et al. in 1989 [9]. They allowed a definition of JPsA to be made in the absence of a psoriatic rash and made it possible to distinguish probable from definite JPsA. In the proposal of a new classification Martini et al. suggest that the presence of psoriasis is not a reliable criterion for classification, and patients with JIA will end up in any of the other categories [4].

Adult psoriatic arthritis (PsA) is considered a unique disease entity, clearly separated from rheumatoid arthritis. CASPAR (classification criteria for psoriatic arthritis) criteria are used as diagnostic criteria in PsA. (Table 3) [10].

**Table 2** *Classification criteria for psoriatic arthritis in children, Vancouver, 1989 (Southwood)*

| **Definite JPsA** |
|---|
| Arthritis beginning before age of 16 years *and either*<br>Typical psoriasis *or*<br>At least three of four minor criteria as follows:<br>1. Dactylitis<br>2. Nail pitting<br>3. Psoriasis-like rash<br>4. Family history of psoriasis (first – or second-degree relative) |
| **Probable JPsA** |
| Arthritis beginning before the age of 16 years *And* Any two of the minor criteria described above |

**Table 3** *The Classification Criteria for Psoriatic Arthritis (CASPAR) 2006*

| **Established inflammatory articular disease with at least three points from the following features:** |
|---|
| Current psoriasis (assigned a score of 2) |
| A history of psoriasis (in the absence of current psoriasis; assigned a score of 1) |
| A family history of psoriasis (in the absence of current psoriasis and history of psoriasis; assigned a score of 1) |
| Dactylitis (assigned a score of 1) |
| Juxta-articular new-bone formation (assigned a score of 1) |
| RF negativity (assigned a score of 1) |
| Nail dystrophy (assigned a score of 1) |

*3a. Clinical features of JPsA*

*I. Articular features*

Joint pattern can be diverse. In the youngest there is often an oligoarticular onset and a polyarticular asymmetrical course. Engagement of the distal interphalangeal (DIP) joints is sometimes seen and is then highly specific for JPsA [11]. Features of spondylarthritis, for example sacroiliitis, sometimes develop over time [12].

*II. Dactylitis*

A key clinical feature recognised to favour the diagnosis of JPsA is dactylitis, defined as a sausage-like or fusiform swelling of a finger or a toe that extends beyond the joint margin to encompass the entire digit [8]. Around 20-40% of patients with JPsA have dactylitis, and there is an even greater proportion in children who present before the age of six years [8, 9]. Studies support that autoinflammation (innate immunity response) can have a pathogenetic role in linking psoriasis and arthritis as well as nail involvement [13].

*III. Extra-articular manifestations*

It is known that the relationship between the onset of joint and skin manifestations varies. In up to 50% the arthritis precedes the psoriasis, sometimes with a long interval between the onset of arthritis and the onset of a typical psoriatic rash [9]. By far the most common extra-articular manifestations are vulgaris lesions in the skin, on extensor surfaces of the knees and elbow joints, scalp and face. Guttate and pustular psoriasis is uncommon in JPsA. Nail pitting is seen in 75% of children with JPsA and often precedes skin manifestations. Multiple pits in a single nail of the finger or toe that is affected by dactylitis or an inflamed DIP joint are highly characteristic of JPsA [14, 15].

*3b. Psoriasis in children*

Psoriasis is a common inflammatory disease with a broad clinical spectrum, but it is uncommon in children. Onset may occur at any age but in 30% the disease starts before 20 years of age [16]. Health insurance data shows a total rate of psoriasis in children younger than 18 years of 0.71%, while in adults the prevalence is 2-3% [17]. A complex interplay of environmental and genetic factors seems to contribute to the risk for psoriasis. A family history of psoriasis is a common risk factor; approximately 30 percent of children with psoriasis reported an immediate family member with psoriasis [18]. Plaque lesions are most frequent but lesions on the face and genitals are also common in children [19]. In adult psoriasis, particularly in severe disease, there is evidence for increased cardiovascular and metabolic comorbidity [20]. Studies of the paediatric population also suggest an increased risk for metabolic dysfunction and impact on quality of life [21, 22].

## 4. Arthritis of the temporomandibular joint

Arthritis of the TMJ, initially often clinically silent with mild symptoms, is a well-recognised entity in JIA, with a prevalence of 40-86 % in different studies. All categories of JIA are at risk of developing TMJ arthritis [23]. There are reported cases of monoarthritis of the TMJ as the only JIA manifestation [24, 25]. The assessment of TMJ arthritis requires multidisciplinary cooperation according to the recommendations of the Temporomandibular Joint Juvenile Arthritis Work (TMJaw) Group [26].

*4a. Anatomy*

The TMJ is a complex joint described as ginglymoarthrodial, meaning that it has both a hinged and sliding motion. There are four articulating surfaces; the glenoid fossa of the temporal bone, the upper and lower surfaces of the articular disc, and the mandibular condyle. The disc divides the joint into the superior and inferior compartments [27].

*4b. Symptoms and complications*

Early during TMJ arthritis, symptoms are often vague and difficult to assess by clinical investigation due to the absence of swelling of the joint. Later on, symptoms such as pain, stiffness and chewing limitations may impair function. Inflammation of the TMJ may impact the condylar growth, and retrognathia and micrognathia may follow. Unilateral TMJ involvement may cause facial asymmetry.

*4c. Imaging of TMJ*

The TMJ is a particularly challenging joint to assess, both clinically and with imaging studies. Optimal evaluation and management of the TMJ remains a matter of ongoing discussion [28]. During the inflammatory process different

abnormalities can be visualised. A variety of modalities can be used to image the TMJ, and the access to different modalities varies between hospitals. As with all joints, plain radiography and computed tomography only detect arthritic sequelae such as flattening of the mandibular head. Computed tomography (CT) provides greater anatomic detail as compared to plain radiography. Cone-beam CT (CBCT) has advantages in providing greater focus on the TMJ, thereby minimising radiation of the surrounding brain and face, and is a well-established method of detecting TMJ deformities [29]. Magnetic Resonance Imaging (MRI) has been shown to be the only method that can diagnose TMJ arthritis early, before structural changes have developed [30] but has the disadvantages of requiring sedation of the youngest children. Ultrasound (US) has advantages with respect to cost and lack of requirement for sedation, but it is unclear as to whether it can identify active inflammation and arthritic sequelae as accurately as MRI with contrast. A review of the literature concluded that US has low sensitivity for detecting joint effusion and may be more valuable for monitoring established TMJ arthritis than for its initial detection [31].

# The Nordic JIA study

This project has its origin in the Nordic Study Group of Paediatric Rheumatology (NoSPeR). In 1997 a group of paediatric rheumatologists and paediatricians with experience in paediatric rheumatology, in Denmark, Finland, Norway and Sweden started to prospectively collect data from children with newly diagnosed JIA. The study design aimed to be population-based. Originally 510 children in the Nordic countries (Denmark, Finland, Norway and Sweden) were included during the three-year collection period. The first published results concerned the incidence of arthritis in children, as well as the nature of the disease. The incidence of JIA in the Nordic countries was found to be similar to that in other Western countries. Approximately 66% of the children in the study were girls, the median age at onset of the disease was six years and about half of the patients had a diagnosis of oligoarthritis at the six-month-visit [32].

In total, 440 children (88%) were re-examined after at least seven years, at a median of 98 months. Clinical data and disease activity were recorded during these monitoring visits according to a specific protocol. Uveitis had developed in 20% of the children [33]. Approximately 50 % had ongoing medication after eight years of the disease onset. On the other hand, 50 % of the participants were in remission without medication, according to the criteria of Wallace [34]: no active arthritis; no fever, rash, serositis, splenomegaly, or generalised lymphadenopathy attributable to JIA; no active uveitis; normal erythrocyte sedimentation rate or C-reactive protein; and a physician's global assessment of disease activity rated at the best score possible for the instrument used, during 12 months. The majority of those in remission belonged to the persistent oligoarthritis category or belonged to the systemic JIA category who had not developed a polyarticular disease [35].

The aim of the18-year follow-up was to examine further the long-term course, remission rate, burden of medication and damage in patients with JIA who fell ill in the very early biologic therapy era. Aspects of pain, sleep, TMJ arthritis and biomarkers were investigated. A total of 434 of the 510 original participants were followed up and almost half of them had active disease [36]. None of the lectin pathway proteins could anticipate the future disease course in terms of remission [37].

The NoSPeR study has so far produced material for three dissertations and a number of publications in international journals of rheumatology. Two more dissertations are planned, one in the autumn of 2020 and one in the spring of

2021. The research group has expanded over the years and offers an active and learning environment for both experienced and young researchers in the field of paediatric rheumatology.

# Aims of the present study

The overarching aims of this study were to contribute to a deeper understanding of the course of JPsA in the first eight years of disease, for improvement of classification and to explore the development of arthritis in the TMJ during the first 17 years of disease in order to improve methods for early detection of damage.

More specifically, we wanted to answer the following questions concerning JPsA:

1. What are the characteristics of patients with JPsA during the first eight years of disease compared to other JIA categories regarding oint pattern, frequency of clinical features like dactylitis, nail pitting, signs of sacroiliitis and heredity?

2. Is the outcome of JPsA after eight years of disease worse compared to the rest of the cohort of patients with JIA? If it differs, is it possible to speculate about why?

3. How many patients with psoriasis could not be classified as JPsA according to the ILAR criteria after eight years of disease and why?

For arthritis of TMJ the specific aims were:

1. To estimate the prevalence of orofacial symptoms in JIA compared to age-matched healthy controls.

2. To estimate the prevalence of TMJ deformities assessed by CBCT.

3. To suggest predictors for developing radiological TMJ deformities.

# Methods

**1. Study population**

In this prospective, multicentre cohort study, consecutive cases of newly diagnosed JIA from defined geographic areas of Denmark, Finland, Norway, and Sweden were included (Fig 1). The inclusion period was from January 1, 1997 to June 30, 2000. The incidence of JIA in the study area in 1997–1998 was 15 per 100,000 children/year [32].

During the study period, paediatric rheumatologists from 12 participating centres registered all children with JIA diagnosed according to the ILAR criteria. In the Nordic countries, visits to primary care physicians and public hospitals are mostly free of charge for children under 16 years of age, and the healthcare systems include regular visits to a child health centre for preschool children. With the aim of making the study as close to population-based as possible, letters were repeatedly sent to the primary health care and all orthopaedic, paediatric, and rheumatology specialists in the catchment areas during the inclusion period, requesting the referral of potentially eligible patients. Family histories, extensive clinical data including complete joint counts, medications used, patient/parent-completed health assessment measures, and results of blood tests were registered per protocol in a database at all study visits. The base line visit took place six months (-1 /+2 months) after disease onset, which was defined as the date of the first symptoms of arthritis described by the patient/parents/doctor. The date of diagnosis was the date the paediatric rheumatologist diagnosed JIA.

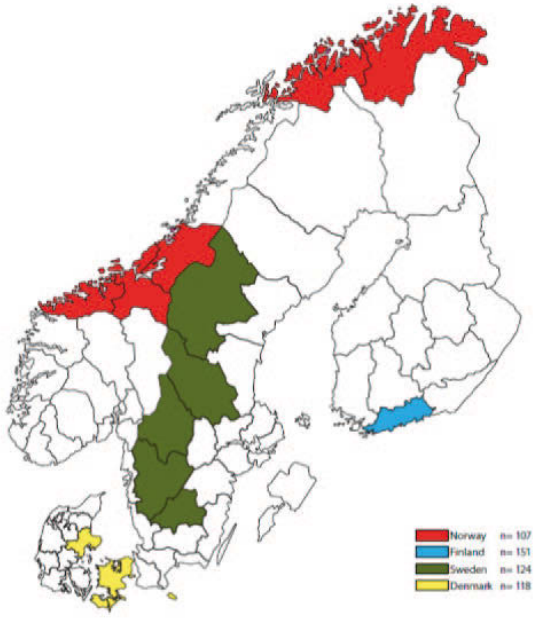


**Figure 1**. *Map of the Nordic countries and the catchment areas*

For the eight-year visit, participants received a letter of invitation followed by a reminder letter; persons who did not respond were contacted by telephone and asked to participate in a visit. In the minority of cases in which a study visit was not possible, the patients were asked to participate in a telephone interview. The standardised telephone interview contained all the information that otherwise, per protocol, was collected during the visits, and these patients were asked to fill in and return relevant questionnaires. Extended information was collected, including an update on family history. In total, 440 participants were followed up for at least seven years, with a median of 98 months (figure 2). The study participants lost to follow-up did not differ from the 440 with follow-up data regarding the number of active joints during the first six months after onset, Childhood Health Questionnaire (CHAQ), Juvenile Arthritis Disease Activity Score (JADAS 27) or proportion with oligoarticular disease at baseline. The occurrence of psoriasis, psoriatic-like rash, dactylitis, enthesitis, first-degree heredity for psoriasis or psoriatic arthritis did not differ between the participants lost to follow-up compared to the study cohort.

For the 17-year follow-up, all 510 previously included participants from the Nordic JIA cohort were invited to participate regardless of medical exposure, disease course, or activity. Participants who were unable to attend a study visit were offered a standardised telephone interview that included electronic completion of the validated Health Assessment Questionnaire (HAQ) and visual analogue scales (VAS). Blood samples were collected from all participants

who took part in the clinical study visit. The study visit also included an updated family and medication history. Clinical data were collected, including joint examination findings and blood samples. To verify the participant-reported data (e.g., in the use of determination of remission status and disease status for the previous 10 years), a cross-check of the electronic records was performed. All participants fulfilling the ILAR criteria for JIA and who had made at least two study visits were eligible for inclusion in the study. For those centres that could offer an examination of the TMJ, by CBCT the study participants also underwent a standardised clinical orofacial examination (Fig 2). For the TMJ study a group of non-selected Danish age-matched individuals (n=200) between 18 and 30 were used for comparison. The control group were young healthy volunteers without a history of arthritis, osteoarthritis, cleft lip/palate or other craniofacial anomalies or ongoing orthodontic treatment. They underwent the same orofacial examination and reported their symptoms in the same web-based questionnaire as the JIA group. For ethical reasons, no CBCT was performed on healthy controls.

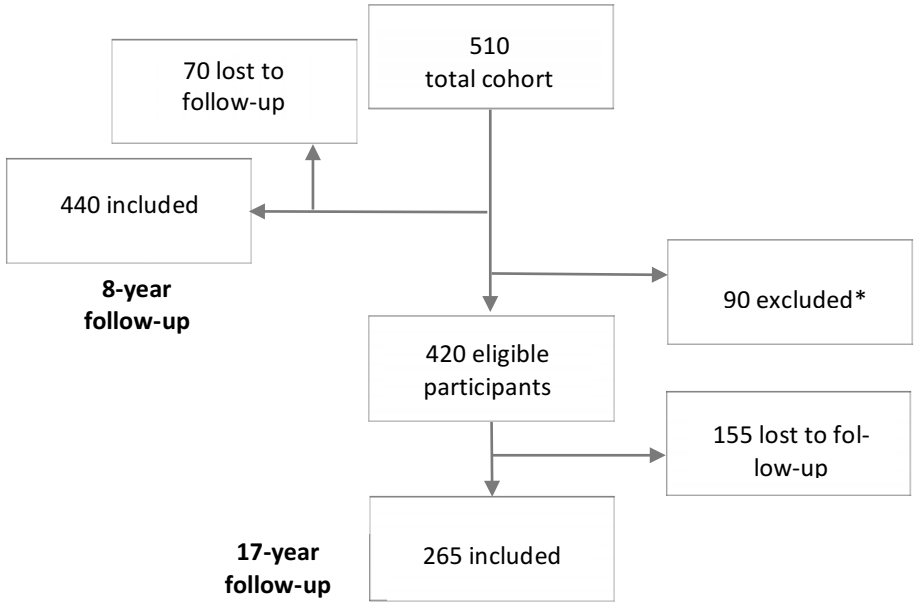


**Figure 2**. *Flow chart of the 8-year study of JPsA and the 17-year follow-up study on TMJ arthritis*

* 6 of the 7 Swedish centres were excluded because they had no access to CBCT.

## 2. Statistical analysis

Paper I: Statistical analyses were performed using the Statistical Package for Social Sciences, version 23 (SPSS Inc., Chicago, IL, USA). Demographics and disease characteristics were described using median and interquartile range (IQR), or total number and percent of study cohort. Statistical analyses of differences between children with and without psoriasis/psoriasis-like rash during the first year of disease were performed using the chi-square test (Fisher's exact test, two-sided) for comparison of dichotomous variables. The Mann-Whitney U-test was used for comparison of non-parametric data and independent samples were used for comparison of median values between the two groups. Binary logistic regression analyses were performed in order to identify the association between the occurrence of psoriasis or psoriasis-like rash and failure of remission eight years after disease onset. The dichotomised variable remission (remission without medication) versus remission with medication or not in remission was used as the dependent variable in the regression model. Results of the regression analyses are shown as odds ratios (OR), 95% confidence intervals (CI) and p-values. The level of significance was set at 5% ($p < 0.05$).

Paper II: Descriptive statistics of normally distributed data (mean +/-SD) and non-parametric data (median/interquartile range) were applied to assess the clinical characteristics of the cohort and disease activity. A chi-square test was conducted to compare dichotomous data. A Mann-Whitney test and standardised test statistics reported as a Z score were used to compare medians on ordinal data. A logistic regression model was used to assess baseline predictors and predictors for the development of condylar changes. All candidate variables were dichotomised and OR calculated using a multivariate logistic regression model. Age at onset and sex were included in the model, and the level of significance was $p < 0.05$. Furthermore, to identify high-risk participants at the 17-year follow-up, we performed a logistic regression analysis of treatment, symptoms, dysfunctions, and JIA category. Cohen's κ coefficient was used to test the interrater agreement for categorical measurements.

## 3. Ethical considerations

An important ethical issue for the study group was the possible risk of the participants suffering extra stress physically or mentally due to participation in the study. The risk was regarded as small. Since data in the study are collected on coded forms and only reported as group data, the risk of invasion of privacy was considered very small. Great care was taken by the study group to deal with any disagreements, and also to guide the participants in case of further need of health care. The participants who were in remission and were offered an extra check-up due to the study were given the opportunity to have an extra conversation about the previous symptoms and treatment. During the

previous parts of the study, the impression has been that many families felt they had received extra care because of the study.

The Research Ethical Committees in each country gave their approval for paper I in accordance with national practices and legislation. In Sweden the Regional research ethics committee at Uppsala University gave their approval, Dnr 2004, M-357. Written informed consent was obtained from children ≥ 15 years of age and from the parents/legal guardians of younger children. Informed assent was obtained from the children < 15 years of age, but with some variation between countries.

For paper II, approval was granted by national research committees in all the countries. For Sweden the Regional research ethics committee at Linköping University gave their approval, Dnr 2014/413-31, and the participants gave their written consent.

# Results

**1. Juvenile psoriatic arthritis**

Clinical findings associated with psoriasis developed consecutively during the follow-up period. In the cohort of 440 children followed for at least seven years after disease onset (median 98 months, range 84–147 months), 14 children developed psoriasis and 13 developed a psoriasis-like rash (Table 4). Only eight of the 14 children with psoriasis and JIA were classified as having juvenile psoriatic arthritis (JPsA) according to the ILAR criteria. The other six were classified as undifferentiated. Four of those were mutually excluded from JPsA as well as ERA, thus they did not fit any category. One boy was excluded because he was older than six at onset and HLA-B27 positive, and another child was excluded because of positive RF. Children with dactylitis and/or nail pitting were found among many ILAR categories. First-degree heredity for psoriasis or psoriatic arthritis occurred in nine of 14 children with JPsA and in 51 of 57 of children classified as having undifferentiated arthritis. In a comparison between the eight children with psoriasis, classified as JPsA (ILAR criteria) at 98 months of disease, and the six children with psoriasis classified as undifferentiated, there was no significant difference in age at onset ($p = 0.34$), first-degree heredity for psoriasis/psoriatic arthritis ($p = 0.53$), dactylitis ($p = 1.0$), nail pitting ($p = 0.30$) or cumulative number of joints ($p = 0.59$), but the cohorts were too small for meaningful statistical analyses. Children with psoriasis ($n = 14$) compared to those with psoriatic-like rash ($n = 13$) did not differ regarding gender ($p = 0.71$), outcome ($p = 0.16$) or the median cumulative number of joints ($p = 0.26$).

**Table 4.** *Clinical characteristics in a Nordic cohort of children with juvenile idiopathic arthritis according to the ILAR classification criteria and followed for at least seven years*

| Clinical characteristics | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Number of patients n | Age at onset median (IQR) | Psoriasis n | Psoriasis- like rash n | Dactylitis n | Nail pitting n | Patients assessed for heredity n | First-degree heredity for psoriasis or psoriatic arthritis n (%) |
| Systemic arthritis | 18 | 4.5 (2.2-6.7) | - | - | - | - | 18 | - |
| Oligoarticular persistent | 133 | 5.1 (2.6-8.5) | - | 1 | 6 | 3 | 123 | - |
| Oligoarticular extended | 78 | 4.1 (1.8-8.4) | - | 2 | 1 | 3 | 74 | - |
| Polyarticular RF negative | 80 | 4.9 (2.2-9.1) | - | 2 | 7 | - | 79 | - |
| Polyarticular RF positive | 3 | 10.2, 13.2, 13.3 | - | - | - | - | 3 | - |
| Psoriatic arthritis | 14 | 5.8 (4.3-7.9) | 8 | 3 | 3 | 7 | 14 | 9 (64.3) |
| Enthesitis-related arthritis | 49 | 10.0 (6.8-12.3) | - | 3 | 1 | 2 | 47 | - |
| Undifferentiated arthritis | 65 | 7.8 (3.2-11.8) | 6[a] | 2 | 6 | 3 | 57 | 51 (78.5) |

[a]None of the six patients with psoriasis at the 8-year follow-up fit any category, four because of mutual exclusion from JPsA and ERA because of enthesitis, one because he was a HLA-B27-positive boy older than 6 years at onset, one because of positive RF
[b]International League of Associations for Rheumatology classification criteria [10] assessed at last study visit (median 98, range 84–147 months)

Clinical features associated with psoriasis developed during the first eight years of disease. Twenty-four children developed dactylitis, 15 of which had dactylitis at onset. The median age at time of onset of JIA in the group with dactylitis was 2.4 (IQR 1.7–5.4) years compared with 5.8 (IQR 2.7–9.9) years in the rest of the cohort (p=0.007). Five of 24 children with dactylitis developed psoriasis or psoriasis-like rash during the first eight years of their arthritis, Table 5. Table 5 also presents the significantly higher cumulative number of active joints in children with psoriasis or psoriasis-like rash as well as the increased frequency of dactylitis, nail pitting, enthesitis, and first-degree heredity for psoriasis compared with children without psoriasis or psoriasis-like rash.

**Table 5.** *Clinical features describing the first eight years of disease in 440 children with JIA according to occurrence of psoriasis or psoriasis-like rash*

| Clinical feature | Number of patients assessed | Total cohort | Psoriasis or psoriasis-like rash *n* = 27 | No psoriasis or psoriasis-like rash *n* = 413 | *p*-value* |
|---|---|---|---|---|---|
| Gender, n (% females) | 440 (66.1) | 440 (66.1) | 27 (48.1) | 413 (67.3) | 0.06[a] |
| Age at time of onset median (IQR) | 440 | 5.5 (2.5-9.7) | 7.2 (3.8-11.0) | 5.3 (2.3-9.4) | 0.08[b] |
| Cumulative joints median (IQR) | 440 | 6 (2-12) | 11 (5-16) | 6 (2-12) | 0.02[c] |
| Dactylitis (%) | 440 | 24 | 5 (18.5) | 19 (4.6) | 0.01[a] |
| Nail pitting (%) | 440 | 18 | 7 (25.9) | 11 (2.7) | <0.001[a] |
| First-degree heredity for psoriasis or psoriatic arthritis (%) | 420 | 51 | 7 (25.9) | 44 (10.6) | 0.03[a] |
| Enthesitis (%) | 438 | 41 | 6 (22.2) | 35 (8.5) | 0.03[a] |
| Tenosynovitis (%) | 436 | 88 | 6 (22.2) | 82 (19.8) | 0.81[a] |

*Patients with psoriasis or psoriasis-like rash compared with those without, [a]Fisher's exact test, [b]Independent samples Mann-Whitney *U* test, [c]Independent samples median test

Features of sacroiliitis (SI) developed in several children with psoriasis or psoriasis-like rash. SI or enthesitis coexisting with psoriasis or psoriasis-like rash lead to mutual exclusion from both the JPsA and ERA categories. Seven of 27 children with psoriasis or psoriasis-like rash were HLA-B27 positive (missing

value in another three) and this group had a high age of onset (median 10.8, IQR 5.9–11.8 years), and a high cumulative number of joints (median 15, IQR 9–18 joints), data not shown. Several of the ERA or SI-like features were clustered together. Six of the 27 children with psoriasis or psoriasis-like rash had inflammatory back pain or buttock pain at some time during the first 98 months of disease, three of those were HLA-B27 positive, and in two sacroiliitis was confirmed by X-ray. In children with psoriasis or psoriasis-like rash or at least two of either dactylitis, nail pitting, or first-degree heredity of psoriasis, the remission rate was significantly lower compared with children without these clinical features, p=0.010 (Table 6). First-degree heredity for psoriasis in children with oligoarticular onset did not increase the risk for oligoarticular extended disease during those first eight years of disease (data not shown).

**Table 6.** Analysis of binary logistic regression for not being in remission related to psoriasis and psoriasis-related variables in 427 children with JIA, followed for at least seven years of disease

| | | Number of patients | Not in remission[c] after 8 years n (%) | *p*-value | OR | 95% confidence interval |
|---|---|---|---|---|---|---|
| Psoriasis or psoriasis-like rash[a] | Yes | 25 | 19 (76.0) | 0.062 | 2.44 | 0.96-6.2 |
| | No | 402 | 227 (56.5) | | | |
| Psoriasis or psoriasis-like rash OR at least two of three[b] | Yes | 31 | 25 (80.6) | 0.010 | 3.32 | 1.33-8.27 |
| | No | 379 | 211 (55.7) | | | |
| Dactylitis | Yes | 24 | 16 (66.7) | 0.36 | 1.5 | 0.63-3.6 |
| | No | 403 | 230 (57.1) | | | |
| Nail pitting | Yes | 18 | 13 (72.2) | 0.21 | 1.96 | 0.69-5.6 |
| | No | 409 | 233 (57.0) | | | |
| Enthesitis | Yes | 40 | 29 (72.5) | 0.046 | 2.08 | 1.01-4.29 |
| | No | 385 | 215 (55.8) | | | |
| First-degree heredity for psoriasis or psoriatic arthritis | Yes | 48 | 28 (58.3) | 0.86 | 1.1 | 0.42-2.82 |
| | No | 361 | 208 (57.6) | | | |
| Total | | 427 | 181 (42.4) | | | |

[a]Data in 13 patients with psoriasis and 12 with psoriasis-like rash
[b]1) dactylitis, 2) nail pitting, 3) first-degree heredity for psoriasis or psoriatic arthritis
[c]Remission was defined as inactive disease off medication for at least twelve months in accordance with the preliminary definition of Wallace [16]

## 2. Arthritis of the temporomandibular joint

In total, 265 participants with JIA were included in the present study (mean age 23.5 ± SD 4.2 yrs). The mean follow-up time from JIA onset to orofacial examination was 17.3 years (SD± 1.3 yrs); 186/265 (70.2%) were girls. The distribution of JIA categories and other clinical data were as described in Table 7. We found no difference in sex, JIA category, number of active joints, or baseline JADAS values between included participants and those lost to follow-up. However, age at onset was lower in the included group (mean 6.0 ± 3.9 vs 6.2 ± 4.0 yrs in those lost to follow-up; p = 0.003). Of the 265 participants completing the clinical orofacial examination, 245 had a full-face CBCT performed with 490 approved high-quality TMJ images. The control group had a mean age of 23.6 ± 2.9 years; 52.5% were girls.

**Table 7.** *Demographic and clinical characteristics by JIA categories in the TMJ study of the Nordic JIA cohort at the 17-year follow-up visit*

| Characteristics | No. Patients | Total Cohort, n = 265 | sJIA, n = 11 | Oligo persist, n = 56 | Oligo ext, n = 58 | Poly RF–, n = 52 | Poly RF+, n = 4 | Psoriatic, n = 14 | ERA, n = 27 | Undiff, n = 43 |
|---|---|---|---|---|---|---|---|---|---|---|
| Women, n (%) | 265 | 186 (70.6) | 8 (72.7) | 40 (71.4) | 44 (75.9) | 38 (73.1) | 3 (75.0) | 10 (71.4) | 9 (33.3) | 35 (81.4) |
| Age at onset, yrs, mean (± SD) | 265 | 6.2 (± 4.0) | 5.0 (± 2.9) | 5.5 (± 3.5) | 4.9 (± 3.9) | 5.9 (± 4.1) | 11.1 (± 2.6) | 6.4 (± 3.7) | 9.0 (± 3.4) | 7.3 (± 4.0) |
| Age at last followup, yrs, mean (± SD) | 265 | 23.5 (± 4.2) | 23.0 (± 3.1) | 22.7 (± 3.5) | 22.0 (± 4.0) | 22.9 (± 4.3) | 28.7 (± 2.6) | 23.4 (± 4.2) | 26.4 (± 3.5) | 24.8 (± 4.5) |
| Disease duration, yrs, mean (± SD) | 265 | 17.3 (± 1.0) | 17.9 (± 0.8) | 17.3 (± 1.1) | 17.2 (± 1.1) | 17.2 (± 1.0) | 17.6 (± 1.0) | 17.0 (± 0.9) | 17.4 (± 1.1) | 17.3 (± 0.9) |
| ANA-positive, n (%) | 234 | 80 (34.2) | 2 (25.0) | 12 (21.4) | 20 (34.5) | 15 (28.8) | 2 (50.0) | 5 (35.7) | 8 (29.6) | 16 (36.4) |
| HLA-B27–positive, n (%) | 264 | 57 (21.6) | 0 (0.0) | 6 (10.7) | 7 (12.1) | 8 (15.4) | 1 (25.0) | 3 (21.4) | 21 (77.8) | 11 (25.0) |
| CRP > 10 mg/l, n (%) | 257 | 14 (5.4) | 0 | 1/53 (1.9) | 2/55 (3.6) | 3/52 (5.8) | 0 | 2/14 (14.3) | 4/27 (14.8) | 2/42 (4.8) |
| ESR > 20 mm/h, n (%) | 218 | 15 (6.7) | 0 | 2/48 (4.2) | 2/48 (4.2) | 3/47 (6.4) | 0 | 3/14 (21.4) | 2/22 (9.1) | 3/33 (9.1) |
| Pain VAS, median (IQR)* | 260 | 1.0 (0–3.5) | 0 (0–2.0) | 0 (0–2.0) | 1.0 (0–4.0) | 1.0 (0–4.0) | 5.0 (2.0–6.5) | 1.5 (0–3.0) | 1.0 (0.5–3.5) | 2.0 (0.5–4.8) |
| PtGA VAS, median (IQR)* | 260 | 1.0 (0–3.0) | 0 (0–1.0) | 0 (0–1.0) | 1.0 (0–2.5) | 0.8 (0–2.8) | 4.0 (1.3–7.8) | 1.0 (0–2.0) | 2.0 (1.0–4.5) | 2.0 (0–4.5) |
| PGA VAS, median (IQR) | 265 | 0 (0–1.0) | 0 (0–0.5) | 0 (0–0) | 0 (0–1.5) | 0 (0–0.8) | 1.0 (0–2.5) | 0 (0–1.0) | 1.0 (0–2.5) | 0 (0–2.0) |
| JADAS71 ≤ 1, n (%) | 244 | 97 (39.8) | 8 (80.0) | 31 (63.3) | 19 (36.5) | 21 (42.0) | 1 (25.0) | 5 (38.5) | 3 (11.5) | 9 (22.5) |

* Statistical significance ($p \leq 0.05$) among the JIA categories. PGA is reported if a followup visit was performed. JIA: juvenile idiopathic arthritis; TMJ: temporomandibular joint; sJIA: systemic JIA; oligo persist: persistent oligoarticular JIA; oligo ext: extended oligoarticular JIA; poly RF–: polyarticular rheumatoid factor–negative JIA; poly RF+: polyarticular RF-positive JIA; ERA: enthesitis-related arthritis; Undiff: undifferentiated JIA; ANA: antinuclear antibody; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; pain VAS: patient's intensity of pain on a 21-numbered circle visual analog scale (0–100); PtGA VAS: patient's global assessment of overall well-being on a 21-numbered circle VAS; PGA VAS: physician's global assessment of disease activity on a 21-numbered circle VAS; IQR: interquartile range; JADAS: Juvenile Arthritis Disease Activity Score.

*Orofacial symptoms*. In total, 87 of the 265 JIA participants (32.8%) reported at least one TMJ-related symptom at the follow-up visit, which was similar to the control group ($p = 0.11$; Table 2=8). Orofacial pain frequency and number of symptoms, TMJ pain, morning stiffness, and limitation of chewing were observed significantly more frequently in the JIA group and occurred in all categories. Overall, 89 (33.6%) participants with JIA reported jaw and/or facial pain within the previous two weeks. Of the controls, 61 (30.5%) reported jaw and/or facial pain within the previous two weeks, which was similar to the reports in the JIA group ($p = 0.48$), but more controls reported pain less than once a week (71% vs 53%) and fewer reported pain several times per day or all the time (7% vs 27%) compared to the JIA group.

*Dysfunction*. In total, 136 (51.3%) participants with JIA had at least one clinical sign of orofacial dysfunction, which was not different from the controls ($p = 0.12$; Table 8). The most frequent clinical findings were TMJ and orofacial pain on palpation in both groups. Mean MIO (maximal incisal opening) was significantly lower in the JIA group (47.2 ± 7.7 vs 56.5 ± 6.8 mm; $p < 0.001$). The prevalence of participants with an MIO < –2 SD was significantly higher among JIA participants than the controls ($p < 0.001$; Table 8). TMJ pain on palpation was more frequent in the JIA group than in the controls ($p = 0.03$). However, no intergroup differences were observed for orofacial pain on palpation or asymmetric mouth opening.

**Table 8.** *Prevalence of orofacial symptoms and dysfunction in the JIA group (n=265) and the control group (n=200)*

| Variables | JIA Group | Control Group | Measures (95% CI) | p |
|---|---|---|---|---|
| Orofacial symptoms | | | | |
| No symptoms | 178 (67.2) | 148 (74.0) | | |
| ≥ 1 symptom | 87 (32.8) | 52 (26.0) | OR 1.4 (0.91–2.14) | 0.11 |
| TMJ pain | 65 (24.5) | 14 (7.0) | OR 4.32 (2.30–8.60) | < 0.001* |
| TMJ morning stiffness | 42 (15.8) | 9 (4.5) | OR 4.02 (1.86–9.60) | < 0.001* |
| Orofacial muscle pain | 74 (27.9) | 44 (22.0) | OR 1.07 (0.70–1.66) | 0.74 |
| Limitation on chewing | 35 (13.2) | 9 (4.5) | OR 3.24 (1.48–7.85) | 0.001* |
| Locking of the jaw | 20 (7.5) | 17 (8.5) | OR 0.88 (0.42–1.84) | 0.71 |
| Orofacial pain intensity | | | | |
| VAS pain > 0, median (IQR) | 25 (5–85) | 19 (6–60) | Z = 0.63 | 0.53 |
| Orofacial pain frequency | | | | |
| Pain frequency > 0, median (IQR) | 1 (1–4)[1] | 1 (1–3)[1] | Z = 2.61 | < 0.01* |
| Orofacial pain profile | | | | |
| Pain index > 0[2], median (IQR) | 30 (5–260) | 20 (6–120) | Z = 1.53 | 0.13 |
| No. symptoms | | | | |
| Per subject, median (IQR) | 2 (1–5) | 1 (1–3) | Z = 2.26 | 0.02* |
| Orofacial dysfunctions | | | | |
| No dysfunctions | 129 (48.7) | 112 (56.0) | | |
| ≥ 1 dysfunction | 136 (51.3) | 88 (44.0) | OR 1.34 (0.91–1.97) | 0.12 |
| Reduced MIO[3] | 51 (19.2) | 3 (1.5) | OR 15.72 (4.94–79.69) | < 0.001* |
| TMJ pain on palpation | 79 (29.9) | 42 (21.0) | OR 0.62 (0.40–0.95) | 0.03* |
| Orofacial pain on palpation | 67 (25.3) | 50 (25.0) | OR 0.99 (0.64–1.50) | 0.94 |
| Asymmetric mouth opening | 29 (10.9) | 32 (16.0) | OR 0.65 (0.36–1.15) | 0.11 |
| No. dysfunctions | | | | |
| Per subject, median (IQR) | 1 (0–2) | 0 (0–2) | Z = 2.34 | 0.02 * |

Values indicate n (%) unless otherwise indicated. * Statistical significance ($p \leq 0.05$). [1] Pain frequency: 1 indicates not every week; 2 = several times a week; 3 = several times a day; 4 = all the time. [2] Pain index: pain frequency × pain intensity. [3] MIO < –2 SD below mean of normative values (< 40.9 mm, ref [27]). JIA: juvenile idiopathic arthritis; TMJ: temporomandibular joint; VAS: visual analog scale; IQR: interquartile range; MIO: maximal incisal opening.

*Disease status and clinical findings*. Inactive disease was found in 162 (61.1%) of the 265 participants with JIA, of whom 34 (12.8%) were in remission on medication, and 99 (37.4%) in remission without medication, while 29 (10.9%) had inactive disease without fulfilling the remission criteria.

Of the participants with inactive disease or in remission 38/162 (23.5%) reported at least one orofacial symptom, and 70 (43.2%) had at least one clinical sign of dysfunction. In the same group, the frequencies of the reported symptoms were: 38/162 (23.5%) orofacial or jaw pain, 16 (9.9%) morning stiffness in the jaws, 11 (6.8%) limitation when chewing, and seven (4.3%) locking of the jaw. Furthermore, a reduced MIO was found in 22/162 (13.6%), TMJ pain on palpation in 37 (22.8%), orofacial pain on palpation in 28 (17.3%), and asymmetric mouth opening in 26 (16.0%; data not shown).

*Radiologic findings*. Normal CBCT of both TMJs was observed in 96/245 (39.2%) of the participants with JIA. Thus, the prevalence of at least one abnormal radiological TMJ appearance was 149/245 (60.8%) participants with JIA. Of these, 104/149 (69.8%) had bilateral TMJ deformities. Of 253 joints with CBCT changes, 119 (47.0%) had score 1 (deformity), 24 (9.5%) score 2

(erosion), and 110 (43.5%) score 3 (deformity and erosion). Abnormal condylar findings were most frequent in the rheumatoid factor-negative polyarticular group (76.5%) and least frequent in the enthesitis-related arthritis (ERA) category (33.3%), but TMJ deformities were present in all JIA categories. TMJ pain on palpation doubled the odds of having an abnormal TMJ on the CBCT scan (OR 2.1, 95% CI 1.08–4.1), and there was a strong association with MIO< –2 SD (OR 7.5, 95% CI 2.7–20.6) and abnormal TMJ on CBCT. Of the 27 (10.2%) participants having at least one intra-articular TMJ injection during the disease course, all had abnormal condylar findings on CBCT, and 17 (63.0%) had erosions and deformities (data not shown).

*Intra-observer reproducibility of the CBCT assessment*. On 30 randomly selected CBCT examinations of 60 TMJ assessed twice, six months apart, intra-observer agreement was found in 53 (88.3%) of the scans. Cohen's $\kappa$ = 0.83 indicated an almost perfect intra-observer agreement.

*Association between baseline predictors/clinical characteristics and abnormal radiologic condylar appearance at the 17-year follow-up.*

From the multivariate logistic regression analysis of the baseline predictors of condylar deformities/erosions, we found a positive association with an active joint count of > 4 at baseline and a negative association with the presence of HLA-B27 (Table 9). At the eight-year follow-up, a cumulative joint count of > 4 and the ERA category was associated with condylar changes. Logistic regression analysis on age at onset and sex did not show any association with condylar deformity. Treatment with biologics during the disease course and orofacial dysfunctions 17 years after onset were associated with a significantly higher risk of TMJ deformity ($p = 0.02$ and $p < 0.01$, respectively). Children in the ERA category had a significantly lower risk of developing TMJ deformities (Table 9).

**Table 9**. *Associations between clinical characteristics at baseline, 8-year followup, or at any time during the disease course, and condylar deformities/erosions at the 17-year follow-up.*

| Variables | Multivariate OR (95% CI) | p |
|---|---|---|
| Predictors early in disease course, n = 211 | | |
| Age at onset < 6 yrs | 1.01 (0.52–1.97) | 0.97 |
| Female sex | 1.08 (0.54–2.17) | 0.84 |
| Active joint count at baseline visit > 4 joints | 2.14 (1.11–4.18) | 0.02* |
| ESR > 20 at baseline | 1.88 (0.95–3.70) | 0.07 |
| HLA-B27–positive | 0.44 (0.20–0.98) | 0.04* |
| Uveitis at baseline | 1.54 (0.48–4.99) | 0.47 |
| Predictors at 8 years of followup, n = 234 | | |
| Age at onset < 6 yrs | 1.31 (0.73–2.36) | 0.11 |
| Female sex | 1.31 (0.60–2.13) | 0.36 |
| Cumulative active joint count > 4 | 2.07 (1.05–4.09) | 0.03* |
| JADI-A > 0 | 1.66 (0.94–2.93) | 0.08 |
| MTX | 1.22 (0.62–2.41) | 0.62 |
| Biologics | 2.10 (0.75–5.86) | 0.16 |
| ERA | 0.35 (0.12–0.97) | 0.04* |
| Associations during the disease course**, n = 244 | | |
| Age at onset < 6 yrs | 1.18 (0.65–2.14) | 0.47 |
| Female sex | 0.78 (0.40–1.53) | 0.47 |
| DMARD during disease course | 1.18 (0.59–2.36) | 0.60 |
| Biologics during disease course | 2.37 (1.18–4.74) | 0.02* |
| Cumulative active joints > 4 at 17-yr followup | 1.94 (0.99–3.80) | 0.06 |
| Orofacial dysfunction at 17-yr followup | 3.13 (1.74–5.62) | < 0.01* |
| ERA | 0.17 (0.06–0.50) | 0.01* |

* Statistical significance ($p \leq 0.05$). ** Associations between clinical characteristics at any time of the disease course and condylar deformities/erosions. ESR: erythrocyte sedimentation rate; JADI-A: Juvenile Arthritis Damage Index–Articular; MTX: methotrexate; ERA: enthesitis-related arthritis; DMARD: disease-modifying antirheumatic drugs.

# Discussion

The participants of the Nordic population-based cohort of children with JIA have now been followed for at least 17 years. A substantial proportion of them did not achieve clinical remission off medication despite new treatment options during the study period [36]. In general, there is a high burden of the disease in persons with JIA that have reached adulthood. This has also been shown in other cohorts [38, 39].

It is obvious that clinical manifestations develop over time and it can be difficult to get the full clinical picture early after onset – i.e. the trajectory becomes important to follow and understand. This is especially true for JPsA and arthritis of the TMJ.

The main findings in this study were that after eight years a considerable proportion of the children with definite psoriasis were classified as undifferentiated JIA based on the exclusion criteria in the ILAR classification. Our data also presents the heterogenicity of JPsA and the development over time of clinical variables supporting a psoriatic diathesis, as well as the overlap between JPsA and enthesitis-related arthritis in a group of patients. We also found that extensive symptoms and dysfunctions of the TMJ are seen in JIA 17 years after disease onset, even in patients registered with inactive disease or remission. Individuals with substantial condylar damage on CBCT were found in all JIA categories.

The Nordic JIA study aimed to be as population-based as possible. During the inclusion period, letters were repeatedly sent to the primary health care services and all orthopaedic, paediatric, and rheumatology specialists in the catchment areas, requesting the referral of potentially eligible patients. It cannot be ruled out that children with arthritis were missed if for some reason they did not have access to health care but the number should be very small. The long follow-up time is, as far as we know, quite unique and requires personal identification numbers and a well-organised health care system, prerequisites which are present in the Nordic healthcare systems.

The ILAR criteria aimed to create homogenous groups for research and for comparison of different populations. For JPsA they seem to be less suitable. A considerable proportion of the children with definite psoriasis were classified as undifferentiated JIA based on the exclusion criteria in the ILAR classification. In a longer perspective we are concerned that those children will be excluded from studies on new biologicals, targeting specific molecules involved in psoriatic disease if ILAR criteria are also used in the future.

A challenge in classification is the progression of the disease over time. Our data show the heterogenicity of JPsA and the development over time of clinical variables supporting a psoriatic diathesis, as well as the overlap between JPsA and enthesitis-related arthritis in a group of patients. The polyarticular disease progression in children with psoriasis and arthritis in our study is in line with earlier studies [9, 15, 40]. Our results indicate a somewhat less favourable outcome in the cohort of children with psoriasis, psoriasis-like rash or at least two well-known features characterising the JPsA group but our numbers do not have the power to allow analysis of each the clinical features as a single trait, and larger studies are needed to confirm our results. Another important feature is heredity for psoriasis. In our cohort, first-degree heredity for psoriasis was common in the undifferentiated JIA category. It has been reported by others that the ILAR criteria excluded almost 60% of those included with the Vancouver criteria [41].

Dactylitis has proven a strong predictor of JPsA [8]. In the criteria for psoriasis in adults, CASPAR, dactylitis is included [10]. In our study cohort occurrence of dactylitis was spread among ILAR categories, but had a strong association with psoriasis or psoriasis-like rash. Also, enthesitis showed a strong association with psoriasis or psoriasis-like rash in our study cohort. Although enthesitis is a well-recognised feature of PsA in adults, it is an exclusion criterion for JPsA in the ILAR classification, and a common reason for exclusion from the JPsA category [35]. Radiographic resemblance of dactylitis in JPsA to the condition in adult psoriatic arthritis and to common features of enthesitis has been reported [42].

Detection of arthritis of the TMJ is a special challenge since it is initially silent with discrete symptoms and no visible swelling. Interdisciplinary collaboration and access to adequate imaging facilities are therefore necessary. In our follow-up study we found that the long-term consequences of TMJ involvement – comprehensive symptoms, dysfunctions and damage of the TMJ – seem to persist into adulthood. The results showed higher prevalence of TMJ pain, TMJ morning stiffness, and chewing limitations in the JIA group. We found a higher prevalence of TMJ pain on palpation and a reduced MIO among the JIA participants; however, the prevalence of orofacial pain on palpation and asymmetric mouth opening was not different from that seen in the control group. The control group's complaints were mild and comparable to what have been reported in TMJ unrelated to arthritis [43]. A large number of JIA participants experienced continued TMJ symptoms/dysfunctions despite inactive disease or remission, indicating a need for continued, standardised orofacial monitoring.

CBCT is a well-established method of detecting deformity and hard tissue changes of the TMJ. Recently, Kellenberger suggested MRI for monitoring TMJ arthritis and published an additive scoring system to assess the osseous deformities [45]. However, it had not been published when our study began, and CBCT has previously been used for assessment of hard tissue changes

[29, 46]. In total, about 61% of the JIA participants had at least one condyle with abnormal CBCT findings, and about 70% of these subjects had bilateral changes. Importantly, the presence of radiographic condylar changes does not necessarily imply the presence of dentofacial deformity. The association between radiographic TMJ changes and dentofacial deformity will be established in a future study

However, our study has limitations. Of the total cohort, 37% were lost to follow-up. Age at onset was lower in the included group, but we found no differences in sex, disease activity at baseline, or JIA category. Considering the fact that most of the participants are not attending paediatric clinic any more, the response rate after 17 years was considered acceptable.

Our findings indicate that extensive symptoms and dysfunctions are seen in JIA even 17 years after disease onset, and even in patients registered with inactive disease or remission. Individuals with substantial condylar damage were found in all JIA categories. We suggest taking account of aspects of TMJ involvement in the general clinical decision-making by including orofacial symptom and dysfunction assessment as an integrated part of general health assessment in JIA, guided by recent consensus-based recommendations [47].

Increased collaboration between paediatric and adult physicians is crucial to the successful transition of young adults with JPsA from paediatric to adult care. Beyond the discussion of clinical aspects, studies on the immunogenicity and pathogenesis of the psoriatic disease in the whole age spectrum may provide the biological knowledge needed to improve diagnosis and therapy. Immunological research has revealed that cytokines of the IL-17 and IL-23 pathways promote skin and joint inflammation in psoriasis [48, 49]. These molecules are now targeted with new biological drugs, which make it even more urgent to diagnose and classify children in a more accurate way. The deeper understanding of a chronic disease over time is crucial for research issues as well as for planning health care. For the same purposes, we need the knowledge from quality registries where data from a person is followed prospectively and continuously, and where patterns from the disease are fed back to others in the registry in a learning network [50]. In the proposal for a new classification of JIA we still find it important to consider psoriasis and associated features. We need to better understand how to predict this category of disease to be able to provide proper treatment for this group of children.

# Svensk sammanfattning

Juvenil idiopatisk artrit, JIA, som på svenska brukar kallas barnreumatism, är ett samlingsnamn för en grupp sjukdomar som karaktäriseras av en långvarig inflammation i en eller flera av kroppens leder. Inflammationen orsakar svullnad, smärta och ibland nedsatt rörlighet. Orsakerna till sjukdomen är inte klarlagda, men det är troligen ett samspel mellan genetiska faktorer och omgivningsfaktorer, så som infektioner, som gör att sjukdomen bryter ut. Det är inte heller känt varför vissa leder drabbas mer än andra. En led som ofta drabbas, och som till att börja med inte behöver ge så mycket symtom, är käkleden. På sikt kan käkledsinflammationen orsaka smärta, svårigheter att tugga och en påverkad tillväxt av underkäken. Vissa former av JIA finns bara hos barn medan andra även finns hos vuxna. Det finns en koppling mellan hudsjukdomen psoriasis och ledinflammation både hos barn och vuxna men hos barn bryter ledinflammationen ibland ut flera år innan hudsymtomen kommer. Det finns kriterier för klassifikation av ledsjukdomen som ursprungligen var tänkta för forskning men som kommit att användas även för att ställa diagnos och välja behandling. För just psoriasisartrit hos barn är de aktuella kriterierna omstridda.

Den här licentiatuppsatsen baserar sig på en stor nordisk multicenterstudie. Mellan 1997 och 1999 inkluderades 510 barn med nyupptäckt JIA från geografiskt definierade områden i Danmark, Finland, Norge och Sverige i en klinisk studie där man över tid har följt sjukdomssymtom, svårighetsgrad, behandling och komplikationer av sjukdomen.

Vid uppföljning åtta år efter insjuknandet undersöktes 440 av barnen på nytt. Vi fann att flera av barnen med psoriasis och samtidig ledinflammation inte kunde klassificeras som psoriasisartrit enligt de nuvarande klassifikationskriterierna. Det visade sig också att sjukdomsbilden hos barn med psoriasisartrit var varierad och att sjukdomssymtom som inte fanns vid debut utvecklades efter hand. Det gjordes också en uppföljning 17 år efter debut. De nu vuxna personerna fick svara på frågor om sjukdomssymtom och funktionsförmåga och lederna undersöktes. Totalt 265 av personerna genomgick en speciell undersökning av käkledernas funktion och en så kallad cone beam computed tomography, CBCT, som är en datortomografiundersökning av käklederna med avgränsade strålfält och därmed mindre strålning. Det visade sig att många av personerna hade omfattande symtom från käklederna och nedsatt käkledsfunktion även om ledsjukdomen generellt var i remission, det vill säga

inaktiv. Med röntgen fann man hos cirka 60 % av deltagarna skador på käkleden, dessa fanns i alla undergrupper av JIA.

En djupare förståelse av hur en kronisk sjukdom som JIA utvecklas över tid är viktig för att kunna utveckla och förbättra behandling och vård för barn och unga vuxna. Våra resultat understryker behoven av en bättre klassifikation av psoriasisartrit hos barn och att käkledsinflammation följs upp som en del i vårdprogrammet för JIA.

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# References


1. Berntson L, Fasth A, Andersson-Gäre B, et al. Construct validity of ILAR and EULAR criteria in juvenile idiopathic arthritis: a population based incidence study from the Nordic countries. International League of Associations for Rheumatology. European League Against Rheumatism. *J Rheumatol*. 2001;28(12):2737-2743.
2. Petty RE, Southwood TR, Baum J, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. *J Rheumatol*. 1998;25(10):1991-1994.
3. Gäre BA, Fasth A. The natural history of juvenile chronic arthritis: a population based cohort study. I. Onset and disease process. *J Rheumatol*. 1995;22(2):295-307.
4. Martini A, Ravelli A, Avcin T, et al. Toward New Classification Criteria for Juvenile Idiopathic Arthritis: First Steps, Pediatric Rheumatology International Trials Organization International Consensus. *J Rheumatol*. 2019;46(2):190-197. doi:10.3899/jrheum.180168
5. Zisman D, Gladman DD, Stoll ML, et al. The Juvenile Psoriatic Arthritis Cohort in the CARRA Registry: Clinical Characteristics, Classification, and Outcomes. *J Rheumatol*. 2017;44(3):342-351. doi:10.3899/jrheum.160717
6. Martini A. Are the number of joints involved or the presence of psoriasis still useful tools to identify homogeneous disease entities in juvenile idiopathic arthritis?. *J Rheumatol*. 2003;30(9):1900-1903.
7. Nigrovic PA. Juvenile psoriatic arthritis: bathwater or baby?. *J Rheumatol*. 2009;36(9):1861-1863. doi:10.3899/jrheum.090510
8. Stoll ML, Zurakowski D, Nigrovic LE, Nichols DP, Sundel RP, Nigrovic PA. Patients with juvenile psoriatic arthritis comprise two distinct populations. *Arthritis Rheum*. 2006;54(11):3564-3572. doi:10.1002/art.22173
9. Southwood TR, Petty RE, Malleson PN, et al. Psoriatic arthritis in children. *Arthritis Rheum*. 1989;32(8):1007-1013. doi:10.1002/anr.1780320810
10. Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum*. 2006;54(8):2665-2673. doi:10.1002/art.21972
11. Ansell BM. Juvenile psoriatic arthritis. *Baillieres Clin Rheumatol*. 1994;8(2):317-332. doi:10.1016/s0950-3579(94)80021-9
12. Flatø B, Lien G, Smerdel-Ramoya A, Vinje O. Juvenile psoriatic arthritis: longterm outcome and differentiation from other subtypes of juvenile idiopathic arthritis. *J Rheumatol*. 2009;36(3):642-650. doi:10.3899/jrheum.080543
13. McGonagle D, Tan AL, Watad A, Helliwell P. Pathophysiology, assessment and treatment of psoriatic dactylitis. *Nat Rev Rheumatol*. 2019;15(2):113-122. doi:10.1038/s41584-018-0147-9
14. Roberton DM, Cabral DA, Malleson PN, Petty RE. Juvenile psoriatic arthritis: followup and evaluation of diagnostic criteria. *J Rheumatol*. 1996;23(1):166-170.

15. Stoll ML, Punaro M. Psoriatic juvenile idiopathic arthritis: a tale of two subgroups. *Curr Opin Rheumatol*. 2011;23(5):437-443. doi:10.1097/BOR.0b013e328348b278
16. Raychaudhuri SP, Gross J. A comparative study of pediatric onset psoriasis with adult onset psoriasis. *Pediatr Dermatol*. 2000;17(3):174-178. doi:10.1046/j.1525-1470.2000.01746.x
17. Augustin M, Glaeske G, Radtke MA, Christophers E, Reich K, Schäfer I. Epidemiology and comorbidity of psoriasis in children. *Br J Dermatol*. 2010;162(3):633-636. doi:10.1111/j.1365-2133.2009.09593.x
18. Gupta R, Debbaneh MG, Liao W. Genetic Epidemiology of Psoriasis. *Curr Dermatol Rep*. 2014;3(1):61-78. doi:10.1007/s13671-013-0066-6
19. Lysell J, Tessma M, Nikamo P, Wahlgren CF, Ståhle M. Clinical characterisation at onset of childhood psoriasis - a cross sectional study in Sweden. *Acta Derm Venereol*. 2015;95(4):457-461. doi:10.2340/00015555-1986
20. Armstrong AW, Harskamp CT, Armstrong EJ. Psoriasis and metabolic syndrome: a systematic review and meta-analysis of observational studies. *J Am Acad Dermatol*. 2013;68(4):654-662. doi:10.1016/j.jaad.2012.08.015
21. Paller AS, Schenfeld J, Accortt NA, Kricorian G. A retrospective cohort study to evaluate the development of comorbidities, including psychiatric comorbidities, among a pediatric psoriasis population. *Pediatr Dermatol*. 2019;36(3):290-297. doi:10.1111/pde.13772
22. Gånemo A, Wahlgren CF, Svensson Å. Quality of life and clinical features in Swedish children with psoriasis. *Pediatr Dermatol*. 2011;28(4):375-379. doi:10.1111/j.1525-1470.2010.01292.x
23. Stoll ML, Sharpe T, Beukelman T, Good J, Young D, Cron RQ. Risk factors for temporomandibular joint arthritis in children with juvenile idiopathic arthritis. *J Rheumatol*. 2012;39(9):1880-1887. doi:10.3899/jrheum.111441
24. Martini G, Bacciliero U, Tregnaghi A, Montesco MC, Zulian F. Isolated temporomandibular synovitis as unique presentation of juvenile idiopathic arthritis. *J Rheumatol*. 2001;28(7):1689-1692.
25. Hügle B, Spiegel L, Hotte J, et al. Isolated Arthritis of the Temporomandibular Joint as the Initial Manifestation of Juvenile Idiopathic Arthritis. *J Rheumatol*. 2017;44(11):1632-1635. doi:10.3899/jrheum.170263
26. Stoustrup P, Resnick CM, Pedersen TK, et al. Standardizing Terminology and Assessment for Orofacial Conditions in Juvenile Idiopathic Arthritis: International, Multidisciplinary Consensus-based Recommendations. *J Rheumatol*. 2019;46(5):518-522. doi:10.3899/jrheum.180785
27. Hammer MR, Kanaan Y. Imaging of the Pediatric Temporomandibular Joint. *Oral Maxillofac Surg Clin North Am*. 2018;30(1):25-34. doi:10.1016/j.coms.2017.08.008
28. Stoll ML, Kau CH, Waite PD, Cron RQ. Temporomandibular joint arthritis in juvenile idiopathic arthritis, now what?. *Pediatr Rheumatol Online J*. 2018;16(1):32. Published 2018 Apr 25. doi:10.1186/s12969-018-0244-y
29. Resnick CM, Vakilian PM, Breen M, et al. Quantifying Temporomandibular Joint Synovitis in Children With Juvenile Idiopathic Arthritis. *Arthritis Care Res (Hoboken)*. 2016;68(12):1795-1802. doi:10.1002/acr.22911
30. Müller L, Kellenberger CJ, Cannizzaro E, et al. Early diagnosis of temporomandibular joint involvement in juvenile idiopathic arthritis: a pilot study comparing clinical examination and ultrasound to magnetic resonance imaging. *Rheumatology (Oxford)*. 2009;48(6):680-685. doi:10.1093/rheumatology/kep068

31. Hechler BL, Phero JA, Van Mater H, Matthews NS. Ultrasound versus magnetic resonance imaging of the temporomandibular joint in juvenile idiopathic arthritis: a systematic review. *Int J Oral Maxillofac Surg*. 2018;47(1):83-89. doi:10.1016/j.ijom.2017.07.014
32. Berntson L, Andersson Gäre B, Fasth A, et al. Incidence of juvenile idiopathic arthritis in the Nordic countries. A population based study with special reference to the validity of the ILAR and EULAR criteria. *J Rheumatol*. 2003;30(10):2275-2282.
33. Nordal E, Rypdal V, Christoffersen T, et al. Incidence and predictors of Uveitis in juvenile idiopathic arthritis in a Nordic long-term cohort study. *Pediatr Rheumatol Online J*. 2017;15(1):66. Published 2017 Aug 18. doi:10.1186/s12969-017-0195-8
34. Wallace CA, Ruperto N, Giannini E; Childhood Arthritis and Rheumatology Research Alliance; Pediatric Rheumatology International Trials Organization; Pediatric Rheumatology Collaborative Study Group. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. *J Rheumatol*. 2004;31(11):2290-2294.
35. Nordal E, Zak M, Aalto K, et al. Ongoing disease activity and changing categories in a long-term nordic cohort study of juvenile idiopathic arthritis. *Arthritis Rheum*. 2011;63(9):2809-2818. doi:10.1002/art.30426
36. Glerup M, Rypdal V, Arnstad ED, et al. Long-Term Outcomes in Juvenile Idiopathic Arthritis: Eighteen Years of Follow-Up in the Population-Based Nordic Juvenile Idiopathic Arthritis Cohort. *Arthritis Care Res (Hoboken)*. 2020;72(4):507-516. doi:10.1002/acr.23853
37. Glerup M, Thiel S, Rypdal V, et al. Complement lectin pathway protein levels reflect disease activity in juvenile idiopathic arthritis: a longitudinal study of the Nordic JIA cohort. *Pediatr Rheumatol Online J*. 2019;17(1):63. Published 2019 Sep 9. doi:10.1186/s12969-019-0367-9
38. Packham JC, Hall MA. Long-term follow-up of 246 adults with juvenile idiopathic arthritis: functional outcome. *Rheumatology (Oxford)*. 2002;41(12):1428-1435. doi:10.1093/rheumatology/41.12.1428
39. Minden K, Niewerth M, Listing J, Biedermann T, Schöntube M, Zink A. Burden and cost of illness in patients with juvenile idiopathic arthritis. *Ann Rheum Dis*. 2004;63(7):836-842. doi:10.1136/ard.2003.008516
40. Lambert J. Psoriatic arthritis in Childhood. *Clin Rheum Dis.* 1976;2:339-352.
41. Stoll ML, Lio P, Sundel RP, Nigrovic PA. Comparison of Vancouver and International League of Associations for rheumatology classification criteria for juvenile psoriatic arthritis. *Arthritis Rheum*. 2008;59(1):51-58. doi:10.1002/art.23240
42. Tuttle KS, Vargas SO, Callahan MJ, Bae DS, Nigrovic PA. Enthesitis as a component of dactylitis in psoriatic juvenile idiopathic arthritis: histology of an established clinical entity. *Pediatr Rheumatol Online J*. 2015;13:7. Published 2015 Feb 28. doi:10.1186/s12969-015-0003-2
43. Slade GD, Bair E, Greenspan JD, et al. Signs and symptoms of first-onset TMD and sociodemographic predictors of its development: the OPPERA prospective cohort study. *J Pain*. 2013;14(12 Suppl):T20-32.e323. doi:10.1016/j.jpain.2013.07.014
44. Resnick CM, Dang R, Henderson LA, et al. Frequency and Morbidity of Temporomandibular Joint Involvement in Adult Patients With a History of Juvenile Idiopathic Arthritis. *J Oral Maxillofac Surg*. 2017;75(6):1191-1200. doi:10.1016/j.joms.2016.11.013

45. Kellenberger CJ, Junhasavasdikul T, Tolend M, Doria AS. Temporomandibular joint atlas for detection and grading of juvenile idiopathic arthritis involvement by magnetic resonance imaging. *Pediatr Radiol*. 2018;48(3):411-426. doi:10.1007/s00247-017-4000-0
46. Stoustrup PB, Ahlefeldt-Laurvig-Lehn N, Kristensen KD, et al. No association between types of unilateral mandibular condylar abnormalities and facial asymmetry in orthopedic-treated patients with juvenile idiopathic arthritis. *Am J Orthod Dentofacial Orthop*. 2018;153(2):214-223. doi:10.1016/j.ajodo.2017.05.037
47. Stoustrup P, Twilt M, Spiegel L, et al. Clinical Orofacial Examination in Juvenile Idiopathic Arthritis: International Consensus-based Recommendations for Monitoring Patients in Clinical Practice and Research Studies. *J Rheumatol*. 2017;44(3):326-333. doi:10.3899/jrheum.160796
48. Hinks A, Martin P, Flynn E, et al. Subtype specific genetic associations for juvenile idiopathic arthritis: ERAP1 with the enthesitis related arthritis subtype and IL23R with juvenile psoriatic arthritis. *Arthritis Res Ther*. 2011;13(1):R12. Published 2011 Jan 31. doi:10.1186/ar3235
49. Hawkes JE, Yan BY, Chan TC, Krueger JG. Discovery of the IL-23/IL-17 Signaling Pathway and the Treatment of Psoriasis. *J Immunol*. 2018;201(6):1605-1613. doi:10.4049/jimmunol.1800013
50. Nelson EC, Dixon-Woods M, Batalden PB, et al. Patient focused registries can improve health, care, and science. *BMJ*. 2016;354:i3319. Published 2016 Jul 1. doi:10.1136/bmj.i3319