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Exploring Disease Patterns in the Long-Term Follow-Up of Juvenile Idiopathic Arthritis

Focus on Psoriasis, HLA-B27, and Temporomandibular Involvement

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Abstract

Ekelund, M. 2024. Exploring Disease Patterns in the Long-Term Follow-Up of Juvenile Idiopathic Arthritis. Focus on Psoriasis, HLA-B27, and Temporomandibular Involvement. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 2096. 85 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-2274-2.

Juvenile idiopathic arthritis (JIA) is an umbrella term encompassing a heterogeneous group of chronic arthritis in children. Many of these have significant differences from adult arthritis, while others possibly represent similar diseases in children and adults. Classification aims to enhance the understanding of the disease's pathogenesis, patterns of phenotypes, disease trajectories, and treatment responses.

Patient-reported outcome measures (PROMs) are invaluable for assessing disease burden and play an important role in co-producing optimal health care for the child with JIA.

This thesis has its origin in the Nordic JIA study, a population-based, prospective study of 510 children with newly diagnosed JIA who were included between 1997 and 1999. In the 8-year follow-up, we found that features associated with psoriasis were linked to more severe disease progression over time. A significant proportion of children with both psoriasis and arthritis were not classified as having juvenile psoriatic arthritis (JPsA). To ensure that these children receive early, personalized treatment, future classifications should include psoriasis and psoriasis-related characteristics as criteria.

In the 18-year follow-up, we studied temporomandibular joint (TMJ) arthritis. Orofacial symptoms and dysfunctions were common, and two-thirds of participants showed condylar deformities or erosions on cone-beam computed tomography (CBCT). An interdisciplinary approach is recommended to optimize management throughout the course of the disease.

The presence of HLA-B27 was associated with an increased risk of not being in remission off medication after 18 years of disease duration in males but not in females. Uveitis in HLA-B27 positive individuals is not always symptomatic, which clinicians need to be aware of.

The Juvenile Arthritis Multidimensional Assessment Report, JAMAR, was translated into Swedish and validated in a clinical setting. The Swedish JAMAR proved to be a reliable tool that can be used in both routine clinical practice and research. The responses from the questionnaire can also serve as a basis for discussions between patients and caregivers.

In conclusion, JIA is a complex disease requiring attention to multiple aspects. Our results highlight the need for better classification of psoriasis in JIA, the importance of careful and multidisciplinary follow-up for TMJ arthritis, and an association between HLA-B27 positivity and more severe disease. The Swedish version of JAMAR serves as a valuable complement to existing PROMs and has the potential to enhance health care for children with JIA.

Keywords: juvenile idiopathic arthritis, outcome, PROMs

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To all children with juvenile idiopathic arthritis

Figure 1. “Portrait of Sir Francis Ford’s Children Giving a Coin to a Beggar Boy”, Sir William Beechey 1793. Used with permission from Tate Gallery, London.

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 Pediatric Rheumatology (NoSPeR). (2017) Psoriasis and associated variables in classification and outcome of juvenile idiopathic arthritis - an eight-year follow-up study.
Pediatric Rheumatology. 2017 Feb 22;15 (1):13

II. Glerup M, Stoustrup P, Matzen LH, Rypdal V, Nordal E, Frid P, Arnstad ED, 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 TK. (2020) Longterm Outcomes of Temporomandibular Joints in Juvenile Idiopathic Arthritis: 17 Years of Followup of a Nordic Juvenile Idiopathic Arthritis Cohort.
The Journal of Rheumatology. 2020;47 (5):730-8

III. Ekelund M, Szentpetery A, Arnstad E D, Aalto K, Fasth A, Glerup M, Herlin T, Myrup C, Peltoniemi S, Rygg M, Rypdal V, Nordal E, Berntson L; Nordic Study Group of Pediatric Rheumatology (NoSPeR). HLA-B27 has wide clinical impact on juvenile idiopathic arthritis - Eighteen years of follow-up from the population-based Nordic cohort study.
Submitted.

IV. Ekelund M, Berntson L, Consolaro A, Bovis F and Ruperto N. (2018) The Swedish version of the Juvenile Arthritis Multidimensional Assessment Report (JAMAR).
Rheumatology International. 2018;38 (Suppl 1):371-7

Contents

Abbreviations

ACPA	Anti-citrullinated protein antibodies
ACR	American College of Rheumatology
ANA	Antinuclear antibodies
CASPAR	Classification criteria for psoriatic arthritis
CBCT	Cone-beam computed tomography
CHAQ	Childhood Health Assessment Questionnaire
CID	Clinical inactive disease
CT	Computed tomography
COX	Cyclooxygenase
DIP	Distal interphalangeal joint
DMARD	Disease modifying anti-rheumatic drug
ERA	Enthesitis-related arthritis
HAQ	Health Assessment Questionnaire
HLA-B27	Human leukocyte antigen B27
HRQoL	Health-related quality of life
ICC	Intraclass correlation coefficients
ILAR	International League of Associations for Rheumatology
JADAS	Juvenile Arthritis Disease Activity Score
JADI	Juvenile Arthritis Damage Index
JADI-A	Juvenile Arthritis Damage Index with Articular damage
JADI-E	Juvenile Arthritis Damage Index with Extra-articular damage
JAMAR	Juvenile Arthritis Multidimensional Assessment Report
JIA	Juvenile idiopathic arthritis
JPsA	Juvenile psoriatic arthritis
MIO	Maximal incisal opening
MMPs	Metalloproteinases
NoSPeR	Nordic Study Group for Paediatric Rheumatology
PhGA	Physician Global Assessment
PR-COIN	The Pediatric Rheumatology Care and Outcomes Improvement Network
PROMs	Patient-reported outcome measures
PREMs	Patient-reported experience measures
PtGA	Patient/Caregiver-Proxy Global Assessment
PsA	Psoriatic arthritis
QOL	Quality of life

RA	Rheumatoid arthritis
RF	Rheumatoid factor
SpA	Spondyloarthropathy
TMJ	Temporomandibular joint
UCR	Uppsala Clinical Research Center
VAS	Visual analogue scale

Preface

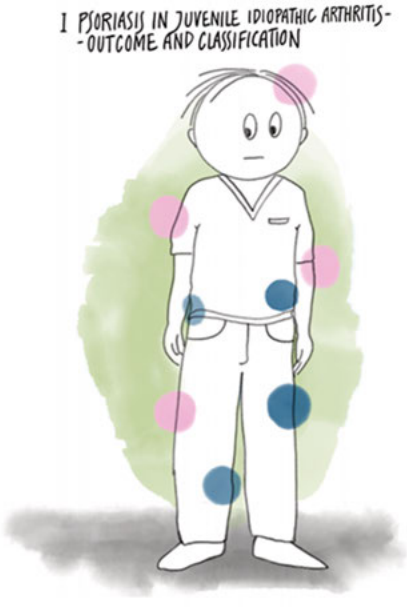
My interest in paediatric rheumatology began by chance during my residency at the department of paediatrics. A young doctor was needed in the rheumatology team and my modest experience from orthopaedics proved useful. The welcoming and supportive atmosphere, both locally and at national paediatric rheumatology meetings, made me feel at home.

Paediatric rheumatology appeals to me for several reasons: the opportunity to meet children of different ages with varying severity of disease, the collaboration with the child, family and healthcare team, and the dynamic nature of the field. When I was a young doctor in the mid-90s, biologics were new and the few available doses were reserved for the most severe cases. At that time, it was not uncommon for patients to need hip replacements before transferring from the paediatric department or to suffer severe visual impairment from uveitis. The field of immunology is fascinating, with significant advancements having been made over the years. The toolkit for treating rheumatic diseases has expanded and while juvenile arthritis cannot yet be cured, treatment options have vastly improved.

I was involved in establishing the first Swedish quality registry for paediatric rheumatology, and later I was invited to join the Nordic Study Group for Paediatric Rheumatology by Dr. Lillemor Berntson, who eventually became my main supervisor. My research journey has been long and somewhat winding. Clinical work, and later management, captured my interest, leading me to pause my research after completing a licentiate thesis in 2020. However, after stepping down from my role as head of department, I was fortunate to be able to resume my research. I am honoured to continue the path of clinical research in paediatric rheumatology that my mentor and former boss, Boel Andersson Gäre, introduced me to. In many ways, it feels like the circle is complete, as my main supervisor, Lillemor, was also supervised by Boel and Anders Fasth. Interestingly, Anders was also Boel's supervisor. Are you following? ☺

With this thesis, I can finally tie up the loose ends. The common theme of the four studies presented here is the pursuit of a better understanding of juvenile idiopathic arthritis, with the ultimate goal of improving outcomes for these children.

Thesis at a glance



Illustrations by Karin Grönberg 2024

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 that affect most of the joints, having 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. Except for the systemic category, JIA is considered an autoimmune disease, probably 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 not known 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 this, we also need a better understanding of different aspects of complex chronic diseases, such as JIA. Patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs) are invaluable complements in assessing disease burden and important for co-producing optimal health care of the child. It is possible that 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.

A historical perspective on JIA

Juvenile arthritis, specifically what is now referred to as JIA, was first described in the late 19th century. The earliest detailed descriptions of the disease were provided by M.S Diamantberger in Paris in 1890. He described three different types of disease course and particularly mentioned the form affecting the eyes (1). In 1897 Sir George Frederic Still, a British paediatrician, described a condition in children characterized by persistent joint inflammation, fever, and enlargement of the spleen and lymph nodes (2). This condition came to be known as Still's disease and is now recognized as systemic

juvenile idiopathic arthritis (sJIA), one of the categories of JIA. Prior to Still's detailed descriptions, there were references to joint pain and swelling in children, but it was Still's work that provided a clear clinical characterization of juvenile arthritis as a distinct entity from adult forms of arthritis.

Children and adolescents with what may have been JIA have been depicted in art works created much earlier. The most famous examples are Botticelli's *Portrait of a Youth* from 1483 (3) and Caravaggio's *Il Amore Dormien* from 1608, although the latter may have depicted rickets rather than JIA (4, 5). In Sir William Beechey's *Portrait of Sir Francis Ford's Children Giving a Coin to a Beggar Boy* from 1793, the beggar boy displays multiple articular abnormalities that are clearly diagnostic of JIA. This differs from previous reports of JIA depicted in other paintings which typically portray only single articular changes (6). If you look closely, you can even detect what appears to be skin rashes on the elbow (Figure 1). Could this possibly be psoriasis? If so, this might be the earliest artistic representation of juvenile psoriatic arthritis.

The treatment of JIA has seen significant advancements over the past century. Improved diagnostic criteria and awareness have enabled earlier detection of JIA, even though children's access to health care varies greatly around the world (7). Early and aggressive treatment, often referred to as a 'treat-to-target' approach, aims to achieve early remission, preventing joint damage and improving long-term outcomes (8-10). The prognosis for children with JIA has improved dramatically. Many children now achieve clinical remission, either with or without ongoing medication, and go on to live active lives (11).

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. Such analyses can, among other things, serve as a basis for healthcare planning.

In paediatric rheumatology, epidemiological studies describe the incidence, prevalence, natural history, and outcomes of different disease entities, and they enable the identification of possible aetiologic and prognostic factors. A population-based study provides the most robust method for obtaining accurate figures for incidence, but is often time-consuming and costly. In order to obtain reliable numbers, it is crucial how the cases are identified and to take into account the population studied. A hospital-based study will recruit more severe cases than an outpatient-based study. Different classification criteria

will also produce different figures. Incidence rates given for chronic arthritis in European studies vary substantially (1.3-31.7/100 000) (12, 13). The large variation can partly be explained by factors such as the use of different methods for recruiting participants, the genetic background of inflammatory diseases, and different infectious panoramas.

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 have been set. Classification also aims to give us a better understanding of the pathogenesis, patterns, disease trajectories and treatment responses. The age limit of 16 years can be debated, especially considering that the WHO defines childhood as extending until 18 years of age. This limit was likely set because, historically, paediatric rheumatologists referred patients at that age to adult rheumatology. There is no data supporting a biological cut-off.

Sets of classification criteria were suggested both in the USA (the ACR-American College of Rheumatology-criteria) (14, 15) and in Europe (the EULAR - The European League Against Rheumatism - criteria) in 1977 (16). Unfortunately, the definitions for inclusion and subgroups were not aligned, 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 (17). The criteria were revised in 1997 and are known as the Durban criteria (Table 1) (18). This classification describes six different, mutually exclusive forms called categories defined by clinical and laboratory measures: systemic arthritis, oligoarticular arthritis (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 cases that 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 also been used for clinical purposes.

Table 1. The ILAR criteria, definitions and exclusions, 1997 (18).

General Definition of JIA
Juvenile idiopathic arthritis is arthritis of unknown etiology that begins before the 16th birthday and persists for at least 6 weeks; other known conditions are excluded**.**

Exclusions
The principle of this classification is that all categories of JIA are mutually exclusive. This principle is reflected in the list of possible exclusions for each category:
a. Psoriasis or a history of psoriasis in the patient or first degree relative.
b. Arthritis in an HLA-B27 positive male beginning after the 6th birthday.
c. Ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis, or a history of one of these disorders in a first-degree relative.
d. The presence of IgM rheumatoid factor on at least 2 occasions at least 3 months apart.
e. The presence of systemic JIA in the patient

Systemic arthritis
Definition: Arthritis in one or more joints with or preceded by fever of at least 2 weeks' duration that is documented to be daily ("quotidian") for at least 3 days, and accompanied by one or more of the following:
1. Evanescent (nonfixed) erythematous rash
2. Generalized lymph node enlargement
3. Hepatomegaly and/or splenomegaly
4. Serositis
Exclusions: a, b, c, d

Oligoarthritis
Definition: Arthritis affecting one to 4 joints during the first 6 months of disease. Two subcategories are recognised:
1. Persistent oligoarthritis: Affecting not more than 4 joints throughout the disease course
2. Extended oligoarthritis: Affecting a total of more than 4 joints after the first 6 months of disease
Exclusions: a, b, c, d, e.

Polyarthritis (RF-negative)
Definition: Arthritis affecting 5 or more joints during the first 6 months of disease; a test for RF is negative.
Exclusions: a, b, c, d, e.

Polyarthritis (Rheumatoid Factor Positive)
Definition: Arthritis affecting 5 or more joints during the first 6 months of disease; 2 or more tests for RF at least 3 months apart during the first 6 months of disease are positive.
Exclusions: a, b, c, e.

Psoriatic Arthritis
Definition: Arthritis and psoriasis, or arthritis and at least 2 of the following:
1. Dactylitis
2. Nail pitting or onycholysis
3. Psoriasis in a first-degree relative
Exclusions: b, c, d, e.

Enthesitis Related Arthritis
Definition: Arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following:
1. The presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain
2. The presence of HLA-B27 antigen
3. Onset of arthritis in a male over 6 years of age
4. Acute (symptomatic) anterior uveitis
5. History of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative
Exclusions: a, d, e

Undifferentiated Arthritis
Definition: Arthritis that fulfills criteria in no category or in 2 or more of the above categories.

Time plays an important role in the classification of JIA. At onset, it can be challenging to accurately classify JIA into a specific category, since the clinical picture may still be evolving. The onset type of arthritis is determined by the clinical findings, including number of joints affected within the first six months of the disease, biomarkers and heredity, whereas the course type reflects the disease's progression after this period. As symptoms develop over time, the initial classification may need revision. Studies have shown that changes in JIA categories continue to occur in 10-13% of patients, even far beyond the first year of the disease (19, 20).

The classification of JIA is a continuous work in progress as new knowledge is accumulated regarding genetics, aetiology and pathogenesis. This has resulted in attempts to reach consensus concerning the identification of more homogeneous clinical groups and to distinguish the forms of chronic arthritis typically seen only in children from their childhood counterparts in adult diseases (21).

The most common onset category of juvenile arthritis is oligoarticular arthritis. 'Oligo' is derived from Greek and means 'few' (22). Although the limit of five joints may be somewhat arbitrary, this category is associated with the best prognosis, including a milder disease course and a higher rate of remission. It is also the category that most frequently changes into other categories.

This thesis focuses on the subgroup JPsA, the clinical manifestations of arthritis of the temporomandibular joint, TMJ, and also the influence of human leukocyte antigen B27 (HLA-B27) on clinical manifestations and outcome. Current views regarding these are presented briefly below.

Psoriatic arthritis in children

Of all children with JIA, only around 5-7% are classified as JPsA in population-based studies (23-25). On the other hand, we know from a long-term population-based follow-up study that the psoriatic arthritis group increased significantly after 18 years since some of the clinical characteristics take time to develop and will therefore change the earlier classification (20). The ILAR criteria for diagnosis of 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 frequently criticized, particularly in the case of JPsA (25-27). A biphasic distribution of age of onset has been noted (17). 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. There are some inconsistencies within the classification itself, particularly with reference to the presence of psoriasis or a family history of psoriasis. The Vancouver criteria (Table 2) were proposed by Southwood et al. in 1989 (28). 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 their proposal for a new classification, Martini et al. suggest that the presence of psoriasis is not a reliable criterion for classification, and patients with JIA will therefore end up in any of the other categories (21).

Table 2. Classification criteria for psoriatic arthritis in children, Vancouver, 1989 (Southwood et al. (28)).

Definite JPsA
Arthritis beginning before age of 16 years *and either* Typical psoriasis *or* At least three of four minor criteria as follows: 1. Dactylitis 2. Nail pitting 3. Psoriasis-like rash 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

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) (29). Applying CASPAR criteria in children with JIA has been proposed, however it has been scarcely studied, especially in patients followed over a long period of time (30, 31).

Table 3. The Classification Criteria for Psoriatic Arthritis (CASPAR), 2006 (29).

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)

Clinical features of JPsA

Articular features

Joint pattern can be diverse. In the youngest children 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 (32). Features of spondyloarthropathy (SpA), for example sacroiliitis, most often develop over time (33).

Dactylitis

It has been recognised that a key clinical feature favouring 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 (34) (Figure 2). Around 20-40% of patients with JPsA have dactylitis, as does an even greater proportion of children who present before the age of six years (28, 34). Studies support the view that innate immunity in an autoinflammatory response can have a pathogenetic role in linking psoriasis and arthritis, as does nail involvement (35).

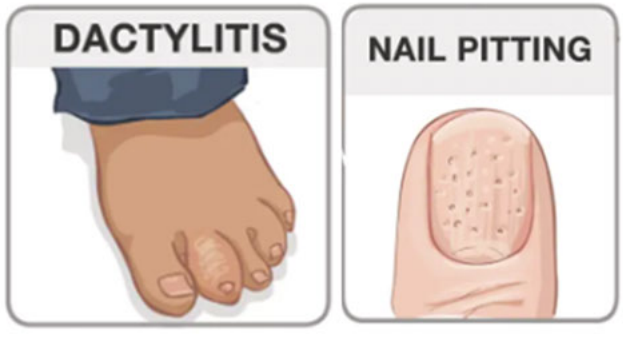


Figure 2. Dacylitis and nail pitting. © 2004-2024 About Kids Health

Extra-articular manifestations

It is known that the relationship between the onset of joint and skin manifestations varies. In up to 50% of patients, the arthritis precedes the psoriasis, sometimes with a long interval between the onset of arthritis and the onset of a typical psoriatic rash (28, 36). By far the most common extra-articular manifestations are vulgaris lesions on the skin, found 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 (Figure 2). 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 (25, 37).

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 starts before 20 years of age in 30% of cases (38). Health insurance data indicate a total rate of psoriasis in children younger than 18 years of 0.71%, while in adults the prevalence is 2-3% (39). 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, with about 30% of children with psoriasis reporting an immediate family member who also has the disease (40). While plaque lesions are the most common, facial and genital lesions are also frequently observed in children (41). In adult psoriasis, particularly in severe disease, there is evidence for increased cardiovascular and metabolic comorbidity (42). Studies in paediatric populations also suggest an increased risk of metabolic dysfunction and significant impacts on quality of life (43, 44).

Arthritis of the temporomandibular joint

Arthritis of the TMJ was described as early as 1897 by Still (2). Although often clinically silent initially, with mild symptoms, it is a well-recognised entity in JIA. Estimates of the prevalence of TMJ involvement vary widely, ranging from 40-86% in different studies. The large variation in estimates likely resulted from differences in inclusion criteria, such as variable types of JIA and differences in disease duration. In a recent population-based study of 613 patients followed for four years, the cumulative incidence of involvement of the TMJ in patients with JIA was 30.1%. Furthermore, 20.6% of the cohort had developed arthritis-induced dentofacial deformity (45). All categories of JIA are at risk of developing TMJ arthritis (46). There are reported cases of mono-arthritis of the TMJ being the only JIA manifestation (47, 48). The assessment of TMJ arthritis requires multidisciplinary cooperation according to the recommendations of the Temporomandibular Joint Juvenile Arthritis Work (TMJaw) Group (49).

Anatomy

The TMJ is a complex joint described as ginglymoarthrodial, meaning that it has both a hinged and a 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 (50) (Figure 3); the disc divides the joint into the superior and inferior compartments (51). The TMJ differs from other joints in the body. Unlike most synovial joints, which are lined with hyaline cartilage, the articular surface of the TMJ is composed of fibrocartilage (52).

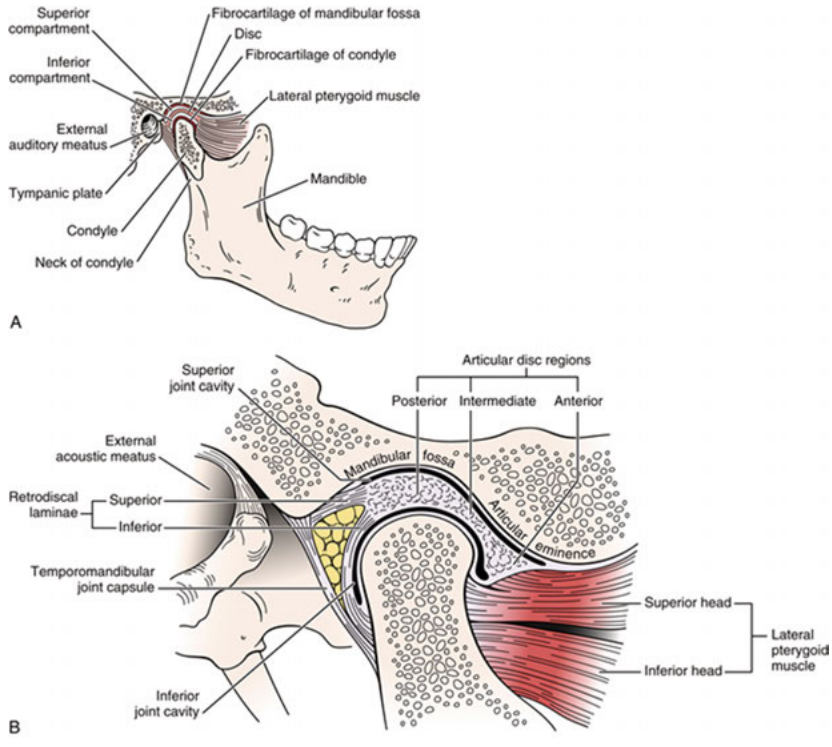


Figure 3. A) The temporomandibular joint (TMJ). B) Close-up of TMJ. From Orthopedic Physical Assessment. Magee D.J. et al, 2021, with permission (50).

Symptoms and complications

Early in the course of TMJ arthritis, symptoms are often vague and difficult to assess by clinical investigation due to the absence of swelling of the joint. Later, symptoms such as pain, stiffness and chewing limitations may impair function. Inflammation of the TMJ may impact condylar growth, and retrognathia and micrognathia may follow (53). Unilateral TMJ involvement may cause facial asymmetry.

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 (54). A variety of modalities can be used to image the TMJ, and access to these 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 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. Magnetic Resonance Imaging (MRI) has been shown to be the only method that can diagnose TMJ arthritis early, before structural changes have developed (55), but has the disadvantage of requiring sedation of the youngest children. Ultrasound (US) has advantages in terms of cost and the lack of need for sedation, but its ability to identify active inflammation and arthritic sequelae as accurately as MRI with contrast remains uncertain. 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 (56).

Human leukocyte antigen-B27 (HLA-B27)

HLA proteins are responsible for presenting antigens to the immune system, helping the body to distinguish between self and non-self. These proteins are encoded by the major histocompatibility complex (MHC). The MHC is divided into two main classes: MHC Class I and MHC Class II. HLA-B27 belongs to MHC Class I, which is found on the surface of nearly all nucleated cells. It is thought that HLA-B27 may misfold or present certain peptides in a way that triggers an inappropriate immune response, leading to inflammation and autoimmunity. HLA-B27 itself encompasses different alleles that encode different proteins. HLA-B*2705 is the most widespread B27 subtype (57).

HLA-B27 occur at varying frequencies in different populations and ethnic groups. For example, 10-16% of the population in Northern Norway, Northern Sweden, Finland, and Iceland carry HLA-B27, while the frequency in Denmark and Western Europe is 6-9% (58, 59).

HLA-B27 is most commonly associated with autoimmune diseases, particularly ankylosing spondylitis and enthesitis-related arthritis, although the exact mechanisms remain unclear (60). While HLA-B27 is not required for the diagnosis of ERA, it is one of the factors included in the ILAR criteria. Characteristic features of childhood arthritis in HLA-B27 positive individuals include: asymmetrical arthritis (involving a few large joints, such as knees, ankles, or hips), enthesitis (inflammation at tendon attachment points), potential progression to axial involvement (affecting the spine and sacroiliac joints) (61). Onset typically occurs in late childhood or early adolescence, with boys being more affected than girls. While HLA-B27 positivity is linked to more severe disease in some cases, the course of the disease can vary widely among individuals (62-64).

Overall, HLA-B27 is a significant genetic factor in the development and management of ERA in JIA, but it is only one piece of the puzzle, with other genetic and environmental factors also playing a role.

Outcome measures and the patient's voice

The measurement of clinical, functional, and quality of life outcomes in JIA is of fundamental importance to patients, families, clinicians and researchers. Numerous clinical measures have been developed and validated to monitor disease and treatment courses over the years (65). The goal of an effective outcome measure is to create an evaluable endpoint that can assess the impact of an intervention or treatment. Ideally, the instruments used should be reliable (consistently producing the same results), valid (accurately measuring what they intend to measure), responsive (able to detect changes over time and differentiate between items), and feasible, according to the core principles of instrument validation in the widely accepted Outcome Measures in Rheumatology (OMERACT) (66) (Figure 4).

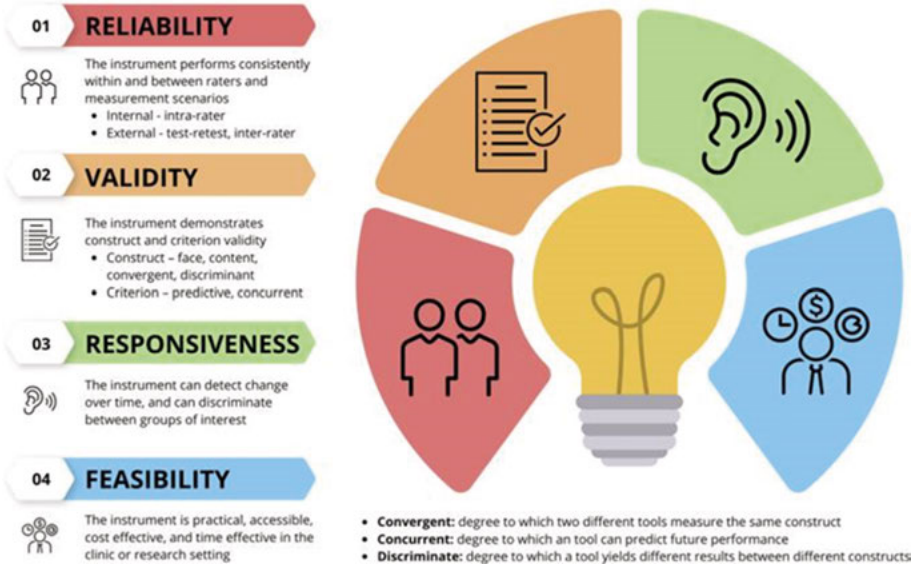


Figure 4. Features of an ideal outcome measure include reliability, validity, responsiveness, and feasibility. Balay-Dustrude et al., Open Access Rheumatology Research and Reviews, 2023 15 189-206. Originally published by and used with permission from Dove Medical Press Ltd (66).

Patient and caregiver-reported outcomes (PROs) and quality of life (QOL) assessments reflect the experiences and difficulties encountered by families

dealing with the disease. These tools offer a detailed understanding of the patient's overall functioning by considering aspects such as medication side effects, the impact of the disease on quality of life, and emotional or psychological and social challenges. Integrating PRO measures into the routine clinical care of patients with juvenile idiopathic arthritis can support a shift from physician-centred to patient-centred care (67, 68), and even further to person/family-centred care (69).

Several clinical outcome measures are used in the Nordic JIA study. Some of them are briefly described here as is the composite tool that was translated into Swedish and validated in paper IV.

Physician Global Assessment (PhGA) is a widely accepted measure of overall JIA clinical disease status used in both clinical practice and research. PhGA captures the examiner's subjective appraisal of a patient's disease activity at the time of visit. It rates the level of a child's disease activity on a visual analogue scale (VAS) with anchors of '0 = no activity' and '100 = maximum activity'. PhGA is a part of multiple other composite disease status assessments, for example juvenile arthritis disease activity score (JADAS) (70) and ACR criteria for defining clinically inactive disease (CID) (71, 72). Several studies show that the scoring of the PhGA is divergent, both between professionals and over time (73-75). Consensus on PhGA scoring guidelines would be required to obtain a consistent assessment of patients.

Patient/Caregiver-Proxy Global Assessment (PtGA)
The PtGA tool is similar to the PhGA and is a VAS scored from 0–100 mm. It is used in both clinical practice and research settings as a general measure of the patient's or caregiver-proxy's perception of the current JIA disease status and overall well-being, as it relates to the patient's rheumatologic condition. Work is currently underway within the OMERACT JIA working group to better define, establish, and validate a tool for measuring patient perception of disease activity and overall well-being.

Childhood Health Assessment Questionnaire (CHAQ)
The CHAQ was developed as early as 1994 by Singh et al. (76). This tool is composed of a disability index with eight domains: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities. Each domain uses a Likert scale to rate the difficulty of completing tasks (0 = no difficulty to 3 = unable to do). The discomfort index has two domains: pain score and PtGA score, each using a 0–100 VAS.

CHAQ is widely used in clinical settings and research studies to monitor the progression of JIA and the effectiveness of treatments in improving a child's functional ability (77).

The Wallace Criteria

The American College of Rheumatology (ACR) Provisional Criteria for Defining Clinical Inactive Disease (CID) and Clinical Remission (CR), the Wallace criteria, were introduced in 2004 and validated in 2006 (71, 72). Five criteria are used for defining CID: no joints with active arthritis; no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; no active uveitis; normal erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) (if both are tested, both must be normal); and PhGA indicating no disease activity (i.e., best score attainable on the scale used, typically 0/10), over 12 months. To be considered in remission on medication, the time criterion is six months.

Juvenile Arthritis Disease Activity Score (JADAS) and its clinical (cJADAS) and systemic (sJADAS) variations

JADAS is used to monitor disease activity over time, guide treatment decisions, and evaluate the effectiveness of interventions in managing JIA (70). JADAS includes four key components:

1. **Number of active joints**: Counts the joints with active inflammation.
2. **Physician's global assessment of disease activity**: A VAS where the physician rates overall disease activity.
3. **Parent/patient global assessment of well-being**: A VAS reflecting how the patient or their parent perceives the patient's overall well-being.
4. **ESR** or **CRP**: These are optional inflammatory markers used to reflect systemic inflammation.

Different versions of JADAS exist, such as JADAS-10, JADAS-27, and JADAS-71, based on the number of joints assessed.

Juvenile Arthritis Damage Index, Articular and Extra-Articular Damage (JADI – A/E)

The JADI, introduced in 2005 by Viola et al., has established a clinical index for the assessment of long-term damage in JIA (78). JADI is divided into two parts:

1. **JADI-A (Articular Index)**: This part assesses damage in the joints. It includes items such as joint deformities, limitations in range of motion, and other permanent joint-related issues.
2. **JADI-E (Extra-articular Index)**: This part assesses damage outside the joints, such as in the eyes (e.g., uveitis), lungs, cardiovascular system, and other organ systems.

The tool uses a scoring system where each item is evaluated, and higher scores indicate more significant damage.

Juvenile Arthritis Multidimensional Assessment Report (JAMAR)
JAMAR is a comprehensive tool used for the assessment of patients with juvenile idiopathic arthritis (JIA) from the patient's and parent's perspectives. It was introduced in 2010 by Filocamo et al. (79), and includes assessments of overall well-being, pain, functional status, and QOL, as well as other PRO not addressed by conventional instruments. These are measurement of morning stiffness and overall level of disease activity, rating of disease status and course, proxy- or self-assessment of joint involvement and extra articular symptoms, description of side effects of medications, and assessment of therapeutic compliance and satisfaction with outcome. The JAMAR questionnaires can be found in Appendix 1.

The tool was designed to be used in a busy clinic, ideally administered prior to the clinic visit while the patient is waiting to be seen, and can be completed in 15 minutes.

The JAMAR has been translated to 54 languages across 52 countries through the Paediatric Rheumatology International Trials Organisation (PRINTO) organization (80).

Aetiology and pathogenesis of JIA

The cause of JIA is complex and several factors seem to play a role. Although knowledge has increased over time, the word "idiopathic" still continues to reflect the uncertainty surrounding its origin.

Genetic factors are known to be of importance in JIA, with different associations in various categories. Prahalad's studies of monozygotic twins with JIA showing 44% concordance, indicate a strong genetic component (81). Studies on affected pairs of siblings also suggest a major contribution of HLA to the genetic susceptibility to JIA (82, 83). Both HLA class I (HLA A-2, and HLA B27) and HLA class II (HLADRB1 and HLA DP) alleles have been reported to be associated with different phenotypes of JIA (84). Non-HLA genetic markers linked to autoimmune responses and immune tolerance mechanisms also seem to be involved. Polymorphisms in genes involved in immune regulation, such as PTPN22 and IL2RA, have also been associated with JIA (85).

Environmental factors have been studied in relation to JIA. It is assumed that a genetically susceptible individual can develop an uncontrolled response towards a self-antigen on exposure to an environmental trigger. The exact pathogens involved remain unclear, but infections can stimulate immune responses that lead to inflammation in joints and the innate and adaptive immune systems closely interact. A prospective study from Sweden, where over 10 000 children were followed from birth, showed that a short duration (< 4 months) of exclusive, as well as partial, breastfeeding was associated with an increased risk of JIA (86). Regarding infections, some studies have shown associations between a recent viral infection and onset of JIA, however other studies have not been able to confirm these results (87-89). A case-control study of 225 JIA cases by Shenoi et al., showed no association with smoking, early-life infection, or breastfeeding and development of JIA (90). Associations between antibiotic exposure prior to JIA diagnosis have been found, suggesting dysbiosis, an imbalance in gut microbiota, as a potential contributor to JIA (91).

JIA is considered to be an autoimmune condition, where the immune system mistakenly attacks the body's own tissues, particularly the synovium in joints. This immune dysregulation is central to the disease process. Earlier research

supports the view that both innate and adaptive immune responses are implicated in JIA development. However, the subtype sJIA is considered an autoinflammatory disease associated mainly with defects in the innate immune system (92).

The key pathological feature of JIA is chronic inflammation of the synovial membrane (93, 94). Dysregulation in T cells, particularly Th17 cells, has been linked to the development of inflammation. Studies have demonstrated that dysregulated function of T cells and/or their inadequate balance are associated with the pathogenesis of autoimmune conditions, possibly also in JIA (95, 96). These cells produce pro-inflammatory cytokines that contribute to joint destruction. The overproduction of pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6 is a hallmark of JIA. These cytokines promote the recruitment of immune cells to the joint, leading to synovitis and joint damage. On the other hand, the normal regulation by anti-inflammatory cytokines (e.g., IL-10, TGF-β) is impaired, allowing chronic inflammation to persist. B cells also have important roles in JIA pathogenesis not only through autoantibody production, but also through cytokine release and/or T cell activation (97). The detection of autoantibodies, such as antinuclear antibodies (ANA), RF and anti-citrullinated protein antibodies (ACPA), supports the idea of a breakdown in B cell tolerance.

In response to chronic inflammation, the synovial lining thickens (synovial hyperplasia) and, over time, pannus formation occurs (Figure 5). This aggressive tissue invades the cartilage and bone causing progressive joint damage. Continuous inflammation leads to the breakdown of cartilage and erosion of bone. This process is mediated by enzymes such as matrix metalloproteinases (MMPs) and osteoclast activation, leading to joint deformity and loss of function (98). Inflammation also promotes angiogenesis, the formation of new blood vessels in the synovium. Increased blood flow perpetuates the inflammatory process, facilitating the recruitment of immune cells to the joint.

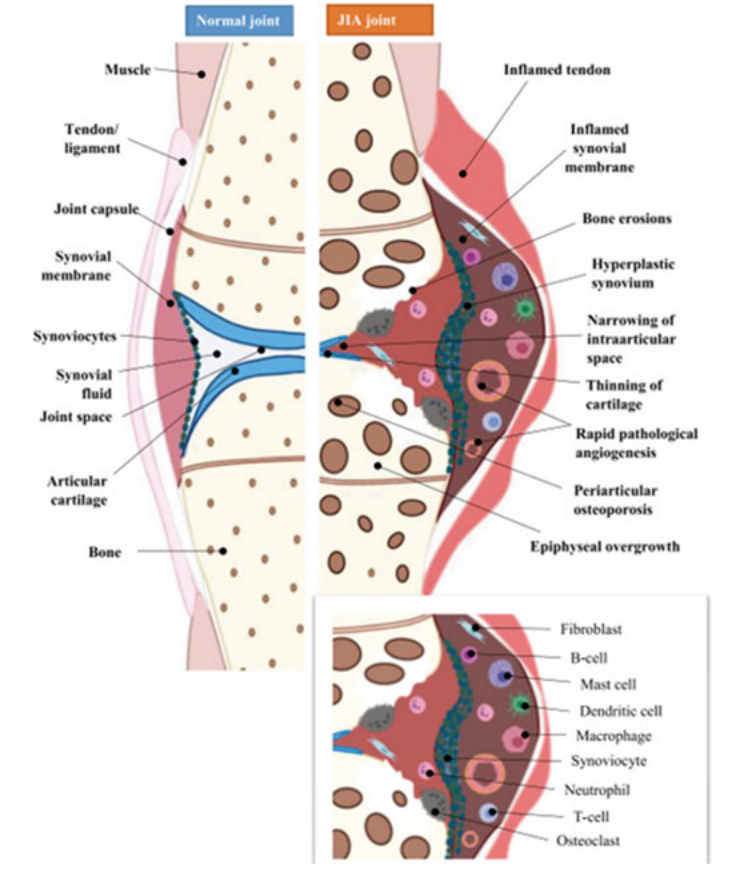


Figure 5. Schematic picture showing the differences between the normal and JIA joint. From Zaripova et al., reprinted with permission (98).

Modern treatment of JIA

While a detailed discussion of the medical treatment of JIA is beyond the scope of this dissertation, it is essential to acknowledge the remarkable treatment possibilities available today. The focus of treatment is on managing symptoms, reducing inflammation, and preventing joint damage. The Treat to Target (T2T) strategy, which involves adjusting treatments to achieve specific outcomes, was officially recommended for the first time by an international task force in 2018 (8). The main treatment options for JIA include:

Pharmacological treatment

1. **Cyclooxygenase (COX) inhibitors:** Reduce pain and inflammation, commonly used as the first line of treatment during a limited period.
2. **Intra-articular corticosteroid injections**: Reduce local inflammation and pain, providing quick and effective relief.
3. **Disease-Modifying Antirheumatic Drugs (DMARDs)**: As the name implicates, these slow the progression of the disease and protect joints from long-term damage. The DMARDs can be divided into:
    1. Conventional Synthetic **(**csDMARDs)
    2. Targeted synthetic (tsDMARDs)
    3. Biologic (bDMARDs)

The most commonly used csDMARD, methotrexate, has been used in Sweden since the mid-1980s. Originally developed for use in haematology and oncology, it is administered in low doses as an immunomodulating drug, given either orally or subcutaneously once a week (99, 100).

When methotrexate is insufficient, a bDMARD is usually added, or sometimes given as a single therapy (101). Tumour necrosis factor (TNF) inhibitors were the first bDMARDs introduced in the early 21st century. TNF inhibitors are either monoclonal antibodies (human or chimeric) that target the TNF receptor, or a human dimeric fusion protein consisting of part of the TNF receptor linked to the Fc portion of human IgG1. TNF inhibitors are administered via subcutaneous injection or intravenous infusion. Other bDMARDs used in JIA

include interleukin (IL) inhibitors, targeting receptors for IL-6 and IL-1, which are also administered by subcutaneous injection or intravenous infusion.

The latest addition to the treatment options is the class of tsDMARDs, which primarily consists of Janus kinase (JAK) inhibitors (102). These work by blocking the autophosphorylation of Janus kinases, which is triggered by cytokine-induced receptor activation. This inhibition impacts intracellular signalling pathways involved in the inflammatory process. Unlike biologics that target extracellular molecules, JAK inhibitors act inside the cell, offering a novel mechanism of action. They also have the advantage of being taken orally, providing a convenient alternative to injectable biologics. However, there is a risk of side effects, as several cellular processes involve JAK-signalling.

Non-pharmacological treatment

In addition to pharmacological therapy, physical therapy is essential for maintaining joint flexibility, strength, and overall mobility. A balanced diet, regular exercise, and psychological support also play key roles in enhancing quality of life and the management of the condition. A dedicated multidisciplinary team, co-producing health care together with the patient and their family, creates the best conditions for successful treatment.

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 was designed to be population-based. Originally 510 children were included during the three-year collection period.

The NoSPeR study has so far produced material for seven dissertations and several publications in international journals of rheumatology. The research group has expanded over the years and offers an active and learning environment for both experienced and less experienced researchers in the field of paediatric rheumatology.

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 seen in other Western countries. Approximately 66% of the children in the study were girls, the median age of onset of the disease was six years, and about half of the patients had a diagnosis of oligoarthritis at their six-month visit (103).

In total, 440 children (88%) were re-examined after at least seven years, with a median follow-up period 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 (104). Approximately 50% had ongoing medication eight years after disease onset. On the other hand, 50% of the participants were in remission without medication, according to the Wallace criteria (71). The majority of those in remission belonged to the persistent oligoarticular category or to the systemic JIA category (19). The occurrence of ankle arthritis during the first year was associated with an unfavourable disease outcome (105).

The aim of the18-year follow-up was to further examine 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. A total of 434 of the 510 original participants were followed up and almost half of them had active disease

(106). Uveitis had developed in 22% and the presence of antinuclear antibodies (ANAs) was a risk factor for developing one or more ocular complications (107). Early self-reported, disease-related pain was common and seems to predict persistent pain and unfavourable long-term disease outcomes (108). Fatigue was found to be a prominent symptom, with higher fatigue burden among participants with poor sleep, pain, self-reported health problems, active disease, or use of DMARDs/biologics (109). The transition to adult rheumatology clinics in the Nordic countries was studied and 40% of the patients were directly transferred to adult rheumatology. As many as 39% of those participants who had not yet transferred were found to have disease activity at the study visit, implicating a need for better transition programs (110). Inflammatory biomarkers measured in serum at baseline have the potential to improve evaluation of disease activity and prediction of long-term outcomes (111). A prediction model for the non-achievement of remission and a severe disease course, combining active joint count, physician global assessment of disease activity, morning stiffness, and ankle involvement, has been developed and tested on a Canadian cohort (112, 113).

Aims

Overall aim

The objective of this thesis was to deepen the understanding of disease activity and long-term outcomes in JIA, focusing on JPsA, TMJ arthritis and HLA-B27, including both clinical and lived experience perspectives, with the ultimate goal of improving treatment strategies and enhancing the overall health and well-being of patients.

Specific aims

Paper I

To describe the disease course of JPsA over the first eight years, focusing on clinical characteristics, classification, and outcomes.

Paper II

To assess the prevalence of orofacial symptoms in JIA compared to age-matched healthy controls, estimate the prevalence of TMJ deformities assessed by CBCT, and identify predictors for developing radiological TMJ deformities.

Paper III

To investigate the associations between HLA-B27, clinical features, and disease outcomes, during the first 18 years after onset of JIA.

Paper IV

To cross-culturally adapt and validate the Swedish child and parent versions of the Juvenile Arthritis Multidimensional Assessment Report (JAMAR).

Methods

Study populations

Papers I-III are based on data from the Nordic JIA cohort, a prospective, multicentre study that included consecutive cases of newly diagnosed children with JIA from defined geographical regions in Denmark, Finland, Norway, and Sweden (Figure 6). The inclusion period spanned from January 1, 1997 to June 30, 2000, during which the incidence of JIA in the study area was 15 per 100,000 children per year (103). Paediatric rheumatologists from 12 participating centres registered all children diagnosed with JIA according to the ILAR criteria.

In the Nordic countries, healthcare services, including visits to primary care physicians and public hospitals, are generally free of charge for children younger than 16 years. In addition, this includes routine visits to child health centres for preschool-aged children. To ensure the study was as population-based as possible, letters were repeatedly sent to primary healthcare services, and to orthopaedic, paediatric, and rheumatology specialists in the catchment areas throughout the inclusion period, urging them to refer potentially eligible patients.

Family histories, comprehensive clinical data, including full joint counts, medications used, health assessments completed by the patient or their parents, and blood test results were systematically recorded at each study visit. The baseline visit occurred approximately six months (-1/+2 months) after disease onset, defined as the date the patient, parents, or doctor first reported arthritis symptoms, defined as swelling of a joint or limitation of motion with heat, pain or tenderness. The date of diagnosis was recorded as the day a paediatric rheumatologist confirmed the JIA diagnosis.

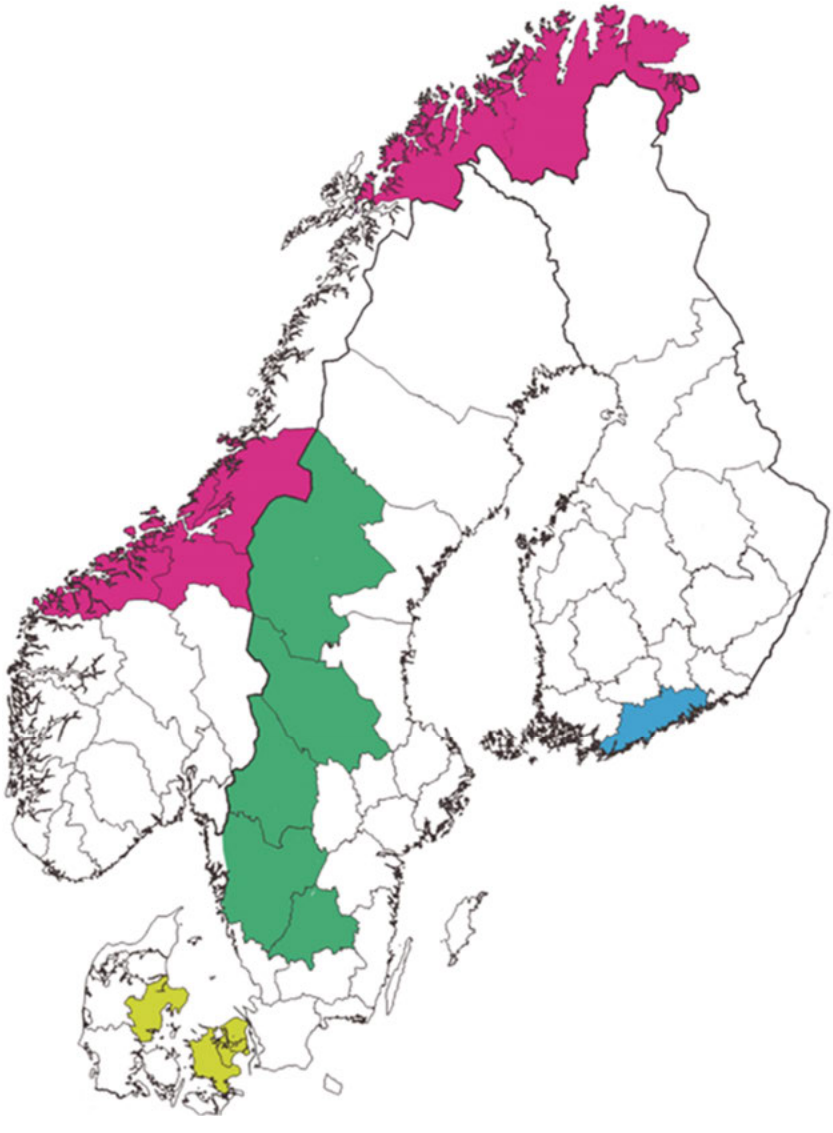


Figure 6. Map of the Nordic countries and the catchment areas.

Study I was based on an eight-year follow-up of participants in the Nordic JIA cohort (Figure 7). Participants were sent an invitation letter, followed by a reminder. Those who did not respond were contacted by phone and invited to attend a follow-up visit. In cases where an in-person visit was not feasible, participants were offered a standardized telephone interview. This interview covered all the data typically collected during an in-person visit, and participants were asked to complete and return relevant questionnaires. Additional

information, including updates on family history, was gathered as part of this process.

Studies II and III were based on the 18-year follow-up of the Nordic JIA cohort (Figure 7). All 510 previously included participants were invited to take part, regardless of their medical history, disease course, or disease activity levels. Participants unable to attend in-person visits were offered a standardized telephone interview, which included electronic completion of the validated Health Assessment Questionnaire (HAQ) and PtGA. For those attending clinical visits, blood samples were collected, and an updated family and medication history was obtained. Comprehensive clinical data, including joint examination findings, were recorded. To ensure accuracy in reported outcomes, such as remission status and disease activity over the previous 10 years, electronic medical records were cross-checked with participant-reported data. All participants who met the ILAR criteria for JIA and had attended at least two study visits were eligible for inclusion.

In centres that were able to offer temporomandibular joint (TMJ) examinations using cone-beam computed tomography (CBCT), study participants also underwent a standardized clinical orofacial examination (Figure 7). In the TMJ study, a control group of non-selected, age-matched Danish individuals (n=200), aged between 18 and 30 years, was included for comparison. The controls were healthy volunteers without a history of arthritis, osteoarthritis, cleft lip/palate, craniofacial anomalies, or ongoing orthodontic treatment. They underwent the same orofacial examination as the JIA group and reported their symptoms using the same web-based questionnaire. For ethical reasons, CBCT was not performed on the healthy controls. This was a case-control study comparing healthy controls with the cases from the Nordic JIA cohort.

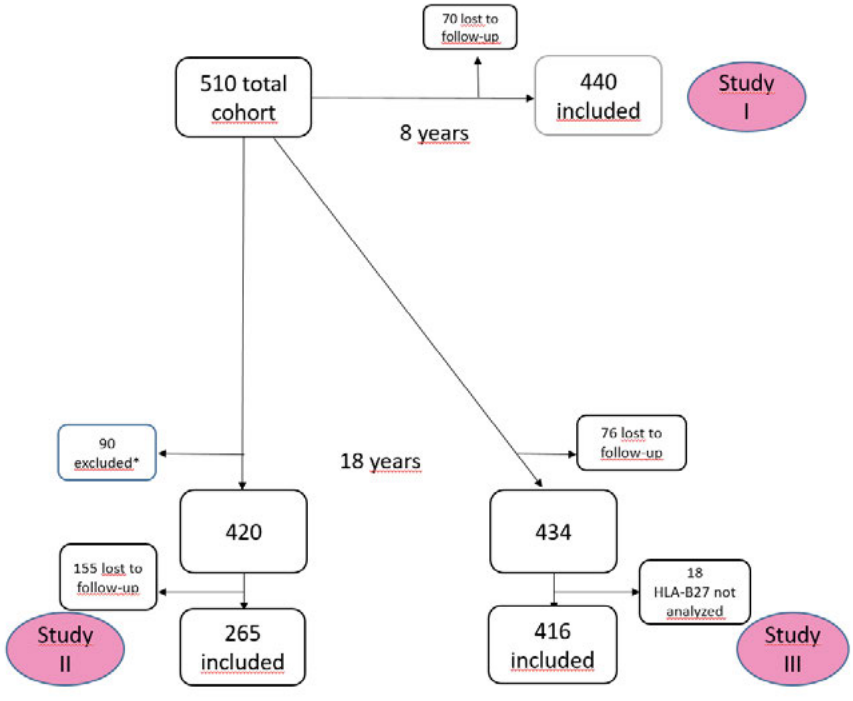


Figure 7. Flow chart of the 8-year follow-up study of JPsA and the 18-year follow-up studies on TMJ arthritis and HLA-B27.

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

Study IV was a cross-sectional study of children with JIA, classified according to the ILAR-criteria. The comprehension and understanding of the translated questionnaire JAMAR were first tested in a pilot sample of ten parents and ten patients and were found acceptable. Following this, clinical data were collected from all consecutive patients seen over a six-month period at the paediatric rheumatology outpatient clinics in Jönköping and Uppsala, and the JAMAR questionnaire was administered. The JAMAR questionnaire was also distributed to a sample of healthy children and their parents for comparison. The controls were siblings of patients with JIA, and children of employees at the paediatric department and their friends.

The JAMAR has been selected for use in the assessment of patient-reported outcome measures (PROMs) in a multinational study aimed at investigating the epidemiology, treatment, and outcome of childhood arthritis worldwide (EPOCA Study). The primary goal of the study is to gather information on the frequency of JIA categories in different geographical regions, the therapeutic interventions used by paediatric rheumatologists across various countries and

continents, and the current disease and health status of children with JIA globally. Additional objectives include examining the availability of biologic medications in developing countries and promoting regular, quantitative, clinical assessments of children with JIA as part of standard clinical care (114, 115).

Statistical analysis

Papers I-III

Statistical analyses were conducted using the *Statistical Package for Social Sciences* (SPSS) versions 22 or 23 (SPSS Inc., Chicago, IL, USA). Depending on the data type and analysis requirements, a variety of descriptive and inferential methods were used.

Descriptive Statistics

- Demographic and disease-related characteristics were described using either mean ± standard deviation (SD) for normally distributed data or median and interquartile range (IQR) for non-normally distributed data.
- Total counts and percentages of study participants were presented where applicable.

Group Comparisons

- The chi-square test, or Fisher's exact test (two-sided) when necessary, was used to compare dichotomous variables.
- For non-parametric data, the Mann-Whitney U test was used to compare medians between groups.
- Z-scores were reported where standardized test statistics were applied to ordinal data.

Logistic Regression

- Logistic regression models were used to analyse associations between various predictors and outcomes, such as remission or the development of specific clinical changes (e.g., psoriasiform rashes or condylar changes).
- Odds ratios (OR) with 95% confidence intervals (CI) were reported along with p-values.
- A significance level of $p < 0.05$ was applied in all analyses. Variables such as age at disease onset and gender were included in certain models.

Interrater Reliability

- Cohen's kappa coefficient was used to assess interrater reliability for categorical measurements in some studies.

Paper IV

The methodology using cross-cultural adaptation and psychometric evaluation of the JAMAR has been described in detail by Bovis et al. (80). Components of validity, internal consistency, inter-scale correlation and reliability were tested using scientifically established methods. Quantitative data were reported as medians with 1st and 3rd quartiles and categorical data as absolute frequencies and percentages.

Ethical considerations

A critical ethical question arises: Is it justifiable to conduct this type of research in paediatric rheumatology? While clinical research inevitably carries some risk, the potential benefits of the studies in this thesis far outweigh the possible harms. Children with JIA endure long-term suffering, and the disease impacts their quality of life and places emotional strain on their families. The lifelong need for costly medications adds a further burden. Conducting research aimed at improving treatment outcomes, enhancing quality of life, and potentially reducing healthcare costs is not only ethically sound but also a societal imperative. This research provides an opportunity to alleviate suffering and contribute to more effective, personalized treatment strategies that benefit both patients and their families.

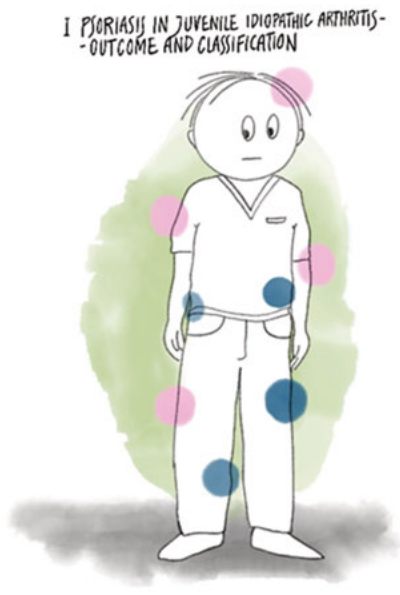
With this ethical foundation, the study group took care to ensure that the well-being of participants was prioritized throughout the research. An important ethical consideration in all studies was the potential risk of causing physical or emotional stress to participants. However, these risks were minimized by data being collected anonymously, coded on forms, and reported only as aggregated group data, reducing the risk of privacy invasion. The design of the study emphasized both ethical rigor and the careful management of potential stress, ensuring the research was carried out responsibly and respectfully.

The investigators in studies I-III took great care to resolve any concerns and provided guidance to participants if further health care was needed. Participants in remission who were offered an additional check-up as part of the study were given the opportunity to discuss their previous symptoms and treatments in more detail. Throughout the study, many participants and families

expressed feeling that they had received additional care as a result of their participation.

The Research Ethics Committees in each country approved the studies in accordance with national regulations. In Sweden, the Regional Research Ethics Committee at Uppsala University granted approval for Paper I (D.nr. 2004, M-357). Written informed consent was obtained from participants aged 15 years and older and from the parents or legal guardians of younger children. Informed assent was also obtained from children younger than 15 years, with slight variations between countries. For Papers II and III, approval was obtained from the national research committees of all participating countries. In Sweden, the Regional Research Ethics Committee at Linköping University granted approval (D.nr. 2014/413-31) and all participants provided written consent. For Paper IV, the Regional Research Ethics Committee at Linköping University granted approval (D.nr. 2012/342-31). Written informed consent was obtained from participants aged 15 years and older, and from the parents or legal guardians of younger children.

Results



Paper I

This paper examines the progression of juvenile psoriatic arthritis (JPsA) over the first eight years of follow-up in the Nordic JIA cohort, with a focus on clinical characteristics, classification, and outcomes.

A total of 440 participants were followed for at least seven years, with a median follow-up period of 98 months. The distribution of different JIA categories is shown in Figure 8. The participants lost to follow-up did not differ from those with complete follow-up data in terms of the number of active joints within the first six months of disease onset, Childhood Health Assessment Questionnaire (CHAQ) scores, Juvenile Arthritis Disease Activity Score (JADAS 27), or the proportion with oligoarticular disease at baseline. Additionally, there were no significant differences in the occurrence of psoriasis, psoriasis-like rashes, dactylitis, enthesitis, or first-degree family history of psoriasis or psoriatic arthritis between those lost to follow-up and those who remained in the study cohort.

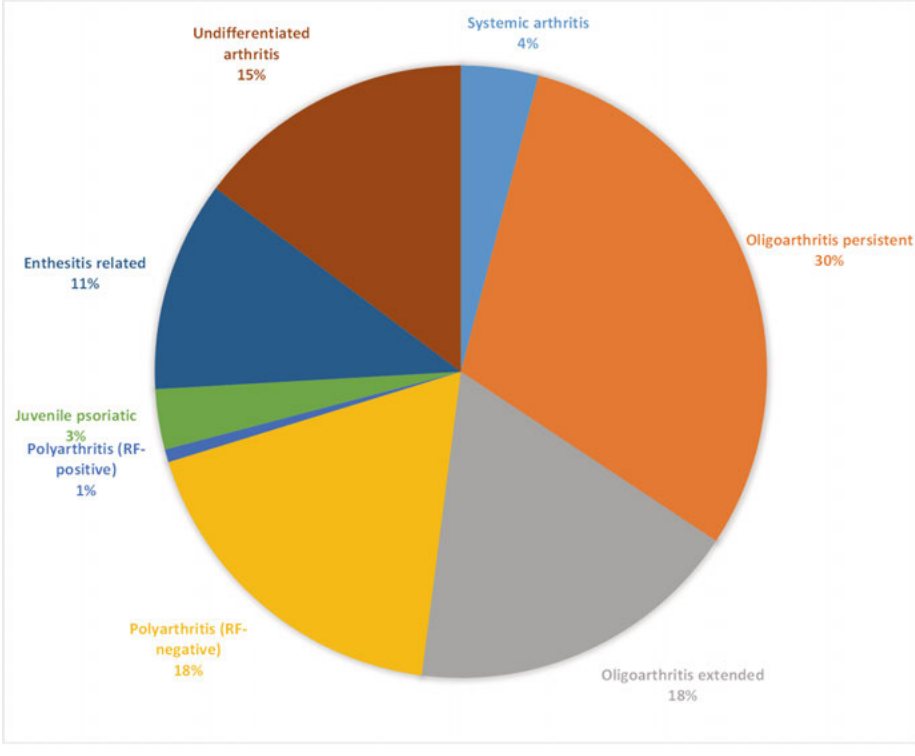


Figure 8. JIA categories at 8-year follow-up of 440 individuals.

Clinical features associated with psoriasis developed progressively during the follow-up period. In a cohort of 440 children followed for at least seven years after disease onset (median 98 months, range 84–147 months), 14 children had developed psoriasis and 13 a psoriasis-like rash.

Of the 14 children with both psoriasis and JIA, eight were classified as having juvenile psoriatic arthritis (JPsA) according to the ILAR criteria (Figure 9).

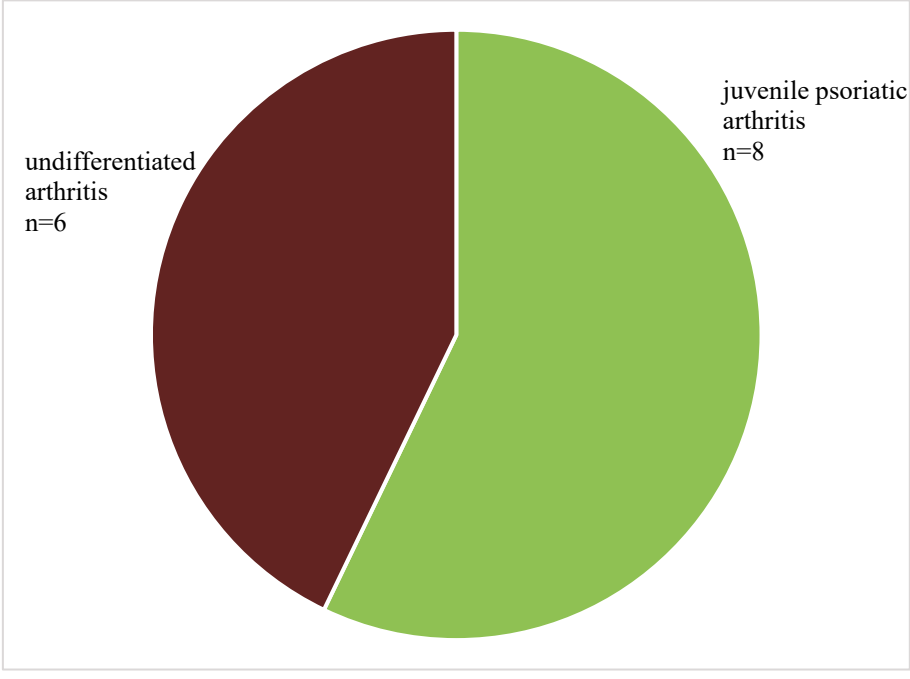


Figure 9. JIA categories at 8-year follow-up of 14 individuals with arthritis and psoriasis.

Clinical features associated with psoriasis emerged during the first eight years of the disease. Twenty-four children developed dactylitis, with 15 of these presenting at the onset of JIA. The median age at JIA onset in the group with dactylitis was 2.4 years (IQR 1.7–5.4), compared to 5.8 years (IQR 2.7–9.9) in the rest of the cohort ($p = 0.007$). Five of the 24 children with dactylitis had developed either psoriasis or a psoriasis-like rash during the first eight years of arthritis (Table 4). Table 4 also shows a significantly higher cumulative number of active joints in children with psoriasis or a psoriasis-like rash, along with an increased frequency of dactylitis, nail pitting, enthesitis, and first-degree heredity for psoriasis compared to children without psoriasis or a psoriasis-like rash.

Table 4. Clinical characteristics according to occurrence of psoriasis or psoriasis-like rash in the Nordic cohort of children with juvenile idiopathic arthritis.

Clinical feature	Total cohort n=440	Psoriasis or psoriasis-like rash n=27	No psoriasis or psoriasis-like rash n=413	p-value*
Female, n (%)	291(66.1)	13 (48.1)	278 (67.3)	0.06[a]
Age at time of onset, median (IQR)	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)	6 (2-12)	11 (5-16)	6(2-12)	0.02 [c]
Dactylitis (%)	24	5 (18.5)	19 (4.6)	0.01
Nail pitting (%)	18	7 (25.9)	11 (2.7)	<0.001
First-degree heredity for psoriasis or psoriatic arthritis (%)	51	7 (25.9)	44 (10.6)	0.03
Enthesitis (%)	41	6 (22.2)	35 (8.5)	0.03
Tenosynovitis (%)	88	6 (22.2)	82 (19.8)	0.81

*Patients with psoriasis and 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) had developed in several children with psoriasis or psoriasis-like rash. The coexistence of SI or enthesitis with psoriasis or psoriasis-like rash led to mutual exclusion from both the JPsA and ERA categories. Of the 27 children with psoriasis or psoriasis-like rash, seven were HLA-B27 positive (with three missing data points). This HLA-B27 positive group had a higher age of onset (median 10.8 years, IQR 5.9–11.8) and a higher cumulative number of joints involved (median 15, IQR 9–18). Several features of ERA or SI-like conditions appeared in clusters. Six of the 27 children with psoriasis or psoriasis-like rash experienced inflammatory back or buttock pain within the first 98 months of disease; three of these were HLA-B27 positive, and sacroiliitis was confirmed by X-ray in two.

Among children with psoriasis, psoriasis-like rash, or at least two of the following features: dactylitis, nail pitting, or first-degree family history of psoriasis, the remission rate was significantly lower compared to children without these clinical features.

Paper II

In this study we aimed to assess the prevalence of orofacial symptoms in JIA compared to age-matched healthy controls, estimate the prevalence of TMJ deformities assessed by CBCT, and identify predictors for developing radiological TMJ deformities.

In total, 265 participants with JIA were included in this study (mean age 23.5 ± SD 4.2 years) (Figure 7). The mean follow-up time from JIA onset to orofacial examination was 17.3 years (SD± 1.3 years); 186/265 (70.2%) were girls. 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 years 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.

Orofacial Symptoms: Out of 265 JIA participants, 87 (32.8%) reported at least one TMJ-related symptom at follow-up, similar to the control group. However, JIA participants experienced higher frequencies of orofacial pain, TMJ pain, morning stiffness, and chewing limitations. Specifically, 89 (33.6%) JIA participants reported jaw and/or facial pain in the past two weeks, compared to 61 (30.5%) in the control group (p = 0.48). Controls reported pain less frequently and less intensively than JIA participants, with more reporting pain less than once a week (71% vs 53%) and fewer experiencing pain multiple times a day (7% vs 27%).

Dysfunction: A total of 136 JIA participants (51.3%) had at least one sign of orofacial dysfunction, similar to controls. The most common findings were TMJ and orofacial pain on palpation. The mean maximal incisal opening (MIO) was significantly lower in JIA participants (47.2 ± 7.7 mm) compared to controls (56.5 ± 6.8 mm; $p < 0.001$). JIA participants were more likely to have a MIO < -2 SD ($p < 0.001$) and more frequent TMJ pain on palpation ($p = 0.03$). No significant differences were found in orofacial pain on palpation or asymmetric mouth opening between the groups.

Disease Status and Clinical Findings: Among the 265 JIA participants, 162 (61.1%) had inactive disease. Of these, 34 (12.8%) were in remission on medication, 99 (37.4%) without medication, and 29 (10.9%) had inactive disease but did not meet remission criteria. In this group, 38 (23.5%) reported orofacial symptoms and 70 (43.2%) showed clinical signs of dysfunction. Specific findings included 38 (23.5%) with jaw or facial pain, 16 (9.9%) with morning stiffness, 11 (6.8%) with chewing limitations, and 7 (4.3%) with jaw locking. Reduced MIO was observed in 22 (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%).

Radiologic Findings: Normal CBCT of both TMJs was found in 96 of 245 JIA participants (39.2%). Abnormal TMJ appearances were noted in 149 (60.8%), with 104 (69.8%) having bilateral deformities. Out of 253 joints with CBCT changes, 119 (47.0%) had deformities, 24 (9.5%) had erosions, and 110 (43.5%) had both deformities and erosions. 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%), although TMJ deformities were present across all JIA categories. TMJ pain on palpation doubled the odds of having an abnormal TMJ on CBCT (OR 2.1, 95% CI 1.08–4.1), and a strong association was found with MIO < -2 SD (OR 7.5, 95% CI 2.7–20.6). All 27 participants who received at least one intra-articular TMJ injection had abnormal condylar findings on CBCT, with 63.0% having erosions and deformities.

Association with Baseline Predictors and Clinical Characteristics: Multivariate logistic regression revealed that a baseline active joint count > 4 was positively associated with condylar deformities/erosions, while the presence of HLA-B27 was negatively associated. At the eight-year follow-up, a cumulative joint count > 4 and ERA category were associated with condylar changes. Treatment with biologics and orofacial dysfunctions at 17 years were linked to a higher risk of TMJ deformity ($p = 0.02$ and $p < 0.01$, respectively). Individuals in the ERA category had a lower risk of TMJ deformities.

Paper III

This study explored the associations between HLA-B27, clinical features, disease category, and long-term outcomes at 18 years after onset of JIA.

A total of 434 of the 510 eligible participants (85%) attended the 18-year follow-up visit. HLA-B27 status was determined in 416 individuals, with 93 testing positive. There was a significantly higher prevalence of HLA-B27 in males compared to females, 30.1% vs. 18.7% ($p = 0.01$). While HLA-B27 positive individuals were represented in all seven JIA categories, the highest prevalence was, as expected, in the ERA category (79.5%), followed by the undifferentiated category (27.3%) (Figure 9).

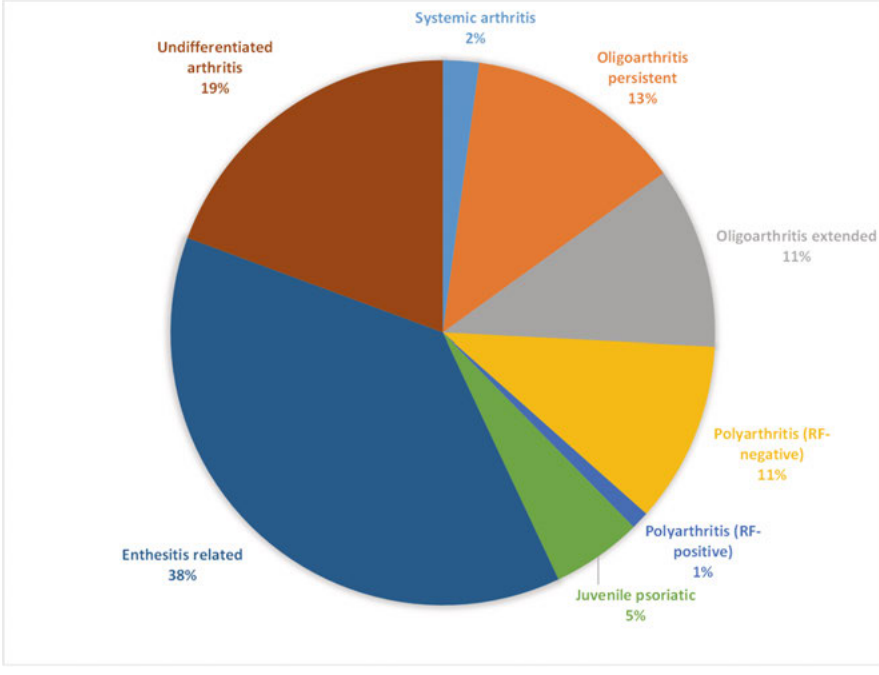


Figure 9. Categories of juvenile idiopathic arthritis in a Nordic cohort of 93 HLA-B27 positive individuals.

The average age at disease onset was higher in HLA-B27-positive individuals (8.3 years) compared to HLA-B27-negative individuals (5.3 years), regardless of gender. Uveitis, inflammatory back pain, tenderness over the sacroiliac joints, sacroiliitis on imaging, and enthesitis during the disease course were all significantly more common in HLA-B27-positive individuals. Among males who were HLA-B27 positive, these clinical features – including inflammatory back pain, sacroiliac joint tenderness, sacroiliitis, and enthesitis – were notably more frequent compared to HLA-B27-positive females. Importantly, 14 out of 30 HLA-B27-positive individuals with uveitis were asymptomatic.

HLA-B27-positive individuals were also more likely to have a first- or second-degree relative with ankylosing spondylitis compared to HLA-B27-negative individuals. Additionally, they were more likely to have a relative with symptomatic uveitis. However, there was no significant difference in the familial occurrence of JIA or rheumatoid arthritis (RA) between HLA-B27-positive and HLA-B27-negative individuals.

Differences in joint involvement over time based on HLA-B27 status were studied. The sacroiliac, hip, and subtalar joints were more frequently affected

in HLA-B27-positive individuals compared to HLA-B27-negative individuals. Among males, involvement of the sacroiliac, hip, subtalar, and metatarsophalangeal (MTP) joints was more common compared to females.

Remission data were available for 406 individuals with known HLA-B27 status. Overall, HLA-B27-positive individuals had an odds ratio (OR) of 2.6 (95% CI 1.5-4.3) for not achieving remission after 18 years compared to HLA-B27-negative individuals. The risk of not being in remission was significantly higher for HLA-B27-positive males (OR = 5.6, 95% CI 2.3-13.7) than for HLA-B27-positive females (OR = 1.7, 95% CI 0.9-3.3).

We also observed that sacroiliitis, enthesitis, and arthritis of the hip, tarsal, and subtalar joints, as well as uveitis, were associated with a significantly higher OR for not achieving remission off medication after 18 years. Among HLA-B27-positive individuals, only inflammatory back pain, enthesitis, and uveitis were linked to an increased risk of not being in remission.

Paper IV

The aim of this study was to cross-culturally adapt and validate the Swedish child and parent versions of the Juvenile Arthritis Multidimensional Assessment Report (JAMAR).

Demographic and clinical characteristics of the subjects

A total of 68 JIA patients and 76 healthy children were enrolled. Among the JIA patients, oligoarthritis was the most common category (44.1%), followed by undifferentiated arthritis (14.8%) and enthesitis-related arthritis (11.8%).

Cross-Cultural Adaptation

The Swedish JAMAR was adapted for cross-cultural use, with high concordance rates between the original English version and the back-translations (88.6% for the parent version, 83.3% for the child version). Both the parent and child versions were well understood, with at least 80% comprehension of all lines by participants.

Validity, consistency and reliability

The JAMAR differentiated between JIA patients and healthy children effectively, highlighting greater disability, pain, and reduced quality of life among the patients (Table 5).

Table 5. Descriptive statistics (medians, interquartile range (IQR) or absolute frequencies and %) for 68 JIA patients and 76 healthy controls.

	All JIA patients n=68	Healthy n=76
Female	48 (70.6 %)	38 (50 %)
Age at visit	12.1 (7.7-16.2)	9.1 (6.3-12.7)
Physical function	2 (0-6)	0 (0-0)
Pain VAS	2.5 (0-5.5)	0 (0-0)
HRQoLPhysical health	4 (1-7)	0 (0-0)
HRQoL Psychosocial health	2 (1-4)	0 (0-2)
HRQoL Total score	6 (2-13)	0 (0-2)
Morning stiffness <15 min	30 (45.5 %)	0 (0 %)
Problems attending school	18/45 (40 %)	0 (0 %)

VAS=visual analogue scale (score 0–10; 0 = no activity, 10 = maximum activity), PF=physical function (total score ranges from 0 to 45), HRQoL=Health-Related Quality of Life (total score ranges from 0 to 30), PhH=Physical Health (total score ranges from 0 to 15), PsH=Psychosocial Health (total score ranges from 0 to 15).
45 of 68 JIA patients were school children.

The psychometric performance of the JAMAR showed strong internal consistency, with Cronbach's alpha values ranging from 0.79 to 0.93 across different subscales, indicating reliable measurements. Inter-scale correlations revealed good alignment between items within scales, and the test-retest reliability demonstrated almost perfect reproducibility, with intraclass correlation coefficients (ICCs) above 0.90.

Convergent validity analysis showed significant correlations between the JAMAR's functional and quality-of-life scales and key clinical outcomes, with the strongest correlations observed for the parent-reported pain and well-being assessments.

Discussion

Discussion of the results

The participants in the Nordic population-based JIA cohort have now been followed for 18 years. A substantial proportion of the individuals did not achieve clinical remission off medication despite the availability of new treatment options during the study period (106). In general, there is a high burden of disease in persons with JIA who have reached adulthood. This has also been shown in other cohorts (116-118). Studies highlight that co-production in health care – where patients, caregivers, and healthcare professionals collaborate in the design and delivery of care – is crucial for achieving optimal results (119). This collaborative approach ensures that care is more tailored to individual needs, enhances patient engagement, and improves overall health outcomes, especially in managing chronic diseases such as JIA (120). The Pediatric Rheumatology Care and Outcomes Improvement Network (PR-COIN) is an example of such an initiative (121).

One key aspect of this collaborative approach is the use of Patient-Reported Outcome Measures (PROMs) and Patient-Reported Experience Measures (PREMs). For example, tools such as JAMAR can provide valuable insights into the effectiveness of treatments and the progression of JIA from the patient's viewpoint. These measures help clinicians understand the subjective experiences of patients, leading to more personalized and effective care plans. On the other hand, PREMs assess patients' experiences of the healthcare service, including their satisfaction with care processes, communication, and overall service quality. By incorporating PREMs, healthcare services can identify areas in need of improvement, enhance patient satisfaction, and foster a more patient-centred approach. Integrating both PROMs and PREMs into the care process supports the co-production model by ensuring that patients' voices are heard and considered in decision-making. This not only leads to better alignment of treatments with patients' needs and preferences, but also promotes a more transparent and responsive healthcare environment. Overall, utilizing these measures within a co-production framework can significantly contribute to improved outcomes and a higher quality of care for patients with chronic conditions such as JIA.

The clinical manifestations of JIA develop over time, making it challenging to obtain a complete clinical picture shortly after onset. Different scores, criteria, and outcome measures are helpful in assessing the disease burden but only give a snapshot of a patient's health at a specific time-point. Dynamics in the disease evolution cannot be captured by recording average changes and subgroups of patients may have a different disease course. Learning from a longitudinal approach using trajectory modelling, which identifies subgroups of patients while simultaneously capturing their evolution across several clinical outcomes, has been reported from adult rheumatology (122) and recently also from the Nordic JIA study where the patient's global assessment of well-being was the most important driver of disease activity into adulthood assessed by cJADAS-10 (123). Hence, understanding, and also monitoring, the trajectory of JIA can be valuable. This can be relevant for JPsA and TMJ arthritis. Additionally, the impact of HLA-B27 can also be better understood through a trajectory-based approach.

Eight years after onset, a considerable proportion of the children in the Nordic JIA cohort with definite psoriasis were classified as undifferentiated JIA based on the exclusion criteria in the ILAR classification. Our data also present the heterogeneity 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 ILAR criteria aimed to create homogenous groups for research and for the comparison of different populations; however, these criteria seem to be less suitable for JPsA. 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 long-term perspective, we are concerned that if the ILAR criteria are used, these children will be excluded from future studies on new drugs targeting specific molecules involved in psoriatic disease. Unfortunately, the proposed new criteria where psoriasis is not considered at all will also be disadvantageous for the patients with JIA and psoriasis (21).

As mentioned earlier, a challenge in classification in general is the progression of the disease over time. Our data show the heterogeneity 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 (25, 28). 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 ILAR category, although our numbers do not have the power to allow analysis of each of 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. Others have reported that the ILAR criteria excluded almost 60% of those included using the Vancouver criteria (124). Dactylitis has proven a strong predictor of JPsA (34). Also, dactylitis is included in the criteria for psoriasis in adults, CASPAR (29). In our study cohort, the occurrence of dactylitis was spread over ILAR categories, but had a strong association with psoriasis or psoriasis-like rash. Enthesitis also 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 (19). Radiographic resemblance of dactylitis in JPsA to the condition in adult psoriatic arthritis and to common features of enthesitis has been reported (125).

Beyond the discussion of clinical aspects, studies on the immunogenicity and pathogenesis of the psoriatic disease over the whole age spectrum may provide the biological knowledge needed to improve diagnosis and therapy. Immunological research has revealed that cytokines in the IL-17 and IL-23 pathways promote skin and joint inflammation in psoriasis (126, 127). These molecules are now targeted with biologic drugs, which make it even more urgent to diagnose and classify children in a more accurate way. Intensified collaboration between physicians in paediatric and adult rheumatology clinics is important for the successful transition of young adults with JPsA from paediatric to adult care.

The detection of arthritis of the TMJ in JIA is a particular challenge, since it is initially silent with discrete symptoms and no visible swelling. Long-term follow-up data on population-based JIA cohorts from the biologic era are lacking, and comparisons with earlier studies are difficult due to differences in study design and definitions. We found no difference in self-reported orofacial pain between individuals with JIA and controls. Orofacial pain is a common finding in healthy adults. In the American OPPERA study of over 4500 adults, the prevalence of TMJ and/or facial pain was 19% (128). In our control group, the frequency was 33%, possibly due to a younger mean age, since the peak incidence of TMJ/facial pain occurs in the 25-34 year age group (129).

Extensive symptoms and dysfunctions of the TMJ were observed 18 years after disease onset, even in patients registered with inactive disease or remission, further emphasizing the need for continued standardized orofacial monitoring. There are few comparable studies concerning TMJ dysfunction. We found a higher prevalence of TMJ pain on palpation and reduced maximal incisal opening among the JIA participants compared to controls. TMJ pain on palpation was reported in 12% of patients in a study by Bakke et al., in contrast to 30% in our study (130). Other studies have reported the prevalence of reduced MIO at a similar frequency to our study (130, 131).

CBCT is a well-established method of detecting deformity and hard tissue changes of the TMJ. In 2018, Kellenberger suggested MRI for monitoring TMJ arthritis and published an additive scoring system to assess the osseous deformities (132); however, this had not been published when our study began and CBCT has previously been used for assessment of hard tissue changes (133, 134). In total, about 61% of the JIA participants in our study had at least one condyle with abnormal CBCT findings, and approximately 70% of these subjects had bilateral changes. This is somewhat higher than the findings in a study by Resnick et al., who reported TMJ abnormalities in 55% of their JIA patients at the age of 26 years, with 79% of those showing bilateral changes (131). Importantly, the presence of radiographic condylar changes does not necessarily indicate dentofacial deformity. However, early diagnosis of dentofacial deformity is crucial, since the success of treatment is significantly influenced by timely intervention (135).

Predictors of TMJ involvement in JIA have been studied over the years. Our finding that an active joint count of more than four is a predictor of TMJ involvement is consistent with previous studies (136, 137). The use of biologic DMARDs reflects a more severe disease and could explain why it predicts TMJ involvement. It is possible that, during the study, biologic treatments were administered only to the most severe cases, which may account for this association. We found a lower risk of condylar changes in the presence of HLA-B27, which has also been reported in other smaller studies (136, 138). One might wonder whether this finding relates to the antigen or the category of JIA associated with HLA-B27. However, the protective effect of the ERA category has not been previously documented. These findings require further investigation, especially since other results from the JIA cohort suggest a more severe disease course associated with HLA-B27. 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 (49, 139).

In our cohort, 22.4% of individuals were HLA-B27 positive, which is approximately twice as common as in the background population, where about 10% are HLA-B27 positive. HLA-B27 positivity was observed across all JIA categories and, not surprisingly, with the highest frequency in the enthesitis-related arthritis (ERA) group. After 8 years of disease, the HLA-B27-positive boys had significantly more cumulatively active joints compared to those who were HLA-B27 negative (64). However, this difference between HLA-B27-positive and negative individuals was not observed after 18 years.

At the 8-year follow-up, HLA-B27 was associated with clinical signs of sacroiliitis and enthesitis in boys. After 18 years, these features still remained

more common in HLA-B27-positive males, particularly affecting the hips and subtalar joints. This gender difference is not commonly reported in other studies. Notably, one-third of those with imaging-proven sacroiliitis in our cohort were HLA-B27 negative. An excessive focus on HLA-B27 in enthesitis-related arthritis (ERA) may lead to delays in the diagnosis of females, who, although they are fewer in number, deserve the same attention.

Uveitis, whether symptomatic or not, was significantly more common in HLA-B27-positive individuals. Our findings support previous studies indicating that uveitis can also be asymptomatic in HLA-B27-negative individuals, a fact clinicians should consider (140). This needs to be studied in more detail.

Interestingly, while HLA-B27-positive individuals were more likely to have first- or second-degree relatives with ankylosing spondylitis, we found no correlation with a family history of JIA or RA. This suggests that HLA-B27 does not influence the occurrence of these conditions.

Our results indicate that HLA-B27 positivity is associated with a higher risk of not achieving remission off medication after 18 years, although this was not significant in females. Despite this, the presence of spondyloarthropathy signs in females warrants attention. Our study confirms the association between HLA-B27 positivity and more severe disease outcomes. A strength of our study is its population-based design and long follow-up period; however, the small number of individuals with SI joint involvement and limited imaging restrict conclusions. Our classification method, combining inflammatory back pain with palpatory SI joint tenderness as clinical sacroiliitis, is supported by a new classification criteria for axial juvenile SpA by Weiss et al. (141). In conclusion, our study offers valuable insights into the long-term effects of HLA-B27 positivity in JIA, emphasizing gender differences and persistent clinical challenges. Our results also raise the question of whether screening for HLA-B27 should be considered for all patients with JIA, primarily to alert and monitor the risk of asymptomatic uveitis.

JAMAR is a relatively new patient/parent-reported outcome measure for JIA. In my experience, it functions well in a clinical setting. The translation into Swedish and the validation process was satisfactory, and the components demonstrated good psychometric properties. However, one concern is that the JAMAR questionnaire is quite extensive and takes time to complete, which can be challenging in a busy outpatient clinic. A digital version would allow patients to complete it in advance, either at home or in the waiting room. Integrating the data into the electronic health records or quality registry would facilitate long-term tracking of outcomes.

Some questions, particularly those related to school attendance difficulties and satisfaction with disease management, are complex and may be sensitive. Healthcare professionals must be proactive in reviewing and following up on any concerning responses. For example, issues related to school attendance may require coordination with teachers or educational support services, while dissatisfaction with disease management might necessitate adjustments in treatment or further counselling. Additionally, anxiety or worry about the disease itself is common in children with JIA and their families, and this emotional burden can significantly impact both quality of life and disease outcomes (142-144). It is, therefore, crucial that any expressions of worry or distress regarding the disease are captured through the questionnaire and addressed promptly.

One challenge in clinical research, especially in chronic conditions such as JIA, is the large number of different assessment scales and questionnaires used. While each tool may have a specific focus – physical function, disease activity, or psychosocial well-being – the total number can become overwhelming for participants. This may lead to response fatigue, rushed responses, or disengagement, which can compromise data quality. For children with a chronic illness and their families, the burden of completing multiple forms can add to their stress, especially when questions feel repetitive. For researchers, managing extensive data obtained from many different tools can be challenging, as it complicates analysis and may make it harder to draw clear conclusions. To address this, it would be beneficial to streamline assessment tools by selecting the most relevant and validated scales. Reducing redundancy and focusing on core outcomes would lessen the load on participants while ensuring high-quality data collection. Ultimately, balancing comprehensive data with minimizing participant burden is essential for both study success and patient experience.

Methodological considerations

Studies on the disease course and long-term outcomes of juvenile idiopathic arthritis (JIA) face significant limitations due to differences in study design. The main challenges include:

- **Selection bias** in study populations, which affects the generalizability of the findings.
- **Lack of standardized outcome measures**, which impairs comparability across studies.
- **Variations in treatment strategies**, making it difficult to compare older studies without biologic treatments with modern studies that have access to such treatments.

The Nordic JIA study uses a population-based cohort design to longitudinally assess JIA, aiming to collect data on the full spectrum of the disease, accurately observe outcomes, and minimize selection bias. Traditionally, many JIA outcome studies have been cross-sectional or retrospective, often from tertiary centres with highly selected cases, potentially skewing results towards more severe disease. The uniform healthcare system in Nordic countries, with free access to healthcare services and medications, provides a unique opportunity to reduce selection bias and study a large, homogeneous cohort (22, 117, 145). The goal was to design a study that was as population-based as possible, including all eligible children within the catchment areas. Undiagnosed cases are probably rare due to the regular check-ups provided by the Nordic healthcare system. Despite free and accessible healthcare services, milder cases might still be missed if not referred to a paediatric rheumatologist. To improve referrals, we sent repeated notifications to rheumatologists, orthopaedic and paediatric specialists, and primary care services in the targeted areas, asking them to refer all eligible children. We only included centres with a strong history in paediatric rheumatology within their catchment areas.

We standardized clinical assessments to minimize misclassification by discussing definitions within the group to reduce observer variation and ensure consistent data collection. Refusal to participate was minimal, with only three eligible patients declining to participate from start. Not everyone participated in the study; 12% in the 8-year follow-up and 15% in the 18-year follow-up did not participate. The average age of patients at the 18-year follow-up study was 24 years, an age when many individuals move around or travel frequently. Given the 18-year gap between baseline and the final follow-up, and that 94% would no longer be under paediatric care, the follow-up loss rate is lower than in other studies and must be judged to be acceptable (117, 146, 147). However, this loss may introduce selection bias. Despite this, lost participants did not differ significantly from those included in terms of baseline factors such as gender, age at onset, JIA category, CHAQ, JADAS, or active joint count. Twenty-four percent of participants in the 18-year follow-up completed a standardized telephone interview. This data is of lower quality compared to clinical visits, affecting the reliability of clinical data such as disease status and treatment. Consequently, we analysed disease status separately for clinical visits. To assess overall remission rates, we included data from both interviewed and clinically-examined participants. Since we cross-checked a majority of the telephone interview data with medical records, the information is reasonably reliable.

To reduce missing data and errors, all questionnaires were completed electronically in the online survey platform SurveyXact. However, transferring data from SurveyXact to Excel and then to statistical software can introduce

errors. We verified JIA category data by reviewing inclusion and exclusion criteria, and correcting inconsistencies in consultation with the responsible doctor, particularly regarding family history.

The population-based cohort design is a major strength of this study. The cohort was derived from a defined geographical area, intentionally including all eligible patients for prospective, longitudinal assessment, which enhances the external applicability of the results. Detailed clinical information and hereditary data were consistently collected, ensuring a well-categorized cohort. We also utilized validated measures, such as disease status of inactive disease, JADAS, and JADI scores, to facilitate comparisons with other studies. Another advantage is that we invited all patients to participate, regardless of their disease status. This contrasts with other long-term studies that typically include only patients receiving medication or those suspected of disease activity based on questionnaires. However, one limitation is that the inclusion period (1997-2000) coincided with the early biologic treatment era, which may affect long-term outcomes. Only six patients received biologic treatment within the median of 12 months post-onset, although 36.7% were using methotrexate within a year, comparable to results from the larger ReACCh-out cohort (148). Guzman et al. note that JIA treatment has evolved even within a short recruitment period, indicating that a long-term study fully applicable to current cohorts and treatment options may be unrealistic.

Additionally, the small sample sizes in some JIA categories, such as systemic, polyarticular RF+, and psoriatic, limit the interpretation and conclusions that can be drawn. It is also important to note that the timing of the baseline visit was approximately six months (-1/+2 months) after disease onset, which was when the assessment of JIA categories was feasible. For some patients, this may have been past the peak of disease activity, particularly affecting the interpretation of baseline predictors. Furthermore, JIA is characterized by a fluctuating course and a limitation of our study is the lack of data from the follow-up period between eight and eighteen years.

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Let us once again consider Beechey's Portrait of Sir Francis Ford's Children Giving a Coin to a Beggar Boy from 1793. In both art and paediatric rheumatology, the full picture is not always immediately clear. Just as a painting reveals deeper layers the more closely it is examined, so do medical conditions such as JIA. Over time, details emerge that may not have been visible at the outset. Longitudinal studies have taught us that certain symptoms, such as psoriasis, may not manifest early in the disease course. Similarly, TMJ arthritis can remain silent for years, making it difficult to detect without careful monitoring. HLA-B27 adds another layer of complexity, as its presence can influence disease progression and may lead to a different long-term outcome, often associated with more severe or persistent symptoms.

Despite these challenges, the outlook for children with JIA has improved dramatically. In Beechey's time there were few, if any, effective treatments for rheumatic conditions. It is likely that the Beggar Boy, even if he did have access to some form of health care, would not have had the means to afford treatment.

Moreover, in an era where patient perspectives were rarely considered, his experience of illness, pain, and disability would probably have gone unnoticed and unaddressed. Today, the situation is markedly different. Not only do we have more advanced treatments, but there is also a greater focus on the patient's voice – on understanding the child's experience, tracking outcomes over time, and tailoring care to improve quality of life.

In both art and medicine, it is through attention to evolving details that we gain a fuller understanding, leading to better outcomes.

Conclusions and clinical implications

In conclusion, this thesis contributes to the current understanding of JIA by describing the disease trajectory in a long-term follow-up during the early biologic era and, in addition, in a population-based setting. The key findings in relation to the aims are as follows:

Clinical findings associated with psoriasis developed progressively over the first 8 years of the disease. Children with arthritis and psoriasis tend to experience more severe disease progression over time. In the ILAR classification, a significant proportion of children with psoriasis and arthritis are not classified as having JPsA. Additionally, in a proposed new classification, psoriasis and psoriasis-related findings are not considered at all in the criteria. To ensure that children with both psoriasis and arthritis receive early, personalized treatment, future classifications should take psoriasis and psoriasis-related characteristics into account.

Orofacial symptoms were reported by one third of the participants 18 years after disease onset. Condylar deformities and/or erosions on CBCT were found in two thirds of the participants, from all JIA categories. Risk factors for condylar deformities were orofacial dysfunction and treatment with biologics, while the ERA category was protective. TMJ arthritis and its consequences can persist into adulthood. An interdisciplinary approach is recommended to optimize management throughout the course of the disease.

The presence of HLA-B27 was associated with an increased risk of not being in remission off medication after 18 years of disease in males but not in females. Uveitis in HLA-B27-positive individuals is not always symptomatic, which clinicians need to be aware of. Screening for HLA-B27 should be considered for all patients with JIA.

PROMs are an essential part of the health care of persons with JIA. The Swedish JAMAR is a valid tool for the assessment of children with JIA and can be used both in routine clinical practice and clinical research. The responses in the questionnaire can also serve as a starting point for conversations between patients and healthcare professionals.

Future studies

The Nordic JIA cohort offers numerous opportunities for further research on JIA. Plans are already in place for the next follow-up, 30 years after initial inclusion. One main challenge will be reaching a sufficient number of the participants, who are now adults with JIA. A significant task will be engaging physicians in adult rheumatology clinics in the follow-up, since their involvement will be crucial for effectively tracking long-term outcomes. The list of questionnaires and examinations that the study group would like to conduct is almost endless and agreeing on priorities, as well as securing funding and staffing, will be another challenge.

The ILAR classification of JPsA is inadequate, and the proposed new classification does not take psoriasis-related findings into account at all. This issue needs to be highlighted further and a better proposal needs to be developed.

JPsA and ERA share several common features and also overlap with SpA in adults. This warrants further detailed study, particularly regarding the potential applicability of the ASAS criteria.

TMJ arthritis is difficult to diagnose and there is a need to develop better clinical tools to identify cases that require further investigation with MRI.

The co-production of care by healthcare professionals and patients and their families is another area of interest for me, and one I would like to explore further, preferably together with patients and next of kin. PROMs and PREMs need to be developed to provide an accurate representation without being unnecessarily extensive and time-consuming. Initiatives such as ‘What Matters to Me’ and the ‘Dreamcatcher Project’ by the patient association Young Rheumatics would be fascinating to focus on. Perhaps we could scientifically examine the impact of these initiatives on well-being and the outcomes of JIA?

I am also interested in questions concerning equal access to care**.** Even when health care for children is free, as in Sweden, does this ensure that all children have the same opportunities when it comes to accessing medical services and medications? How can the healthcare system compensate for, and strengthen,

efforts to achieve equitable care for all children, regardless of their background or geographical location?

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 oftast 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. Möjligheterna att med läkemedel behandla JIA har dramatiskt förbättrats sedan 1990-talet och utsikterna ser allmänt mycket bättre ut för barn i den rika delen av världen, och risken för bestående skador på leder och ögon, som också kan drabbas, är betydligt mindre nuförtiden.

Tre av delarbetena i denna avhandling 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 cirka 18 år efter insjuknandet där 434 av de ursprungliga deltagarna deltog. De nu vuxna personerna fick svara på frågor om sjukdomssymtom och funktionsförmåga och lederna undersöktes.

Det framkom att nästan hälften fortfarande hade aktiv sjukdom, även om den i många fall var ganska mild. Hos en tredjedel hade sjukdomen gått i remission, det vill säga blivit inaktiv. Bara 42 % hade uppföljning hos läkare vilket tyder på att en del tappats bort i överföringen till vuxensjukvården. Mer än en tredjedel av individerna behövde regelbunden läkemedelsbehandling för sin JIA.

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.

På data som samlades in vid 18-årsuppföljningen har vi också studerat hur förekomsten av en genetisk markör, HLA-B27, påverkar sjukdomens utveckling. Vi fann då att män som var HLA-B27-positiva, det vill säga hade markören, löpte en större risk för att fortfarande efter 18 år ha en aktiv sjukdom. Vi fann också att vissa leder i större omfattning var drabbade och att individerna med HLA-B27 inte bara hade risk att drabbas av akut symptomgivande ögoninflammation, utan även riskerade få den symptomfattiga ögoninflammationen.

I omhändertagandet av långvariga sjukdomar som JIA är så kallade patientrapporterade utfallsmått viktiga när symtom ska värderas och läkemedelsbehandling justeras. Som en del i avhandlingen översattes ett funktionsformulär, JAMAR, från engelska till svenska och testades på en grupp barn med JIA och en grupp barn utan kronisk sjukdom samt deras föräldrar. Testerna visade att funktionsformuläret var enkelt att använda och hade bra prestanda samtidigt som det var lite för omfattande för ett vanligt mottagningsbesök.

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. Vi har visat att HLA-B27-positivitet innebär risk för sämre prognos och HLA-B27 behöver därför kontrolleras på alla barn med JIA. Det är också viktigt för läkare att känna till att ögoninflammation hos barn med JIA kan vara symptomfattig och att käklederna följs upp som en del i vårdprogrammet för JIA.

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