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Disease activity and outcome in juvenile idiopathic arthritis;

A longitudinal cohort study in the Nordic countries

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"Nå ser vi som i et speil, i en gåte..."

To Rasmus, Hanna, Marie, Kristian, Berit and Rasmus

CONTENTS

PREFACE

Pediatric rheumatology is a young speciality, and research in the field has been limited until the last few decades (1, 2). Traditionally children with rheumatic diseases have been treated by adult rheumatologists, while the field is gradually more dominated by pediatricians. In northern Norway the first clinical service was established at the pediatric department by professor Gudmund Marhaug in the 1970's, after training in Lund in Sweden. Together with Marite Rygg he developed a full clinical care with multi-disciplinary team for all children with rheumatic diseases from Finnmark and Troms, the two northernmost regions of Norway. In addition to the clinical service, research was initiated, first in basic science, later in epidemiological clinical research in collaboration with other Nordic centers. The present study has developed from this Nordic collaboration. Important initiative to establish the Nordic JIA cohort was taken by Anders Fasth and Boel Andersson Gäre, being supervisors of Lillemor Berntson in her PhD on incidence and classification issues in the Nordic JIA cohort.

My personal interest originates from several years of clinical experience with JIA in children. In spite of recent advances in medical treatment, there is still no cure for JIA. The children have to live with the disease for many years, taking medicines and experiencing waxing and waning disease activity. I am impressed by the children's and their families' way of coping with this chronic disease. I am curious about the outcome, and I am also intrigued by the complexity of the disease.

Treatment and expectations for remission have changed even during my limited time working in this field. There are ongoing changes of established "truths" in medicine, reminding us to keep up critical thinking around common practices in clinical care. During these years our knowledge regarding JIA has increased due to high-quality basic and clinical research. My hope is that our study can contribute by one little piece in the big puzzle of understanding more about predictive factors, disease activity and outcome in JIA.

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During this study I have learnt that cooperation is a basic skill also in science, and I want to thank all that have contributed to this teamwork. First of all I want to thank all children and parents for their willing participation and interest. My warmest thanks go to my supervisor Marite Rygg for excellent guidance and enthusiastic support all the way through this project. You have been my mentor in clinical skills of pediatric rheumatology, and also introduced me to research. You have taught me critical thinking through interesting discussions on clinical research and on medicine and life in general. I appreciate your clear sense for quality, details and design. The 1200 kilometre distance between our working places has not been a problem, because your e-mail replies always come promptly. I think during this period you have been waiting more for me than I for you! Along with all the hard work, there have also been fun and pleasures at art exhibitions in Copenhagen, swimming in the Mediterranean, and skiing in the Rocky Mountains.

I also want to thank Bjørn Straume for being an excellent co-supervisor. You are one of the founders of EPINOR, the PhD research school, which has been of great value for me through these years. You have given clear answers, when I needed help in statistics or methodological questions. I appreciate your style of not interfering, but always willing to help when needed. Your comments have sometimes been rather critical and "annoying", but as I have taken time to consider, it has mostly been important points of great relevance – thank you!

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I am happy to have great colleagues and friends at the Pediatric Department at the University Hospital of North-Norway. A special thanks to Tove, Claus, Nils Thomas, Marianne, Niklas, Bård, Martin, Arild, Tore, Jochen, and Randi. Thanks to Trond for an always positive approach, and to present and past leaders for your willing support; Elin, Gunnel, Per Ivar and Hans Petter. I want to thank the whole multi-disciplinary pediatric rheumatology team at UNN for inspiring cooperation through many years, and the pediatric nurses Sigrid Ann, Torunn, Tove and Mariann, the last two for valuable assistance collecting "control" blood specimens. A very special thank to Oddrun for keeping records of our local study participants.

The EPINOR group has been a great support while struggling with STATA and basics concepts of epidemiology, but most of all I appreciate the small talk and social gatherings with you all; Anita, Laila, Linda, Trine, Solrunn, Cibele from Brasil, sister Josepha from Sri Lanka, and Anna Sofia from Færøyene.

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I am most grateful to my mother, my father, and my brothers for all love and support, and also my grandfather Severin for teaching us the value of the education you never got. Thanks to Herdis and Ditlev for kindness and support. I want to thank my friends for being there. Now I look forward to travelling with Elisabeth, biking with Hege, skiing with Tove and Kari, reading with Hanne and the literature group, and droddle with Torunn, Kari and Merete,. Finally, I thank Kristian for love, fun and fellowship, and our children Marie, Hanna and Rasmus for being just who you are and all the happiness you bring; you give me reason to live <3.

ABBREVIATIONS

ACR	American College of Rheumatology
ACPA	Anti-citrullinated protein antibody
ADD	Attention deficit disorder
ANA	Anti-nuclear antibody
AHA	Anti-histone antibody
Anti-DNA	Anti-deoxyribonucleic acid
ARA	American Rheumatism Association
CHAQ	Childhood health assessment questionnaire
CHQ	Child health questionnaire
CRP	C-reactive protein
CVD	Cardio vascular disease
DMARD	Disease-modifying antirheumatic drugs
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ESR	Erythrocyte sedimentation rate
EULAR	European League against Rheumatism
FDA	Food and Drug Administration
GA	Global assessment
HAQ	Health assessment questionnaire
HLA-B27	Human leucocyte antigen B27
HRQoL	Health related quality of life
IACS	Intraarticular corticosteroid treatment
IF	Immunofluoresence
IL	Interleukin
ILAR	International League against Rheumatism
IQR	Interquartile range
JADAS	Juvenile arthritis disease activity score
JADI	Juvenile arthritis damage index
JCA	Juvenile chronic arthritis

JIA	Juvenile idiopathic arthritis
JRA	Juvenile rheumatoid arthritis
LDL	Low-density lipoprotein
MRI	Magnetic Resonance Imaging
NoSPeR	Nordic Study group of Pediatric Rheumatology
PRO	Patient-reported outcome
PRINTO	Pediatric Rheumatology International Trials Organization
PRCSG	Pediatric Rheumatology Collaborative Study Group
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
RF	Rheumatoid Factor
SF36	Short form 36
SLE	Systemic Lupus Erythematosus
SUN	Standardization of uveitis nomenclature
TNF-α	Tumor Necrosis Factor-alpha
VAS	Visual analogue scale

List of papers

Paper I

Ongoing Disease Activity and Changing Categories in a Long-Term Nordic Cohort Study of Juvenile Idiopathic Arthritis

Ellen Nordal, Marek Zak, Kristiina Aalto, Lillemor Berntson, Anders Fasth, Troels Herlin, Pekka Lahdenne, Susan Nielsen, Bjørn Straume and Marite Rygg for the Nordic Study Group of Pediatric Rheumatology. Arthritis Rheum 2011;63(9):2809-18.

Paper II

Validity and predictive ability of the Juvenile Arthritis Disease Activity Score (JADAS) based on C-reactive protein in a population-based Nordic cohort of juvenile idiopathic arthritis

Ellen Nordal, Marek Zak, Kristiina Aalto, Lillemor Berntson, Anders Fasth, Troels Herlin, Pekka Lahdenne, Susan Nielsen, Suvi Pältoniemi, Bjørn Straume and Marite Rygg for the Nordic Study Group of Pediatric Rheumatology. Ann Rheum Dis 2011; accepted for publication.

Paper III

Biomarkers of chronic uveitis in juvenile idiopathic arthritis: predictive value of antihistone antibodies and antinuclear antibodies

Ellen Nordal, Nils T. Songstad, Lillemor Berntson, Torolv Moen, Bjørn Straume and Marite Rygg. J Rheumatol 2009;36(8):1737-43.

SUMMARY

This thesis is based on the Nordic juvenile idiopathic arthritis (JIA) cohort study. In a multi-centre population-based setting a prospective followup of juvenile idiopathic arthritis (JIA) was performed. Pediatric rheumatology centers in Denmark, Finland, Norway and Sweden included children with newly diagnosed JIA during a 3.5 year period starting January 1st 1997. The study was focused on outcome in terms of disease characteristics, course, activity and damage the first eight years after onset. Validation of the Juvenile arthritis disease activity score (JADAS) was performed. Incidence, clinical risk factors and biomarkers of JIA-associated uveitis were also studied.

The first paper described outcome in the Nordic JIA cohort eight years after disease onset. Of the 500 children included at baseline, 440 children (88%) were followed more than 7 years. A change in JIA category during disease course was observed in 10.8% of the children, in addition to extended oligo-arthritis developing in one-third of the oligoarticular group. Disease activity was mostly mild, with low impact on daily life in patient-reported health-related quality of life (HRQoL). However, the chronicity of the disease was demonstrated as 57.6% of the children were not in medication-free remission at the final visit.

In the second paper the JADAS was validated with C-reactive protein (CRP) replacing erythrocyte sedimentation rate (ESR) as an inflammatory marker. JADAS based on CRP correlated closely with the version based on ESR. JADAS was shown to be a feasible and valid tool in assessing disease activity in children with JIA in a population-based setting.

In the third paper the predictive value of biomarkers and clinical characteristics at disease onset in regard to development of uveitis was studied in a pilot study of the Norwegian cohort of 100 children with JIA. During a mean observation time of 7 years, 16 children developed chronic uveitis. Antihistone antibodies (AHA) ≥8 U/ml,

anti-nuclear antibodies detected by immunofluoresence (IF) ≥320 titer and young age at disease onset were significant predictors of uveitis development in JIA. Presence of ANA detected by enzyme-linked immunosorbent assays (ELISA) showed no association to development of uveitis, and should never be used to determine frequencies of eye examinations in children with JIA.

The main findings of this study support the understanding of JIA as a long-term chronic disease. Further, we found that ILAR categories changed over time, JADAS based on C-reactive protein was a valid tool for evaluation of JIA disease activity in a population-base setting, and also that predicting uveitis in JIA remains a challenge.

1 INTRODUCTION

1.1 Chronic arthritis in children

Visual arts may tell more than scientific descriptions, and a painting by Sandro Boticelli "Portrait of a youth" from 1483 shows a young boy with swollen finger joints who probably had chronic arthritis (1, 3). The first recognized medical description of chronic arthritis in childhood is, according to Schaller, found in an English textbook of pediatrics by Thomas Phaer "The book of Chyldren" from 1545 referring to the "stiffness of limes" thought to be a result of exposing children to the cold (1, 4). Childhood arthritis cases are reported by Cornil in 1864, Charcot in 1866, Bouchet in 1875, all in Paris, and Lewis-Smith and Garrod from New York and London in 1876. The Brasilian Moncorvo reported from Paris in 1880, West from London in 1881, and Marfan from Paris in 1896 (1, 5-11). In a thesis from Paris in 1890, Diamantberger describes that chronic arthritis in children differs from adults as it often starts in large joints and may involve other organs as the eye (iritis) and the heart (pericarditis) (12, 13). He also stated that the prognosis is better than in adults although growth disturbances in the jaw (micrognathia) may occur, and suggests both salicylic acid drug therapy and physiotherapy (12, 13). Even if preceded by Diamantberger, Georg Friedrich Still is famous for his publication in 1897 with case descriptions "On a form of chronic arthritis in children", where he also suggests that childhood arthritis is a separate disease entity, and gives a detailed description on systemic juvenile arthritis (14, 15). Chronic arthritis in children was then for many years named Still's disease, even though G.F. Still's later publications were on other childhood diseases, and he was among the first to describe attention deficit disorder (ADD) in children (16). The term Still's disease has later been used for the systemic category of JIA, and even today the adult form of systemic JIA is called Still's disease.

1.1.1 Definition of arthritis

Arthritis is an inflammatory condition in a joint, and the word arthritis is derived from "arthron", the Greek word for joint (17). Arthritis is defined as a clinical finding of

swelling within a joint, or limitation in the range of joint movement with joint pain or tenderness, excluding primarily mechanical disorders and other identifiable causes (18).

1.1.2 Differential diagnoses of arthritis in children

When a child presents with a swollen joint, many different conditions must be considered (19, 20). Septic arthritis and osteomyelitis are diseases in urgent need of antibacterial treatment and must always be ruled out as differential diagnoses in any child presenting with a joint swelling or a limp (21-23). Other infectious, para- and post-infectious forms of arthritis should also be considered (20). Transient coxitis is the most common form of arthritis in young children (24, 25). Trauma, child abuse, malignancy and hematological conditions as bleeding disorders, sickle-cell anemia, and leukemia may present with painful joint swellings (21, 24, 26-28). Chronic arthritis in children can also be a manifestation of other auto-immune diseases, auto-inflammatory syndromes, and a wide range of other inborn or acquired conditions (27, 29, 30). Other identifiable causes of arthritis should be ruled out by a thorough history, clinical examination and diagnostic work-up before juvenile idiopathic arthritis is diagnosed in a child (26).

1.1.3 Classification of chronic childhood arthritis

During the last decades several terms and classifications have been used for this diverse clinical entity encompassing different disease categories of childhood arthritis (31). Previously, the terms juvenile rheumatic arthritis (JRA) and juvenile chronic arthritis (JCA) was used. In 1973 classification criteria for JRA were published by the American Rheumatism Association (ARA) (later named American College of Rheumatology (ACR)). JRA was defined as an idiopathic arthritis of minimum 6 weeks' duration in an individual <16 years of age, and three onset types were described; the systemic, the pauciarticular and the polyarticular forms (32). In 1977 criteria for JCA were proposed by the European League Against Rheumatism (EULAR), defining JCA as idiopathic arthritis of minimum 3 months' duration in the

same age group (33). The term JCA also included the categories of juvenile ankylosing spondylitis, arthritis associated with inflammatory bowel disease (IBD), and juvenile psoriatic arthropathy, while these were defined as separate entities not included in the JRA criteria. JRA has been widely used in the United States and Canada, while the term JCA was mainly used in Europe. Finally, universal agreement has been reached since the 1990's on the classification criteria of juvenile idiopathic arthritis (JIA) (Table 1) (18, 34).

Juvenile idiopathic arthritis is, according to the International League Against Rheumatism (ILAR), defined as swelling within a joint, or limitation in the range of joint movement with joint pain or tenderness, which persists for at least 6 weeks in a child under 16 years of age, observed by a physician, and not due to primarily mechanical disorders or to other identifiable causes (18). The aim of the classification criteria is to be useful both in the pragmatic setting of clinical everyday work and in providing the precise definitions needed for research. There is an ongoing discussion how to improve the disease descriptors in order to refine classification and identify more homogenous disease groups for both clinical and research purposes. The ILAR classification criteria are stated to be a "work in progress" rather than a static framework (18). The criteria have been revised twice, latest in 2001 (18, 34). Heredity for psoriasis in second degree relatives was removed in 2001 as an exclusion criterion, because a disproportionately high number of children were otherwise designated to the undifferentiated arthritis category (18, 35).

Juvenile idiopathic arthritis is the most common chronic rheumatic disease of childhood (26). The clinical spectrum spans from time-limited monoarthritis to ongoing aggressive polyarticular disease, and may include severe systemic features or sight-threatening uveitis. The broad spectrum in symptoms and signs, clinical findings and course, implies that JIA is probably not one specific disease, but rather a group of disease entities. There is no simple diagnostic test, but the diagnosis of JIA is based on a combination of clinical findings, duration and exclusion of other conditions. The term JIA is still used for adult patients that have had juvenile onset of a chronic

idiopathic arthritis. The varying definitions used in different time periods and parts of the world may partly explain the diverging results both in incidence and disease outcome in studies of chronic childhood arthritis. The universal acceptance of the ILAR classification criteria for JIA is a giant step forward and an important prerequisite to gain new and valid knowledge on the disease.

Table 1. International League of Associations for Rheumatology (ILAR) classification of JIA.*

Category	Definition	Exclusions
Systemic onset JIA	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 (non-fixed) erythematous rash 2. Generalised lymph node enlargement 3. Hepatomegaly and/or splenomegaly 4. Serositis‡	A. Psoriasis or a history of psoriasis in the patient or a 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
Oligoarthritis	Arthritis affecting 1–4 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	A–D above, plus E. The presence of systemic JIA in the patient
Polyarthritis (RF-negative)	Arthritis affecting 5 or more joints during the first 6 months of disease; a test for RF is negative	A, B, C, D, E
Polyarthritis (RF-positive)	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	A, B, C, E

Psoriatic arthritis	Arthritis and psoriasis, or arthritis and at least 2 of the following: 1. Dactylitis§ 2. Nail pitting** and onycholysis 3. Psoriasis in a first-degree relative	B, C, D, E
Enthesitis-related arthritis	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	A, D, E
Undifferentiated arthritis	Arthritis that fulfils criteria in no category or in 2 or more of the above categories.	

*Adapted from McCann LJ et al in Arch Dis Child Educ Pract Ed 2006 and Petty R et al in J Rheumatol 1994 (18, 36).
†Quotidian fever is defined as a fever that rises to 39˚C once a day and returns to 37˚C between fever peaks.
‡Serositis refers to pericarditis and/or pleuritis and/or peritonitis.
§Dactylitis is swelling of one or more digits, usually in an asymmetrical distribution, which extends beyond the joint margin.
**A minimum of 2 pits on any one or more nails at any time.
††Enthesitis is defined as tenderness at the insertion of a tendon, ligament, joint capsule, or fascia to bone.
‡‡Inflammatory lumbosacral pain refers to lumbosacral pain at rest with morning stiffness that improves on movement.

1.1.4 JIA categories

According to the ILAR classification criteria for JIA, seven different categories are described in addition to an undifferentiated group (Table 1) (18).

1.1.4.1 Systemic JIA

The systemic form of JIA is characterized by high spiking fever, a non-fixed erythematous rash, and systemic features as liver, spleen or general lymph node enlargement (37). Fluid may accumulate in the serosal linings of the heart, the lungs or the abdomen due to inflammation. Arthritis may be present at onset or develop later, and the diagnosis may be difficult to ascertain if the arthritis present late (26). Although monocyclic limited disease is described in almost half of the children, the most severe polyarticular disease courses are also seen is this group (38).

1.1.4.2 Oligoarthritis persistent

Oligoarticular arthritis is defined as involvement of less than five joints during the first six months of disease. If the number of involved joints remains less than five during the following disease course, then oligoarticular persistent disease is present (18). There are several exclusion criteria regarding psoriasis, enthesitis-related and systemic features (Table 1). Although a limit of five joints may be arbitrary, this category is associated with the best prognosis regarding milder disease course and a higher rate of remission (38).

1.1.4.3 Oligoarthritis extended

From 20-50% of the children with oligoarthritis the first six months will later have involvement of five or more joints, and this group is defined to have extended disease (39-41). Exclusion criteria are applied as for persistent oligoarthritis (18). The disease activity is often more severe, with a course and outcome closer to polyarthritis rather than the persistent oligoarticular category (39).

1.1.4.4 Polyarthritis rheumatoid factor-negative

Polyarthritis is defined as involvement of at least five joints during the first six months of disease (18). There are also several exclusion criteria regarding psoriasis, enthesitis-related and systemic features (Table 1). This category is characterized by a negative test for rheumatoid factor, and tends to have ongoing disease activity and lower rates of remission, in line with the oligoarticular extended category (42).

1.1.4.5 Polyarthritis rheumatoid factor-positive

As above polyarthritis is defined as involvement of at least five joints during the first six months of disease, with several exclusion criteria (Table 1). In addition this category is characterized by the presence of rheumatoid factor (RF). Two tests should be positive taken at least three months apart (18). Rheumatoid factor-positive polyarticular disease is mostly found in older girls (26). The age definition of JIA up to 16 years may seem somewhat arbitrary, and this category may represent a subset with an early-onset of adult seropositive type rheumatoid arthritis (43). The few children that belong to this category are shown to often have an ongoing and destructive arthritis, with a more severe prognosis than rheumatoid factor-negative polyarthritis (44-47).

1.1.4.6 Psoriatic arthritis

Arthritis in combination with psoriasis is defined as psoriatic arthritis (18). Psoriasis may develop many years later than the arthritis or vice versa (48). If psoriasis is not present, the child is also defined to have psoriatic arthritis if there is heredity for psoriasis, presence of finger swellings (dactylitis) and/or characteristic nail changes (18). The psoriasis must be diagnosed by a physician.

1.1.4.7 Enthesitis-related arthritis

Enthesitis is an inflammation of the area of insertion of a tendon, ligament, joint capsule or fascia to bone (18). Typical localizations of enthesitis are the heel insertion of the achilles tendon and the tibial insertion of the patellar tendon below the knee. Inflammatory low back pain, sacroileitis and acute uveitis are also common features. This is the only JIA category with a majority of boys, and there is a close association to HLA-B27 (26). Enthesitis-related arthritis has somewhat different inclusion criteria than the previously used terms juvenile ankylosing spondylitis (JAS), seronegative enthesopathy and arthropathy (SEA) and juvenile spondylarthropathy (JSp) (49).

1.1.4.8 Undifferentiated arthritis

In order to define as homogeneous groups as possible, there are exclusion criteria for all JIA categories. Those that do not fulfill any JIA category due to the exclusion criteria, or fulfill criteria of more than one category, are defined to have undifferentiated arthritis (18). In this way a child may first fulfill the criteria of one category; for example the oligoarticular persistent, if one of the parents develop psoriasis then undifferentiated arthritis is the correct category as this heredity is an exclusion criterion. If the child later develops nail pitting or dactylitis, then the criteria of psoriatic arthritis are fulfilled. In this way the category may change over time as the characteristics of the disease reveal.

1.1.5 Disease biomarkers and predictors of outcome

In a heterogeneous disease group as JIA, predictors of disease course and outcome are of crucial value. Biomarkers are any substance, structure or process that can be measured in bio-specimens and may influence, explain or predict health-related outcomes (50). Clinical findings may in the same way as biomarkers predict certain outcomes. Clinical characteristics and inflammation markers at onset, early disease course, early radiographic findings, response to therapy, and autoantibodies have been of particular interest as potential predictors in JIA (46, 51-53). ESR and CRP are

unspecific inflammation markers often used to monitor disease activity in JIA. Autoantibodies are directed against "self", that is antibodies produced by the individual's adaptive immune system against its own body components.

1.1.5.1 CRP

C-reactive protein is part of the acute phase response to tissue injury. The name originates from the discovery of CRP as a serum substance reacting to infection with the capsular (C-) polysaccharide of Streptococcus Pneumoniae (54). It is a pentameric protein produced in the liver, and considered as part of the body's innate immune system (55). Inflammation is a key regulator of CRP synthesis. CRP is extensively used as a marker of inflammation. In an acute infection a high value indicates bacterial agents, while viral infections usually have lower values. CRP has physiologic functions through binding to membranes of bacteria and damaged cells, activating the classical, but also modifying the alternative-pathway complement system (54, 55). Elevated CRP is associated with active synovitis in JIA, and CRP may be used to monitor effect of treatment (56). CRP is included in recent treatment algorithms as predictors of severe disease course (46, 56).

1.1.5.2 ESR

The erythrocyte sedimentation rate is simply the rate at which red blood cells sediment when blood is placed in a vertical column for one hour. It is an indirect marker of blood levels of fibrinogen, other acute phase proteins and immunoglobulin (55). This presence of various cationic proteins promotes the formation of "roleaux" structures increasing the sedimentation rate (57). The phenomenon was already known in medicine in ancient Greece. The test has later been described and in periods named after the Polish physician Biernacki in 1897, and the Swedish physicians Fähraeus and Westergren (58, 59). High ESR is commonly found in infections, anemia, malignancies and rheumatic diseases. Early and persistently elevated ESR in JIA has been shown to predict adverse outcome in several studies (44, 45, 49, 60).

1.1.5.3 Rheumatoid factor and anti-citrullinated protein antibodies

Rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) are autoantibodies found in a minority of children with JIA, although they are commonly found in adult rheumatoid arthritis (61-64). RF was first described by the Norwegian physician Waaler in 1940 as a factor that clotted sera in adults with rheumatoid arthritis (65). ACPA are antibodies against the modified amino-acid citrullin. ACPA are produced locally in the inflamed synovium, and serum levels are measured by ELISA tests for anti-CCP (66). Both in children and adults these autoantibodies are reported to be associated with a more severe prognosis (45, 53, 61). In adult RA, some recent studies have shown that ACPA has higher diagnostic and prognostic value than RF (61, 67-70). In older children with chronic arthritis the presence of RF and/ or ACPA may indicate an early-onset of adult rheumatoid arthritis even if the child is less than 16 years of age (43).

1.1.5.4 Antinuclear antibodies and antihiston antibodies

Antinuclear antibodies (ANA) are autoantibodies against intracellular nuclear antigens. ANA and several antigen-specific nuclear antibodies are present in many rheumatic diseases (71). Anti-DNA and anti-SM is among the antigen-specific subtypes of ANA, listed among the 11 ACR classification criteria for SLE (72, 73). The presence of circulating ANA in JIA is well documented, and the prevalence varies in different studies, probably due to both ethnic differences and laboratory methodology (74). The sub-specificities of ANA in JIA have not been fully elucidated in spite of several studies (75-77). Traditionally ANA has been detected by immunofluorescence method using Hep-2 cells (IF-ANA) (71, 78-80). This method has been criticized for lack of specificity, it is highly operator-dependent and satisfactory standardization has been difficult to achieve (79). Enzyme-linked immunosorbent assays (ELISA) enables automated identification of antigen-specific ANA. ELISA-ANA is increasingly used, but is rarely positive in JIA (74).

Histones are basic DNA-binding proteins that are subcomponents of chromatin, and arrange in highly organized nucleosomal particles. The five histone molecules enable formation of the double helix DNA, and the core histones (H2A, H2B, H3, H4) are evolutionary highly conserved between species (81). New interest for histones has emerged through the recent findings in epigenetics (82). Antihistone antibodies are among the ANA subtypes identified in subsets of children with JIA (75, 81, 83-88). AHA are in some studies associated with early-onset JIA, oligoarticular onset and uveitis (83, 88).

1.1.6 Etiology

It seems clear that JIA is a multi-factorial disease, although etiology remains largely unknown (37, 38, 89). There is strong evidence of genetic factors conferring an overall susceptibility to JIA (90-94). In other words JIA is viewed as a complex polygenic disease (95). The human major histo-compatibility complex (MHC) plays an important role in the body's recognition of self, and it is closely linked to autoimmunity. Associations with multiple MHC-class II molecules and with specific genes have been shown for certain categories of JIA (43, 49, 96-100). The human leucocyte antigen B27 (HLA-B27) is a MCH-class I molecule found more commonly in JIA than in healthy children (62). HLA-B27 shows a strong association to enthesitis-related arthritis (62, 101, 102). In addition, epigenetics has recently been shown to play an important role in autoimmunity, and may also be involved in the pathogenesis of JIA (89, 103).

Environmental factors as infections and vaccinations have been suggested as triggers of onset and relapses in JIA, but no single trigger has been identified (89, 104). A sequence of triggering events preceding onset of JIA in a genetically predisposed individual seems likely (89, 105). The range of triggers may cause a break in the self-tolerance of the individual. A disturbed balance between pro-inflammatory effector cells and anti-inflammatory regulatory cells may result in synovial inflammation in the joints (37). Auto-reactive T-lymphocytes play key roles, and T-helper17 cells are

among the pro-inflammatory lymphocytes that are selectively recruited from the blood and found in synovial fluid in JIA (89). These effector T cells in JIA are recently shown to be resistant to immunoregulation by functional regulatory T-lymphocytes, possibly contributing to the ongoing inflammation (106, 107).

Hormonal factors may play a role as increased levels of prolactin have been detected in children with JIA and ANA positivity (108). A study of pregnancies in patients with JIA showed that a majority experienced improvement of arthritis during pregnancy, but disease flares were common after birth (109). There is some evidence that stromal cells and mechanical stress may play a role in the pathophysiology of enthesitis in spondyloarthropathy and psoriatic arthritis (110-112). The role of diet is unclear in JIA. In adult rheumatology, however, intake of oily fish is associated with a modest decreased risk of developing rheumatoid arthritis (113). In rheumatoid arthritis in adults large scale epidemiologic studies have shown genetic susceptibility for environmental factors such as smoking (114-116). There is also some evidence that maternal smoking in pregnancy increase the risk of chronic childhood arthritis in their children (117).

Systemic JIA seems in many ways different from other JIA categories, and has lately been suggested to belong to the group of autoinflammatory rather than the autoimmune diseases (37, 118). This is suggested by the excellent clinical response to anti IL-1 and IL-6 treatment and lack of autoantibodies or antigen-specific T-cells (37). The autoinflammatory diseases arise primarily from defects in the innate immune-system characterized by specific genetic associations and prominent systemic features (118-120).

1.1.7 Symptoms and clinical findings

A limp and morning stiffness, joint swelling, pain and restricted movement in one or more joints are the most common symptoms and clinical findings at onset of JIA (38). General malaise, fever and exanthema may occur (26). While localized symptoms as

joint stiffness and pain dominates in older children, general symptoms such as loss of appetite, irritability and increased need for rest and disturbed sleep may characterize the onset in early childhood (21). Blood tests may be normal, but unspecific markers of inflammation as anemia, thrombocytosis, raised ESR and/or CRP are common findings. Specific immunological markers as ANA, RF, ACPA and HLA-B27 may be found, but are not a prerequisite for the diagnosis and is not present in many children with JIA (18, 56, 76, 121-125).

1.1.8 Uveitis

Uveitis is the most common extraarticular manifestation in JIA, and occurs in 2-24% of children with JIA (126-131). Uveitis is defined as inflammation in the uvea of the eye (iris, ciliary body and choroid) (Figure 1) (132).

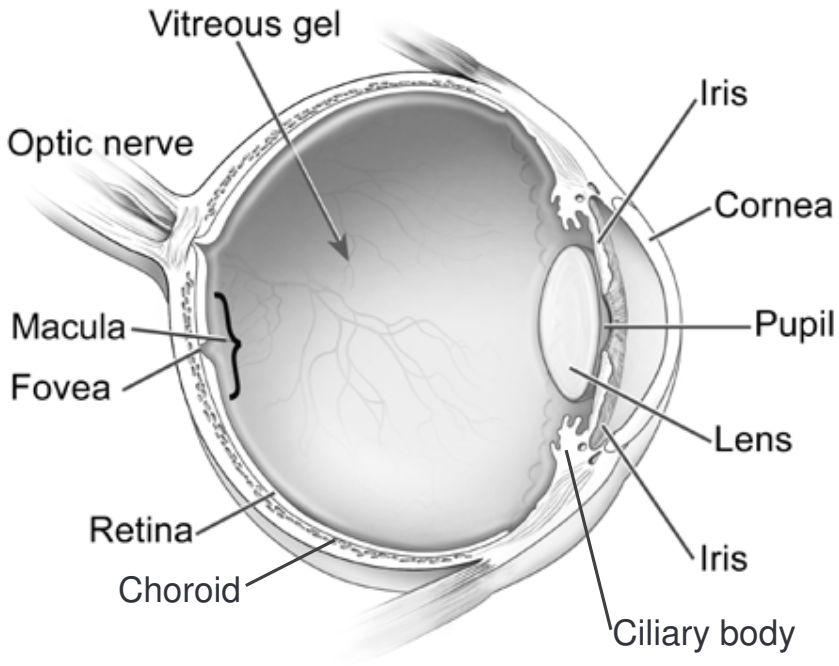


Figure 1. Schematic drawing of the human eye, showing the uveal tract composed of the iris, the ciliary body and the choroid. (Adapted and used with permission from National Eye Institute, National Institutes of Health.)

Uveitis is described as anterior, intermediate, posterior or pan-uveitis depending on the localization of the inflammation in the uvea. Uveitis is also defined according to the onset type, duration and course (Table 2) (132). In addition to the association to JIA, uveitis may be idiopathic or associated to other rheumatic or infectious diseases (132-134). The JIA-associated uveitis is almost always an inflammation of the anterior uvea (iridocyclitis), is often bilateral, and may have an acute or a chronic form (135, 136).

Table 2. The Standardization of uveitis nomenclature (SUN) Working Group Descriptors of Uveitis*.

Category	Descriptor	Comment
Onset	Sudden	
	Insidious	
Localization	Anterior	
	Intermediate	
	Posterior	
	Panuveitis	
Duration	Limited	≤3 months duration
	Persistent	>3 months duration
Course	Acute	Episode characterized by sudden onset and limited duration
	Recurrent	Repeated episodes separated by periods of inactivity without treatment ≥3 months in duration
	Chronic	Persistent uveitis with relapse in <3 months after discontinuing treatment

*Adapted from Jabs et al in Am J Ophtalmol 2005 (132).

The acute form of uveitis usually has a sudden onset, limited duration, and presents with a painful, red eye in older children with JIA (130). Acute uveitis is often associated with a positive HLA-B27 antigen and enthesitis-related arthritis, and is usually diagnosed promptly because it has obvious clinical symptoms and signs (126). Chronic insidious and asymptomatic uveitis is the most common form of uveitis in JIA (126, 137). Chronic uveitis is usually without symptoms until reduced vision or pain occurs as a consequence of the complications of the inflammation.

Traditionally early-onset arthritis, oligoarticular onset, presence of ANA, and female gender has been associated with increased risk of development of uveitis (Table 3). Young age at onset of arthritis is the most important risk factor for development of chronic uveitis in JIA, and an association between uveitis and early-onset arthritis has been a consistent finding since the first report in 1957 (138-140). Increased risk of uveitis has been reported for the category of oligoarticular JIA, but several recent studies show the same risk in polyarticular compared to oligoarticular categories (129, 141). Uveitis is rare in systemic JIA (142). Presence of ANA and female gender has been reported to be associated to uveitis (141). However, there are recent studies showing no increased risk in ANA positive children (143, 144). Several studies have also shown no predilection for females to develop uveitis, when it is taken into account the higher number of girls with JIA in general (127, 129, 143). The risk of uveitis development may be strongly related to young age at onset and ANA positivity, in girls, but not in boys, independent of JIA category (145). Early diagnosis and treatment of uveitis is essential to avoid complications leading to reduced vision or blindness (135, 143, 146, 147). The most frequent complications of JIA-associated uveitis are cataract, glaucoma, band keratopathy, synecchiae, and macular and/ or optic disc oedema (126, 127, 142, 148, 149). Phtisis bulbi may occur in the end stage (127, 143). Even in recent publications the rate of complications remains high (Table 3). As uveitis is mostly asymptomatic, regular slit-lamp examination at specific intervals in all children with JIA is strongly recommended (143). Different screening programs are suggested based on the reported risk factors (127, 143, 146, 150).

Table 3. Incidence, complications, and reported risk factors of JIA-associated uveitis.*

Author, year (n)	Study design	Obs. time (years)	Uveitis (%)	Complication rate (%)	Factors associated with development of uveitis			
					Early-onset arthritis	Oligoarthritis	ANA	Female
Kotaniemi 2001 n = 426	Prospective cohort, tertiary center	5	24	24	+	-	+	-
Minden 2002 n = 215	Retrospective, combined population-based and tertiary center	16	14	48	n.a.	-	n.a.	n.a.
Packham 2002 n = 259	Retrospective , tertiary center	28	22	n.a.	n.a.	n.a.	n.a.	n.a.
Flato 2003 n = 268	Retrospective , tertiary center	15	19	n.a.	n.a.	n.a.	n.a.	n.a.
Zak 2003 n = 65	Retrospective, tertiary center	26	20	45	+	+	+	-
Grassi 2007 n = 309	Retrospective, tertiary center	9‡	20	35	+	+	+	-
Heiligenhaus 2007 n=3271	Retrospective, register from referral centers	6‡	12	56	+	+	+	+
Saurenmann 2007 n = 1081	Retrospective, tertiary center	7	13	37	+	+	+	+

Bolt 2008† n = 265	Retrospective, tertiary center	5	13	34	+	-	+	-
Reininga 2008 n = 153	Retrospective, referral center	7‡	18	48	+	-	-	-
Nordal 2009 n = 100	Prospective cohort, population-based	7	16	n.a	+	-	+	-
Skarin 2009 n = 350	Retrospective, tertiary center	24	16	58	n.a.	n.a.	n.a.	n.a.

*References for the studies (39, 45, 127, 129-131, 142, 143, 151-154); JIA = juvenile idiopathic arthritis; Obs = observation; n.a. = not available; ANA = antinuclear antibodies.
†Age at onset of arthritis was significantly lower in the uveitis group in univariate, but not in multivariate analysis.
‡Followup in years after onset of uveitis.

1.2 Epidemiology

Considerable differences in incidence and prevalence of JIA, uveitis and associated biomarkers are reported worldwide (155, 156). These diverging numbers may illustrate real regional differences, but may also illustrate the difficulties of performing high-quality epidemiologic studies in JIA, and the validity of some of the data may be questioned (157). Epidemiology can be defined as studies of patterns of diseases in defined populations to help understand both their causes and the burden they impose (158). True differences in incidence of juvenile arthritis between different regions, countries and populations can generate hypotheses of etiology and reveal the natural history of JIA under current treatment (156).

Study design and methods for patient recruitment obviously have major impact on the results (159). Three major points have to be considered; First, uniform classification criteria for juvenile arthritis are needed to avoid comparing "apples and pears". The inclusion criteria of JCA requires a longer disease duration than JRA and JIA, and the criteria differ in whether the psoriatic and enthesitis-related arthritis are included or not (18, 32, 33, 160). Secondly, methods of case identification and ascertainment are important (155-157). Disease registries, practioner surveys and hospital populations have mostly been used to identify cases. Numbers may be underestimated due to undiagnosed cases in the community, or some categories may be overrepresented in hospital-based cohorts (155). Thirdly, there must be a clear definition of the study population and the time period. To collect the whole spectrum of a heterogeneous disease as JIA, ideally all children in the population should be examined. This is often not feasible in a relatively rare disease as JIA. In other approaches studying a given population, local hospitals, private specialists and general practitioners must be included in addition to referral centers. Otherwise this will influence both findings on incidence and prevalence, but also outcome and prognosis because the study group may be quite different from the total group of children with JIA. When comparing the epidemiologic studies of JIA; crucial questions remain what are due to methodological problems, and what are the real geographical and ethnic differences.

A universal finding is that juvenile arthritis is the most common rheumatic disease of childhood (159). Girls are also more frequently affected than boys (26, 125). In most population-based studies there is a peak of incidence in early childhood, especially in girls 1-3 years of age, while onset in boys is more evenly distributed through childhood (102, 122, 125). Reported annual incidence numbers of chronic childhood arthritis differ from 1.3 to 22.6 per 100 000 children (102, 161). Incidence figures from Europe indicate a north to south gradient even when methodological differences are considered (159). The highest annual incidence is reported from Northern Norway, and these numbers are confirmed by overlapping confidence intervals in another prospective study in the same region (102, 125). An epidemiologic study from the Oslo region in 2008 found an annual incidence of 14 per 100 000 and a recent prospective study from Catalonia in Spain showed an incidence of 6.9 per 100 000 (24, 162).

A cross-sectional study based on examination of 12-year old Australian school children, showed a surprisingly high prevalence figure of 400 pr 100 000 children for juvenile chronic arthritis in 1996 (163). There are wide confidence intervals because this calculated prevalence is based on nine identified cases, and the figure thus overlaps with a Belgian study with the same design (164). Within the same range is the results of a retrospective hospital-based study in Northern Norway showing 164 pr 100 000 children (102). Three prospective studies in well-defined populations of Sweden, Spain and Costa Rica show prevalence of 86 (95% CI 77-96), 40 (95% CI 36-44) and 31 per 100 000 (95% CI 25-37) and indicate that there are true differences in genetic or environmental factors between these populations.

Genetic factors are probably involved in the etiology of JIA. The frequencies of HLA-B27 among children with JIA are higher in Northern parts of Scandinavia than in other studies from Europe and the United States (102, 165). In an Eskimo population particularly high incidence of spondyloarthropathy were found in male children, and there was also a high prevalence of HLA-B27 in the general population (166, 167). A

frequency of 14-17% of HLA-B27 is found in the general population in Northern Norway, Northern Sweden and Finland, whereas less than 10% are reported HLA-B27 positive in southern Norway and other parts of Europe (168).

There are also diverging numbers regarding risk for uveitis among children diagnosed with JIA. In the Nordic countries high numbers are reported, showing that 9-24% of children with JIA developed uveitis (Table 3) (129, 131, 137). In Costa Rica, Singapore and India both uveitis and ANA are rarely found in children with JIA (128, 169, 170). In multi-ethnic JIA populations, the non-European decent group is shown to have less uveitis, fewer children with early-onset ANA positive disease, and more RF positive polyarthritis compared to the group with European decent (171). The relatively low frequencies of uveitis and positive ANA are suggestive of different disease patterns in these populations. This may be an indication of true genetic and environmental differences in JIA susceptibility, disease determinants and manifestations.

1.3 Treatment options in JIA

At present there are no treatments that can cure JIA; still recent advances in medical treatment have changed the goals of treatment over time, with higher expectations for achieving inactive disease (46, 172, 173). In a historic perspective there is a long list of more or less "useless treatments" that has been given to children with JIA. Penicillamine and gold are examples of drugs with numerous side effects and no proven efficacy (1). The spontaneous variations in disease activity made it difficult to prove efficacy until systematic trials were performed. The old term "slow-acting antirheumatic drugs" (SAARD) is indicative of the time and patience needed until improvement could be expected (1). Newer medical treatments are effective, but have a high cost, and long-term safety is a major concern in children.

1.3.1 Current medical treatment

With the introduction of more effective and targeted antiinflammatory drugs during the last decade, three major changes have occurred.

1. Full remission of the disease has recently been stated as the paramount goal for treatment of children with JIA (172). The criteria of remission in JIA, is defined as clinically inactive disease either on or off medication (173-175).
2. There is emerging evidence of a "window of opportunity" when early medical treatment can change the disease course in a milder direction in JIA, in the same way as previously shown in adults with RA (40, 44, 176-178). Therefore early introduction of DMARD is recommended in children with high or moderate disease activity and/ or features of poor prognosis (46).
3. The recommendations towards early treatment have changed the approach from starting with the less potent medications to more aggressive treatment upfront (46, 174, 179). In this way the traditional "pyramid of treatment" has been dismantled (180).

The so-called "pediatric rule" implemented by the Food and Drug Administration (FDA) and the European Medicine Agency (EMA) stimulate to research on therapeutic agents in children, aiming for safer and better use of medicines in children (37). Companies that wish to register a new treatment in adults, have to test their product in children if there is a pediatric counterpart of the disease (37). Randomized controlled trials (RCT) are powerful in testing the effect of new interventions and treatments (181). A novel trial design, first used by Lovell et al in the etanercept study, solves the ethical dilemma of RCT in potent treatments by offering the active agent to all the children, and finding efficacy by withdrawal of the active agent after the first treatment effect is achieved (182, 183). During the last decade an increasing number of RCT are done in children with JIA. There is an increasing challenge to recruit enough children for RCTs on the emerging new biologic treatments. Obviously, international collaboration is needed for performing high-quality therapeutic trials in selected subsets of JIA. Large pediatric rheumatology networks have been established, such as the Pediatric Rheumatology Collaborative Research Group (PRCSG) in the USA, and

the Pediatric Rheumatology International Trials Organization (PRINTO) based in Europe (2). ACR recommendations of treatment in JIA have been published in 2011 with a current consensus on medical treatment based on JIA categories and baseline predictors of disease course (46).

1.3.1.1 Intraarticular and systemic corticosteroids

In active arthritis the use of intraarticular corticosteroid joint injections (IACS) is recommended and usually very effective, regardless of concomitant therapy and JIA category (46). Triamcinolone hexacetonide is a long-acting depot formulation shown to be superior to other glucocorticoid formulations in a RCT (184, 185). The efficacy and safety is well proven, but a drawback is that most children need sedation or general anaesthesia for the procedure (184, 186-189). Although most studies show good response, and remission may be sustained, raised CRP levels, negative ANA, and ankle injection has been shown to predict synovitis flare (184). Ultrasound guidance has been recommended used in the ankle/ tarsal joints and in the hip for correct intraarticular administration to improve efficacy (190, 191). To achieve the goal of early inactive disease and remission, IACS remains a simple and important treatment modality, also in the biologic "era".

Minimal use of systemic glucocorticoids in children is recommended due to the unwanted side-effects such as growth retardation, metabolic alterations and loss of bone-mass density (192). Glucocorticoids can be useful as a "bridging" therapy until an effect of slower acting DMARD is seen. In systemic JIA with active fever, the standard treatment has been systemic glucocorticoids, even though there is a recent report on alternative upfront treatment with IL-1 blocking agents (193). Recent research indicates a favourable effect of the anti-diabetic drug metformin in reducing the metabolic side effects of glucocorticoids (194, 195).

1.3.1.2 Nonsteroidal antiinflammatory drugs

Even though IACS and early DMARD currently are introduced early, NSAID has been the most frequently used medication in JIA for decades (46, 196, 197). NSAID is still the analgesic drug of choice in JIA, but other treatments are recommended for long-term antiinflammatory effects (46). The frequency of gastrointestinal and other side effects, and also drug discontinuation due to toxicity is not significantly different from DMARD (198).

1.3.1.3 Methotrexate

Methotrexate (MTX) is the cornerstone of long-term disease-modifying therapy in JIA (46). MTX together with IACS is recommended as the initial treatment in high and moderate disease activity, with the aim of inducing early inactive disease and remission (46). MTX can be taken orally, but the parenteral route ensures better absorption (196). Improvement cannot be expected until 6-12 weeks after starting treatment, and efficacy has been shown in several trials (199, 200). PRINTO has conducted a large scale RCT on methotrexate dosing in JIA, concluding that a medium dose of 15 mg MTX/ m^2 is as effective as higher doses (201). A major limitation of concern is liver toxicity and gastro-intestinal side effects (198). A small study on interaction between NSAID and MTX indicate that side effects usually attributed to MTX, may be caused by increased levels of concomitant NSAID (202). Folic acid supplementation may reduce the gastrointestinal side effects (203).

1.3.1.4 Other DMARD

Other DMARD such as leflunomide, sulphasalazine, hydroxychloroquine and cyclosporine are sometimes used in the treatment of JIA (46). There are some evidence for superior effect of the combination therapy of methotrexate, sulphasalazine and hydroxychloroquine to methotrexate alone in early polyarticular JIA (204). Leflunomide and sulphasalazine are both shown to have effect in monotherapy for selected categories, but the clinical improvement seems to be inferior to methotrexate

(176, 205, 206). A disease-modifying effect of cyclosporine or hydroxychloroquine has not been proven, but the latter has a metabolic effect in lowering blood glucose, low density lipoprotein (LDL) and cholesterol levels, and can diminish the increased cardiovascular risk inflicted by oral corticosteroids (205, 207).

1.3.1.5 Biologic treatment

Advances in the understanding of the immune system have led to development of new targeted drugs that interfere with key cytokines of inflammation (208). These drugs are called biologic agents in contrast to methotrexate and the other synthetic DMARDs. Etanercept, infliximab and adalimumab are potent TNF-blocking agents all shown to be effective and generally well-tolerated in JIA (183, 209-211). Only etanercept and adalimumab are licensed for use in children with JIA, while adalimumab and infliximab has the advantage of being effective both for the arthritis and for JIA-associated uveitis (212-214). Another biological agent is abatacept, targeting CTLA-4, shown efficacious for polyarticular course-JIA in a RCT (215). For the systemic category of JIA the interleukin-blocking agents anakinra (IL-1) and tocilizumab (IL-6) are shown to have a profound effect, and may be used as first-line disease-modifying treatment (193, 216-218). Further biologic agents are available, some are currently being studied for use in children and new drugs are steadily emerging (219).

1.3.1.6 Medical treatment of uveitis

Systemic medical treatment is indicated if topical corticoid treatment cannot control the uveitis (220). Local corticosteroid injections may be used (220). Methotrexate is reported effective in an observational study. It is the most commonly used systemic antiinflammatory drug, although no RCT has been performed (221). Mycophenolate mofetil and cyclosporine A have also been used (220). Among the biologic agents, infliximab, adalimumab, and rituximab are in several case series shown effective against uveitis (148, 213, 214).

1.3.2 Other treatment options

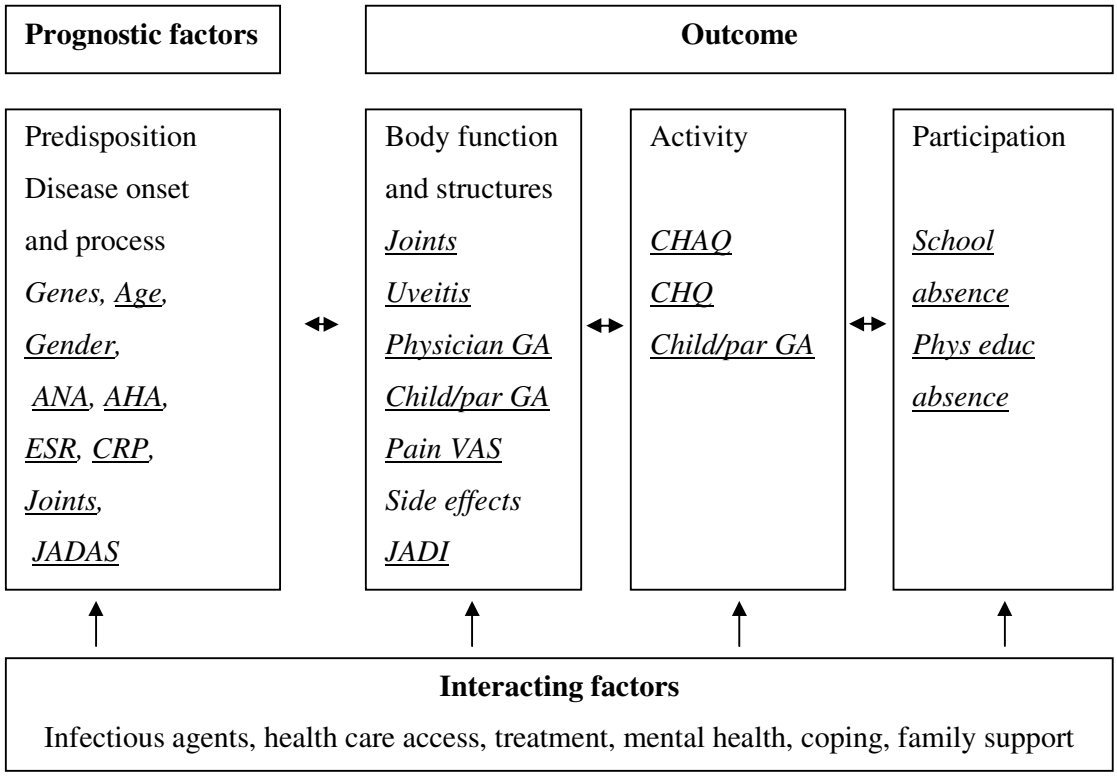
Although there have been great advances in medical treatment, the followup of a child with JIA is still considered to be a multi-disciplinary task (37). The specialized multi-disciplinary team has an important role in assessing the individual needs of the child and family, and to facilitate that these needs are met locally in school, kindergarten and in the primary health care (192).

There has been a dramatic shift in attitude regarding physical activity for children with chronic arthritis (222). Recent advances in treatment have led to less disability, and therefore less need for mechanical aids, splints and surgery. In earlier days bed rest and immobilization in general or as a consequence of frequent use of orthoses, casts and splints, was widely advocated for children with JIA (223). Replacing the previous traditions of giving advice to avoid many activities, all physical activity is now generally recommended (222, 224). There is some evidence that structured aerobic and neuromuscular training may improve exercise capacity, functional performance, and quality of life in children and adolescents with JIA (222, 225). Recent research also points to an anti-inflammatory effect of exercise that may be mediated by muscle-derived cytokines (226, 227). Different physiotherapeutic approaches are used in different centers around the world (228). A RCT could not show any beneficial effect of hydrotherapy compared to land-based physiotherapy, but in both treatment groups there was an improvement in the core variables of JIA, and also improvement in HRQoL and cardiovascular fitness (229). A time-limited, intensive training period of physiotherapy may facilitate participation in ordinary activities as sports and physical education in school. The pediatric nurse has an important role giving information regarding vaccines and teaching safe administration of injections and other medications. An occupational therapist with knowledge on hand function and helping aids, and a social councilor are also important members of the multidisciplinary team. The pediatric rheumatologist is usually the coordinator of the team, which may involve other professionals as an ophthalmologist, orthopedic technician, orthopedic surgeon, pediatric radiologist, pedodontologist and psychiatrist (172, 230).

1.4 Outcome

JIA may have considerable impact on growth and development, physical and psychosocial functioning. There is a wide range of potential consequences, and therefore no single measure of outcome. Knowledge on the long-term outcome of JIA is important to guide treatment, for information to the individual child and family, and for the society in providing health services (156).

Outcome can be defined as consequences of the disease process over time. Strictly speaking, outcome can be described precisely only at the end of the disease process, still both short- and long-term studies provide valuable information. A conceptual framework of the disease process, prognostic and interacting factors, and outcome is suggested in figure 2. Robust definitions of disease activity, remission and other standardized outcome measures are essential so that outcome studies can be compared (173).



* ANA = antinuclear antibodies; AHA = antihistone antibodies; JADAS = juvenile arthritis disease activity score; Physician GA = physicians global assessment of disease severity; Child/par GA = child/parent global assessment of overall well-being; Pain VAS = pain visual analogue scale; CHAQ = childhood health assessment questionnaire; CHQ = child health questionnaire; JADI = juvenile arthritis damage index; Phys educ = Physical education.

Figure 2. A framework for prognostic factors and outcome in the disease process of JIA. The main prognostic markers and outcome measures used in the present study are underlined. Modified from WHO framework for consequences of disease in the International Classification of Functioning, Disabilities and Health (226), Spector and Hochberg (232), Fries (233), Andersson Gäre (234) and Flatø (235).

1.4.1 Current knowledge on outcome in JIA

A common belief as late as in the 1990's was that most children with JIA would achieve permanent remission before adult age (208). This view has changed because several recent studies have demonstrated ongoing or cyclic disease activity into adulthood for about two thirds of the children (42, 45, 63, 236, 237). Outcome studies show inconsistent and conflicting results, and reflect methodological problems such as study design, study population and method of case accrual (156). In most studies the number of patients in each category is low, so the category-specific results must be interpreted with caution. Hospital-based studies from tertiary pediatric or adult rheumatology centers will evaluate a selected cohort with an outcome that may differ from population-based studies. On the other hand, cross-sectional studies miss fluctuations in disease activity over time, and cannot measure sustained clinical remission off treatment (42). Disease activity should therefore be assessed over time to avoid underestimation of duration and chronicity of the disease.

Even if ongoing disease is found in a majority of children with JIA, the disease activity seems generally low (39, 63, 237). Many children do not have joints with active inflammation or restricted movements at followup in long-term studies, probably reflecting that therapeutic interventions are promptly started at disease flares (44, 237).

Physical functioning is in average lower than in healthy controls, but the difference is small in most studies, assessed by CHAQ and CHQ (39, 237). Disease-related pain is reported present in 40-86% of the patients on followup, not necessarily proportional to other measures of disease activity (238, 239). Psychosocial functioning is in the normal range for most patients with JIA, although some conflicting data exist (238-240). School attendance and participation in social activities are often influenced by the disease, but the majority of long-term followup shows that educational levels and spousal relationships are similar to healthy controls (39, 45, 240). In some studies there is a lower employment rate of adults with juvenile onset arthritis compared to the background population (240, 241).

Remission rates in recent studies range from 33 – 61%, and are summarized in table 4. These rates are however assessed at the final study visit, reporting the disease state of the last 1-2 years depending on which criteria of remission is used. When the whole disease course is assessed, Wallace et al found that only 36% of remission episodes were sustained for 2 years and only 6% for 5 years (42). In a similar way Lurati et al report sustained remission for 2 years in only 25% of 761 Italian children in a 7.6 year followup (236). Both these studies from tertiary referral-centers are retrospective, and there is a need for population-based prospective studies to confirm this high grade of chronicity in JIA.

A Steinbrocker functional class III and IV indicate significant physical disability. Approximately 10% or less of the patients with JIA belongs to these functional classes, even in recently published studies that assess patients after many years of disease (44, 237, 242). Permanent damage has also been assessed by juvenile arthritis damage index (JADI) from different parts of the world, showing diverging results (237, 243-245). Visual impairment is a significant problem with severe consequences for children with difficult-to-treat JIA-associated uveitis (136).

There are other long-term consequences of JIA beyond functional disability and joint damage. In adults with rheumatic arthritis there is a marked increase in cardiovascular disease (CVD) risk associated with chronic inflammation, comparable to the increased risk of CVD in diabetes mellitus (246). In children with JIA there is so far not shown increased risk of CVD, but there are indications of blood wessel endothelial dysfunction, that may be attributed to inflammation or medications (247). A small but significant increased risk of cancer has been found in children with JIA diagnosed after the mid-eighties (248). A large international long-term surveillance study is started to clarify whether this is related to the disease per se or to the treatment with methotrexate, biologic or other antiinflammatory agents (249). The mortality rate in JIA has been slightly raised compared to the background population in some studies, but a recent report from the USA showed no increased mortality in JIA (250).

Table 4. Recent outcome studies in juvenile arthritis.*

Author, year (n)	Study design	Followup (years)	CHAQ median/ >0 (%)	Present use of Drugs/DMARD/ MTX (%)	Remission Total (%)†	Damage JADI/ Steinbrocker class III/IV(%)	Classification
Gäre 1995 n = 124	Prospective cohort population-based	7	0.19/60	49/-/-	61‡	-/ 5	JCA
Zak 2000 n = 65	Retrospective Tertiary center	26	-	-	73	-/11	JCA
Arguedas 2002 n = 47	Prospective cohort population-based	4	-	49/25/25	51§	-/-	JCA
Minden 2002 n = 215	Retrospective Combined Population-based and tertiary center	16	0.22/39	-/-/-	40	-/10	JCA
Oen 2002 n = 382	Retrospective cohort Tertiary centers	10	-/55	-/21/-	39	-/3	JRA
Packham 2002 n = 246	Retrospective Tertiary adult rheumatology center	28	-/43**	>80/36/-	-	-/37	JIA

Fantini 2002 n = 683	Retrospective Tertiary center	10	-	-/-/-	33	-/-	JCA
Flato 2003 n = 268	Case-control Tertiary center	15	-/36	-/-/-	50	-/-	JRA
Foster 2003 n = 82	Retrospective Tertiary center	21	1.1/-	68/28/15	61§	-/-	JIA
Arkela-Kautiainen 2005 n = 123	Retrospective Tertiary center	16	-/-	- /- /58	37	-/-	JIA
Solari 2008 n = 310	Cross-sectional Tertiary center	7	0/49	77/-/53	22§	>34/4	JIA
Nordal 2011 n = 440	Prospective cohort Population-based	8	0/32	35/31/23	42	23/-	JIA

*References for the studies (39, 47, 49, 128, 151, 237, 240, 242, 251-253); CHAQ = Childhood health assessment questionnaire; DMARD = Disease-modifying antirheumatic drugs; MTX = methotrexate; JADI = Juvenile arthritis damage index; - = not available; JCA = Juvenile chronic arthritis; JRA = Juvenile rheumatic arthritis; JIA = Juvenile idiopathic arthritis.

† The EULAR and several different study-specific definitions of remission are used. In the studies of Solari, and Nordal the Wallace criteria of remission are used (175).

‡ Extrapolated remission rate from the examined cohort to the original population-based cohort, other outcomes are from the examined cohort.

§ Inactive disease and remission, the EULAR and several different definitions of inactive disease and remission are used.

** Percentage of patients with CHAQ >1.5.

1.4.2 Validated outcome measures

Disease-related outcome measures are necessary for reliable and valid evaluation of disease activity and outcome. Validated tools for assessment of self-reported health and functional status, remission and damage are essential to describe the effect of treatment in trials, and the disease course and outcome in epidemiologic studies (Table 5) (254).

1.4.2.1 Disease activity measures

Simple measures of disease activity are; the number of inflamed joints, tender joints, joints with restricted movement, inflammatory markers and visual analogue scales of pain, and global assessment of disease severity. Among these physicians global assessment of disease activity and active arthritis joint counts show high correlation to other measures of disease activity and has a high responsiveness to change (255, 256). A composite disease activity score combining four of these simple measures was recently developed and validated (257). Juvenile Arthritis Disease Activity Score includes the following measures; (1) number of joints with active arthritis assessed in 10, 27 or 71 joints, (2) parent/patient's global assessment of well-being, (3) physician's global assessment of disease activity, and (4) ESR. The sum of these four components yields a number on a continuous scale to quantify disease activity. The ACR pediatric response criteria (ACRpedi30, 50, 70) are standardized treatment response measures defining clinical improvement (258). This core set of six variables include the CHAQ score and the number of joints with restricted movements, in addition to the variables included in the JADAS. The score is a calculation of improvement in these variables over time. An advantage of JADAS is the ability to measure disease activity in individuals or groups of patients at a single visit. Both JADAS and ACRpedi are validated for use in JIA in large populations (257, 258).

1.4.2.2 Patient-reported outcome

Questionnaires that encompass broad aspects of functioning, pain and health-related quality of life (HRQoL) are useful in daily clinical care (259). A generally accepted definition of Health Related Quality of Life (HRQOL) is the patient's subjective perception of the impact of his disease and its treatment on daily life; physical, psychological, social functioning and well-being, while QOL is usually described as an overall assessment of well-being (255). In children self-reported measures is filled in by their parents/ proxies until the child is able to report themselves. This is a practical, although not perfect way of reporting, because discordance between proxy-reported and observed assessment of functional ability is found (261). Questionnaires can be filled out in the waiting room before the visit. This allows the patient to consider the impact of disease on their daily life recently, and at the visit the physician can get an impression of disease activity and impact by a quick glance.

To secure the perspective of the child and the parents, Child Health Assessment Questionnaire (CHAQ)) and Child Health Questionnaire (CHQ) are translated and validated in many languages, including Norwegian (262, 263). CHAQ measures physical functioning in 30 items divided into 8 domains (dressing, arising, eating, walking, hygiene, reach, grip, activities), including registration of aids and devices, and help from other persons for physical functioning. It also includes two visual analogue scales on pain and overall well-being. CHAQ is the most extensively used patient-reported outcome measure in JIA, has a high reliability, but only a moderate correlation with other disease activity indices, and shows a low responsiveness to change. A ceiling effect may be a problem, because most children with JIA report low levels of disability according to the CHAQ (263). The CHQ is a family of generic quality of life instruments measuring 14 physical and psychosocial domains. These cover broad aspects of daily functioning and the domains can be combined in a psychosocial and physical summary score (264).

1.4.2.3 Inactive disease and remission

Several different definitions of inactive disease and remission in chronic childhood arthritis have been used. ACR provisional criteria for inactive disease and remission are recently published by Wallace et al in order to standardize this important outcome measure (Table 5) (173).

Table 5. American College of Rheumatology provisional criteria for inactive disease and the preliminary criteria for clinical remission of juvenile idiopathic arthritis (JIA).

Inactive disease:*   No joints with active arthritis   No fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA   No active uveitis as defined by the SUN Working Group†   ESR or CRP level within normal limits or, if elevated, not attributable to JIA‡   Physician's global assessment of disease activity score = best possible on the scale used   Duration of morning stiffness of <15 minutes
Clinical remission: Two types of clinical remission are proposed§   **Clinical remission on medication.** The criteria for inactive disease must be met for a minimum of 6 continuous months while the patient is on medication in order for the patient to be considered to be in a state of clinical remission on medication   **Clinical remission off medication.** The criteria for inactive disease must be met for a minimum of 12 continuous months while off all anti-arthritis and anti-uveitis medications in order for the patient to be considered to be in a state of clinical remission off medication

*All criteria must be met.
†The Standardization of Uveitis Nomenclature (SUN) Working Group defines inactive anterior uveitis as "grade zero cells," indicating <1 cell in field sizes of 1 mm by a 1-mm slit beam.
‡ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.
§ Based on the previously published preliminary criteria of remission and inactive disease in select categories of JIA (175). Adapted from Wallace et al in J Rheumatol 2004 and Wallace et al in Arthritis Care Res 2011 (173, 175).

1.4.2.4 Other outcome measures

Steinbrocker functional class has been used for more than six decades to describe function and damage in rheumatic diseases (265). Due to significantly improved outcome during the last decades, this measure is less used nowadays. Juvenile Arthritis Damage Index (JADI) is a newer validated clinical tool for physicians to assess permanent articular and extraarticular damage in JIA (245).

Bone erosions are a sign of joint damage caused by the disease, but even severe bony destruction may to some degree be reversible in children. Several radiological scores have been developed for JIA to standardize descriptions of bony erosions, destruction and growth disturbances (266-268). Recently, a standardized score for magnetic resonance imaging (MRI) in children with JIA is also proposed, but more knowledge on normal MRI of the growing skeleton is clearly needed (269-271).

1.4.2.5 Developing validated outcome measures

Outcome tools have been derived in many different ways. When there is clinical need for a precise measure, creativity methods may be used (254). In a structured form of brainstorming, experts in the field generate a wide range of answers to the topic discussed, and then the variables are narrowed down to the most important items. Examples of this process are the Delphi and the nominal group technique (254). Such proposed consensus criteria, followed by several validation studies, have resulted in the provisional ACR criteria for inactive disease in JIA (173, 175, 272). Some measures have been adapted from adult rheumatology for use in children, i.e. the CHAQ is a children's version of HAQ developed for rheumatoid arthritis (233, 273).

A thorough testing for reliability and validity is necessary before an outcome measure can be trusted. Face validity is an important aspect describing that the outcome measure is feasible and user-friendly. Content, criterion and construct validity must be verified, showing that the tool measures essential items, can predict certain outcomes, and measures what it is intended to measure. Discriminative ability ensures that the

measure is able to detect clinically important differences, for example between healthy children versus children with JIA or low versus high disease activity (254). The tool should also be sensitive to measure change over time, for example before and after an intervention, and test-retest reliability should be present.

Table 6. Disease activity and outcome measures commonly used in JIA.

	Patient/parent-reported versus Physician	Generic versus disease-specific measure	Description
Disease Activity			
Child/parent global assessment of overall well-being (VAS 0-10)	PR	Generic	Overall well-being
Physician global assessment of disease severity (VAS 0-10)	Physician	Generic	Disease severity
Pain (VAS 0-10)	PR	Generic	Pain
ACR Pedi30, 50, 70 = ACR pediatric measures of improvement criteria	Physician	Disease-specific	Composite improvement
JADAS = Juvenile arthritis disease activity score	PR/ physician	Disease-specific	Composite disease activity
Function and HRQoL			
CHAQ = Childhood health assessment questionnaire	PR	Disease-specific	Physical function
CHQ = Child health questionnaire	PR	Generic	Physical function, Psychosocial function
JAQQ = Juvenile arthritis quality of life questionnaire	PR	Disease-specific	Physical function, psychosocial function, and general symptoms
Steinbrocker functional class (I-IV)	Physician	Disease-specific	Physical function
JAMAR = Juvenile arthritis multidimensional assessment report	PR	Disease-specific	Physical function, psychosocial function, HRQoL, compliance, side effects, and general symptoms
JAFAR = Juvenile arthritis functional assessment report	PR	Disease-specific	Physical function
CHAIMS = Childhood Arthritis Impact Measurement Scales	PR	Disease-specific	Physical function and pain
Damage			
JADI = Juvenile arthritis damage index	Physician	Disease-specific	Articular and extraarticular damage
Radiology scores	Physician	Disease-specific	Bony destruction, growth disturbance

*VAS = Visual analogue scale; PR = Patient/parent-reported; ACR = American College of Rheumatology; HRQoL = Health-related quality of life; references for the outcome measures (245, 257-259, 263-268, 273-278)

1.4.3 Contextual factors in outcome

There are numerous factors in addition to the disease itself that influence outcome. Access to adequate care for children with chronic diseases is a global challenge. A goal must be that adequate health care and treatment is available to all children also in less privileged countries. According to the UN convention on rights of the child, children has the right "to the enjoyment of the highest attainable standard of health and to facilities for the treatment of illness and rehabilitation of health" (273) . Late access and poor health care for less privileged groups is a political issue, when there are short-comings of governmental health care. Children with JIA in the USA are less likely to have the recommended eye screening if they are not covered by a private insurance (280). Biologic agents for control of arthritis and uveitis are expensive and therefore not available to many children worldwide.

A prolonged interval from onset of symptoms to the diagnosis is established and treatment started, may adversely affect clinical outcome. Longstanding arthritis before joint injection is performed is shown to increase the risk of leg length discrepancy, muscle wasting or functional disability (281). Longer time interval until start of DMARD treatment is a predictor of lower treatment response (44, 177). Health care workers should be trained in musculoskeletal examination in order to recognize signs of rheumatic disease in children and avoid prolonged delay. A statement on standards of care for JIA is recently developed by British pediatric rheumatologists to ensure adequate health care for children with JIA (172, 230, 282).

Compliance to prescribed treatment is an under-recognized problem in medicine. Adherence to medical regimens may influence the outcome in JIA. Nausea and other gastrointestinal side effects of methotrexate are common, and often increase over time (198). This problem is increasingly recognized and non-medical techniques as cognitive therapy and hypnosis is described to be helpful (283). Adolescence is a particularly vulnerable age, where the motivation to regular intake of medicines is variable. The transition from pediatric to adult health care can be problematic, and the

challenge is to provide developmentally appropriate and uninterrupted health care (284-286). Knowledge on the disease, self-management strategies and meaningful social support was rated by young people to be important factors in this period of transition (287). Young people should be given the chance to express their views and be seen without their parents at visits (284). Continuity in health personnel, individualized timing of information and transition, and increasing self-advocacy over several years are important elements of a successful transition process (288, 289). A structured and evidence-based transitional care program is shown to increase health-related quality of life in adolescents moving on from pediatric to adult care (290).

1.5 Study design in JIA research

Historically, knowledge in pediatric rheumatology was based on case reports, case series and hospital-based retrospective cohorts. In spite of numerous studies reporting incidence, course and outcome in JIA, results are difficult to compare, and evidence-based knowledge is still sparse. Selection bias is a common problem, limiting generalizability of the findings. Important recent contributions come from population-based cohorts and registries, cross-sectional studies, and also randomized controlled trials (181). Case reports, case series, case-control and prospective cohort studies may all play important hypothesis-generating roles, while experimental studies are considered gold-standard of elucidating causal mechanisms (158). There is increasing attention to the need for translational research, moving scientific results from basic science into better clinical outcomes (89, 291). Epidemiologic research in JIA is an important source for new hypotheses on etiology, clearer definitions and classification of categories, disease course and outcome (159). RCT and metaanalyses of RCT are considered to give the most important contribution to evidence-based medicine (Figure 2). However, many important research questions cannot be answered by a RCT. Criticism have been raised that the “hierarchy of evidence” is a narrow idea that only applies to therapeutic evaluation, particularly of drugs (158). Other designs are more important in understanding causality, and the spectrum and burden of the disease.

Therapeutic trials on treatment are based on knowledge from epidemiologic, basic and translational research. A wide range of research methods are needed to gain more knowledge on JIA to refine treatment and clinical care.

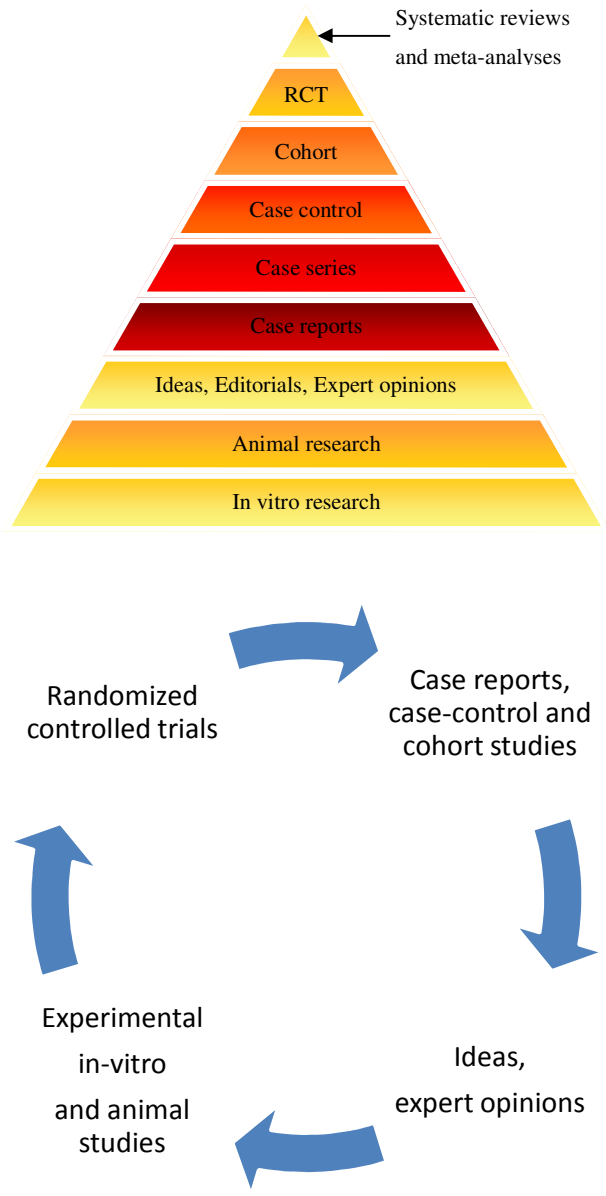


Figure 3. "Dismantling the pyramid"; from a hierarchical to a circular model of interdependency between different study designs.

2 AIMS OF THE STUDY

To study disease activity and outcome in JIA in a prospectively collected cohort of children included shortly after diagnosis in defined geographical areas of the Nordic countries by;

I. Assessing disease characteristics, course and long-term outcome including changing JIA categories, medical treatment, damage, and remission status in a population-based setting.

II. Evaluating the newly developed disease activity score (JADAS) by;
   a. Comparing the JADAS based on CRP to JADAS based on ESR.
   b. Testing JADAS in a population-based setting.

III. Evaluating biomarkers and clinical risk factors for development of chronic uveitis; antihistone antibodies, ANA by immunofluoresence and ELISA analyses, and other disease defining characteristics.

3 MATERIAL AND METHODS

The study was initiated and designed by The Nordic Study group of Pediatric Rheumatology (NoSPeR), a researcher-initiated group of experienced pediatric rheumatologists. Members of the group have initiated and conducted other large scale prospective epidemiologic studies on incidence and outcome in JIA in southern Sweden and in Costa Rica (47, 122, 124, 125, 128, 137, 292). The Nordic JIA study has previously been the basis of a thesis of medicine (PhD) by Dr. Lillemor Berntson, Göteborg in 2003, and also resulted in several publications in international journals of rheumatology (35, 62, 125, 160, 256, 293). Meetings in the steering group of NoSPeR have been held twice yearly since 1995 for planning, initiating and conducting the study. Protocol details and definitions have been discussed and clarified throughout the study period. In case of missing or conflicting information, each center has been asked for clarifications repeatedly during the study period.

3.1 Study design

The Nordic JIA study is a prospective, multi-center cohort study of juvenile idiopathic arthritis in defined geographical areas in Denmark, Finland, Norway and Sweden.

3.2 Inclusion criteria

All children with a new diagnosis of JIA according to the ILAR criteria within the study period and living in the study areas at disease onset were included. Study areas and inclusion periods are described in table 7. The minimum requirement for continued inclusion in the followup study was 2 registered visits, including the baseline visit and a followup visit more than 7 years after disease onset for study I, and a followup visit more than 3 years after disease onset for study III. All study visits with JADAS variables recorded in children included during an extended study period (Table 7), were analyzed in study II. During the study period, pediatric

rheumatologists from 12 participating centers registered all consecutive new patients with JIA diagnosed according to the ILAR criteria. With the aim of making the study as close to population-based as possible, letters were repeatedly sent to the primary health care and all orthopedic, pediatric, and rheumatology specialists in the catchment areas during the inclusion period, requesting referral of potentially eligible patients. To our knowledge only 3 of all eligible patients did not wish to take part in the study. In the Nordic countries, all visits to primary care physicians and public hospitals are mostly free of charge for children under 16 years of age, and the health care systems include regular visits at a child health center for preschool children. The health care system of the four countries is rather uniform and mostly public.

Table 7. Inclusion periods of the different studies in geographical areas of the Nordic juvenile idiopathic arthritis cohort included in the thesis.

	Study I	Study II	Study III
	Population-based	Partly population-based	Population-based
Denmark, East	01.01.1997- 31.12.1999	01.01.1997- 30.06.2001	-
Denmark, Århus	01.07.1997- 31.12.1998	01.01.1997- 31.12.1998	-
Finland	01.07.1997- 30.06.2000	01.01.1997- 30.06.2001	-
Norway	01.01.1997- 30.06.2000	01.01.1997- 30.06.2000	01.01.1997- 31.12.2002
Sweden	01.01.1997- 31.12.1999	01.01.1997- 31.12.1999	-

3.1 Patients and settings

The study areas are shown in figure 4. The centers and corresponding areas taking part in the study were those that had a tradition of diagnosing and treating all new cases of JIA in their catchment areas. The incidence of JIA in the study area in 1997- 1998 was 15 per 100.000 children/ year (range 9 - 23 in different areas) as previously reported (11). The estimated population at risk in the study areas were 1 413 738 children aged <16 years in 1999 (11). Iceland, the fifth Nordic country, was part of the initial incidence study, but has not taken part in the present followup study. The inclusion period for Study I was the period that all centers put in maximum efforts to include all eligible children from their area (Table 7). In Study II the aim was to validate JADAS, and we decided to include all visits with all JADAS items available in the study database, extending the inclusion period to include some patients not included in study I (38 of the 389 patients). The overlap between the study cohorts of studies I - III are shown in Figure 5. The followup period of study I and II was up to 12 years. In Study III the Norwegian children from Troms, Finnmark, Nord-Trøndelag, Sør-Trøndelag and Møre- og Romsdal regions were included from the study centers of Tromsø and Trondheim (Figure 4, red areas). Study III was started as a pilot study of all Norwegian children that were registered in the Nordic JIA database, and the data and laboratory analyses were performed before the 8-year followup was finalized. A majority of the patients in study I were also part of study II and III. The followup period of study III was up to 11 years. The numbers of patients lost to followup and time points of dropping out of the followup group are shown in the flowchart in figure 6 and figure 7. Among the 60 patients lost to followup, 17 had moved, 12 did not wish to participate in further followup, and the rest gave no response or “unknown reason” was noted. Comparing the followup group and the 12.0% lost to followup, there were no significant differences in baseline characteristics with respect to number of active joints during the first six months after onset, CHAQ and JADAS27 score, or proportion with oligoarticular subtype. However, higher median age at onset and presence of RF, lower median ESR, CRP and presence of ANA, were found in the group lost to followup (Table 8).

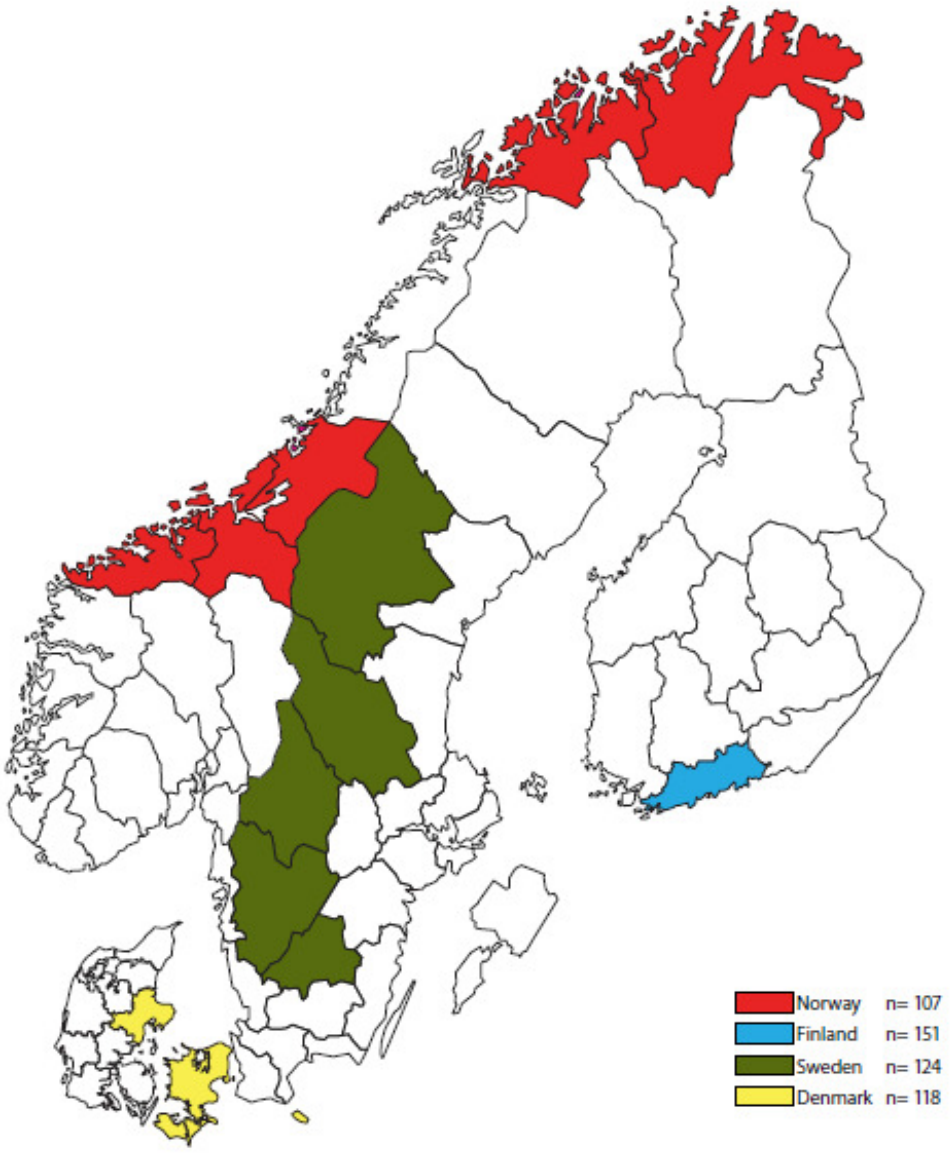


Figure 4. Map of the Nordic countries showing the geographical areas of the Nordic JIA study; study I and II: all colored areas, study III: red colored areas.

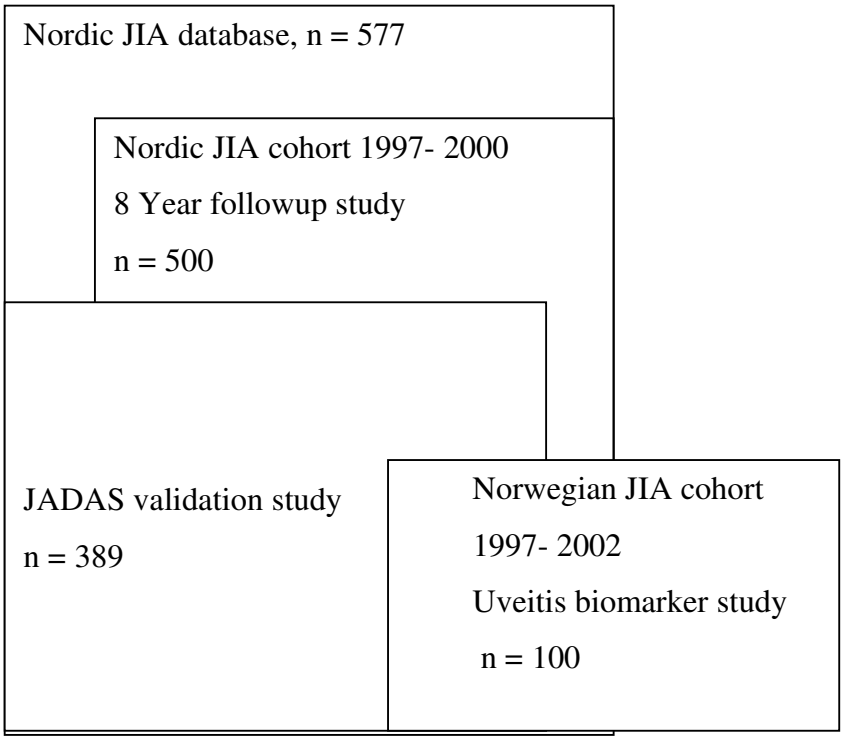


Figure 5. Diagram showing the partially overlapping study cohorts of the Nordic JIA database, the population-based Nordic JIA cohort, the JADAS validation study, and the Norwegian uveitis biomarker study.

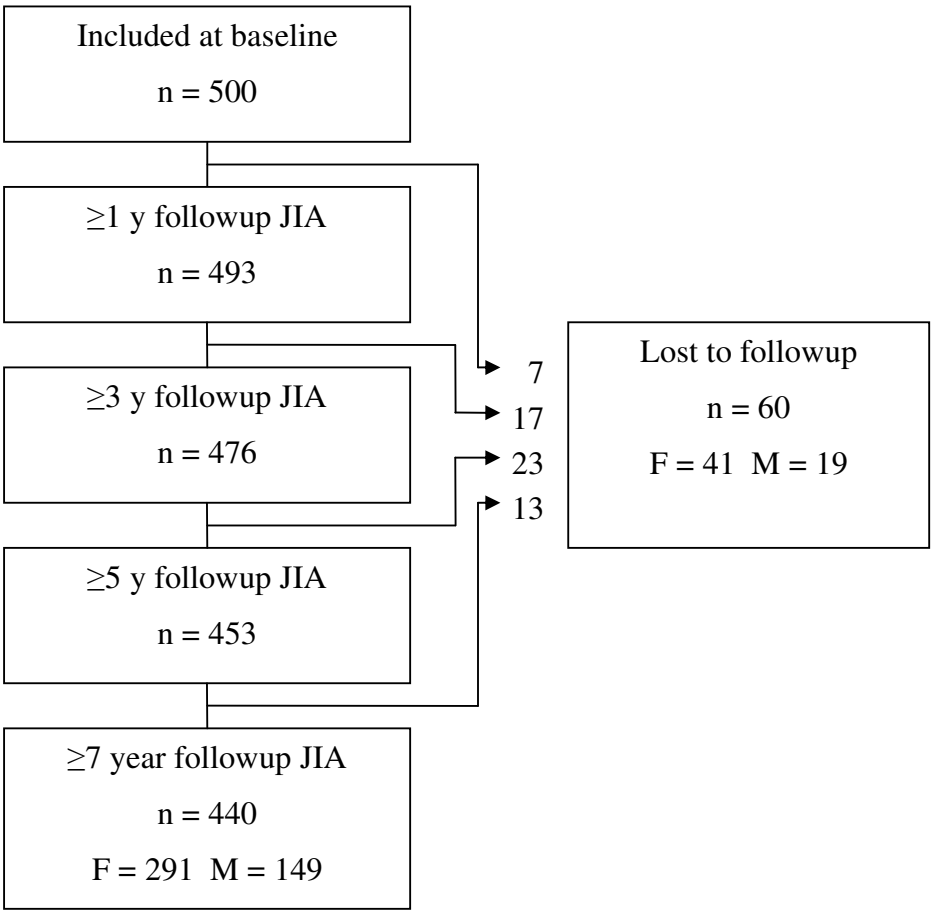


Figure 6. Flow chart of the Nordic JIA study showing the proportion of children lost to followup during the study period.

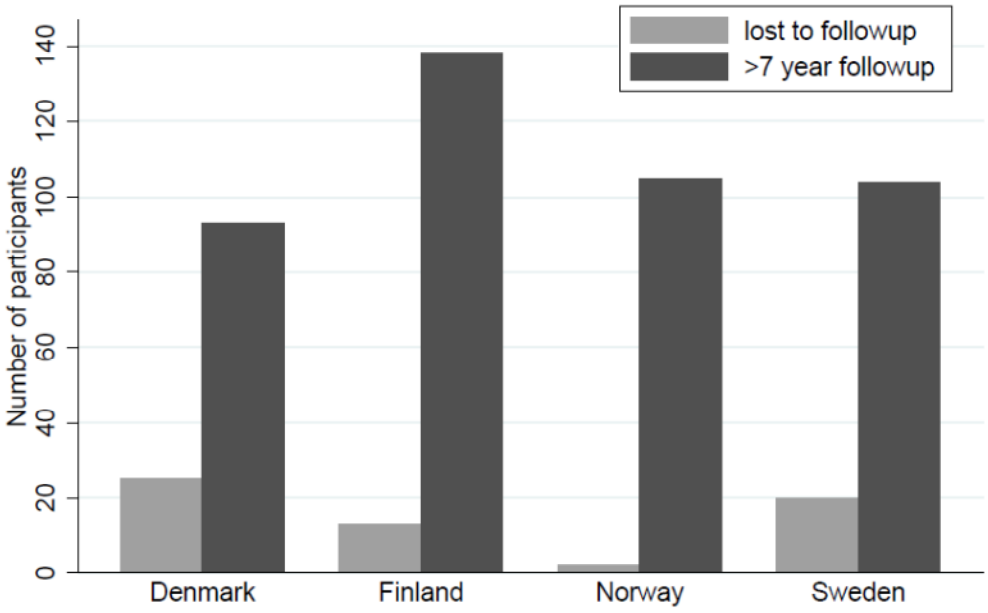


Figure 7. Diagram of number of participants and children lost to followup during the study period in the different countries in the Nordic JIA study.

Table 8. Clinical characteristics of participants in the Nordic juvenile idiopathic arthritis (JIA) cohort at the first study visit, median seven months after disease onset

	Total		Followup participants		Participants lost to followup		*P**
	No.	No. (%)	No.	No. (%)	No.	No. (%)	
Female gender	500	332 (66.4)	440	291 (66.1)	60	41 (68.3)	NS
Oligoarticular†	500	262 (52.4)	440	225 (51.1)	60	37 (61.7)	NS
ANA positive‡	449	113 (25.2)	391	107 (27.4)	58	6 (10.3)	0.005
RF-positive‡	439	15 (3.4)	389	10 (2.6)	50	5 (10.0)	0.006
HLA-B27 positive	431	91 (21.1)	385	83 (21.6)	46	8 (17.4)	NS
		Median (IQR)		Median (IQR)		Median (IQR)	
Age at onset (years)	500	5.9 (2.7-10.0)	440	5.5 (2.5-9.7)	60	8.8 (4.7-12.0)	0.0006
Active joints first six months	453	3 (1-6)	399	3 (1-6)	54	2 (1-5)	NS

CRP§	395	0 (0-10)	354	0 (0-10)	41	0 (0-0)	NS
CRP maximum value§	368	13 (0-33)	332	14 (0-35)	36	0 (0-18)	0.023
ESR§	399	13 (8-27)	358	14 (8-28)	41	10 (5-15)	0.025
ESR maximum value§	368	33 (15-35)	333	35 (16-56)	35	18 (10-36)	0.014
Parent/pat global assessment§	299	1.0 (0.2-3.0)	271	1.0 (0.2-3.0)	28	1.0 (0.0-2.3)	NS
Physician global assessment§	278	1.0 (0.5-3.0)	248	1.0 (0.5-3.0)	30	1.0 (0.9-2.0)	NS
CHAQ§	309	0.3 (0.0-0.9)	278	0.3 (0.0-1.0)	31	0.1 (0.0-0.4)	NS
JADAS27	220	5.0 (2.0-10.2)	197	5.0 (2.0-10.5)	23	4.4 (2.0-8.0)	NS

* Chi-square test for dichotomous outcomes and Mann-Whitney U test for comparison of median values. *P* values are obtained comparing the followup study group with participants lost to followup. NS = not significant.
† Oligoarticular JIA six months after onset of disease, according to the International League of Associations for Rheumatology (ILAR) classification criteria (5).
‡ ANA = antinuclear antibodies and RF = rheumatoid factor; two positive tests taken >three months apart in participants with one or more tests taken.
§ Disease activity characteristics; CRP = C-reactive protein and ESR = erythrocyte sedimentation rate, at six months and maximum value reported during the first six months; Parent/pat global assessment = parent's (child <9 years) / patient's (child ≥9 years) global assessment of overall well-being 10-cm visual analogue scale (VAS) (range 0-10); Physician global assessment = Physician's global assessment of overall disease activity 10-cm VAS (range 0-10); CHAQ = Child health assessment questionnaire; JADAS27 = Juvenile arthritis disease activity score based on 27 joints (range 0-57).

3.2 Data collection

Family histories, extensive clinical data including complete joint counts, ophthalmologic status, medications used, patient/parent-completed health assessment measures, and results of blood tests were registered per protocol in a database at all study visits. A study visit was planned every 6 months during the first year after disease onset and then every 1-2 years during the observation period. Fewer visits were registered mainly in Finland and Denmark, and totally a mean of 5 visits were registered per participant. A minimum of two registered visits were required for staying included in the study. At the final study visit of study I, 8 years after disease onset, extended information was collected, including an update on family history. For the final visit of study I, participating patients received a letter of invitation followed by a reminding letter; patients who did not respond were contacted by telephone and asked to participate in a visit. In the few cases in which a final study visit was not possible to obtain, the patients were asked to participate in a telephone interview. This standardized telephone interview contained all information that otherwise, per protocol, was collected during visits. This included the patient's own description of involved and restricted joints, presence of uveitis and systemic features. The patients were asked if they were willing to fill in and return relevant questionnaires sent by ordinary mail. In all participating children the JIA categories were determined according to the ILAR criteria (18), based on all available information that was registered at each visit during the study period. Uveitis was defined as present, when the ophthalmologist prescribed treatment of uveitis. The uveitis was described in terms of presence of symptoms, duration, and course of uveitis in the database, and retrospectively classified according to the recommendations by the Standardization of Uveitis Nomenclature (SUN) working group (132). Uveitis was then defined as "acute," symptomatic with acute onset and limited duration, or "chronic" insidious onset, mainly asymptomatic with chronic recurrent or persistent course. The Juvenile Arthritis Damage Index (JADI) (245) was scored by the pediatric rheumatologist; articular damage was scored on a scale in which 0 = no damage and 72 = maximum damage, extraarticular damage was scored on a scale in which 0 = no damage and 17 =

maximum damage, and global damage were scored on a 10-cm VAS in which 0 = no damage and 10 = maximum damage.

3.2.1 Patient/parent-reported measures

Questionnaires on self-reported health-related quality of life were registered; the Child Health Questionnaire (CHQ) was used for patients younger than 18 years (259;283-286), and the HAQ (233) (0 = best and 3 = worst) and Short Form 36 health survey (SF-36) (294) were used for patients older than 18 years. The CHQ and the SF-36 are generic instruments comprising subscales on aspects of physical, emotional, and social health, yielding a physical score and a psychosocial summary score, with higher scores indicating better health (range 0- 100, mean SD 50 +/- 10) (264). Scores for the Childhood Health Assessment Questionnaire (C-HAQ; 0 = best and 3 = worst) (16–20) and scores on a 10-cm visual analog scale (VAS) for pain (0 = no pain and 10 = worst pain) and overall well-being (global health; 0 = best and 10 = poorest) were provided by patients who were older than 9 years and by the parents of younger patients. Global disease activity was assessed by the physicians, using a VAS (0 = no activity and 10 = maximum activity).

3.2.2 Laboratory methods

C-reactive protein was measured with immunoassays, with upper normal values ranging from 3-10 mg/liter; in the study protocol, the cut-off value for the whole population was set to <10 mg/liter. HLA-B27 antigens were analyzed. RF status was determined by ELISA (Denmark), nephelometry (Norway and Sweden), latex agglutination testing (Sweden), and immuno-turbidimetric testing (Finland), performed twice, at least 3 months apart. For study I and II, analyses of antinuclear antibodies (ANA) were performed twice, at least 3 months apart at the local laboratory. Each physician interpreted the results of the ANA and RF analyses as positive or negative according to the reference values used by the local laboratory. In Sweden, Denmark, Finland, and Trondheim, Norway, ANA were measured using immunofluorescence on HEp-2 cells (IF-ANA). In Tromsø, Norway, an ANA

enzyme-linked immunosorbent assay (ELISA-ANA) was used; these results were later excluded from the analyses in study I and II, due to the limited clinical value in JIA (295). In study III, ELISA-ANA, IF-ANA and AHA were analyzed in serum samples collected within the first year after disease onset. ELISA-ANA and IF-ANA were performed at the same laboratory technicians at the same laboratory and during a short time period at St. Olav's Hospital in Trondheim, Norway, and the results were evaluated by Torolv Moen, one of the co-authors of the paper. AHA analyses were performed by one laboratory technicians and Ellen Nordal at the same laboratory and during a short time period at University of Tromsø, Norway. Details regarding the analyses and kits are given in the paper on study III. The control sera in study III were collected in order to provide information on the presence of ELISA-ANA, IF-ANA, and mean serum values of AHA in a healthy childhood population. The control sera were obtained from routine blood tests in 58 children undergoing elective outpatient procedures, with no diagnosis of inflammatory diseases.

3.3 Data base and data handling

A 4D database was designed specifically for the Nordic JIA study. Patient data from each visit was entered into the data base and stored at the participating centers. By the end of 2008 all data were sent from the study centers to Tromsø, Norway. The data were transferred to Excel 2002 for Windows and pooled for a common Nordic data-file. Using the Excel file, all patient data were scrutinized for all disease descriptors and JIA categories decided at each visit by Ellen Nordal. For the majority of patients JIA categories were determined separately by Ellen Nordal and Lillemor Berntson, one of the co-authors of the papers. A few differences were found, mainly due to the updated ILAR criteria published in 2004, discarding the influence of psoriasis in a second degree relative. The discrepancies were settled by joint discussion and evaluation. Data regarding remission status recorded by the examining physician was cross-checked for inconsistencies with disease activity variables; active joint count, inflammatory markers and patient/parent and physicians VAS scales should all be zero

according to the definitions of inactive disease and remission (175). Any inconsistencies were noted and participating centers asked for clarifications.

3.4 Statistical methods

Statistical analyses were performed using Stata version 10, 11 and 12 software, and details of the statistical analyses are described in the method sections of the papers. Descriptive statistics were used to summarize the clinical characteristics of the population and measures of disease activity. Chi-square and Fisher's exact tests were used as appropriate for comparison of dichotomous variables, and the Mantel-Haentzel method was used for stratified analyses to control for confounding. The Mann-Whitney U test was used for comparing medians for skewed data. The Student's t-test and analysis of variance, with Bonferroni contrasts, were used to compare means in continuous outcome variables between groups, logarithmic transformation of the variable was carried out, and geometric means reported for skewed data when appropriate. Odds ratios (OR) with 95% confidence intervals (CI) were calculated using logistic regression. Linear mixed model analyses of z scores were used to account for dependence between repeated measures within study participants over multiple visits in study II. Bland-Altman plot was used to assess the magnitude of any systematic difference and random error between the two JADAS measures in study II. Sensitivity, specificity, the likelihood ratio (LR), and the positive and negative predictive values were calculated to describe the test performances of predictors of uveitis in study III. Receiver operating characteristics (ROC) curve and the corresponding area under the curve (AUC) was used to assess the sensitivity and specificity of AHA as a predictor of uveitis in study III. P-values less than 0.05 were considered significant.

3.5 Ethical considerations

Approval from the Regional Committee for Medical Research Ethics of Northern Norway and the corresponding ethic committees and data inspectorate agencies of each participating country was granted. Written informed consent was obtained from the parents of children younger than age 16 years and from the children who were age 16 years or older.

4 SUMMARY OF THE RESULTS

Paper I

Ongoing Disease Activity and Changing Categories in a Long-Term Nordic Cohort Study of Juvenile Idiopathic Arthritis.

Ellen Nordal, Marek Zak, Kristiina Aalto, Lillemor Berntson, Anders Fasth, Troels Herlin, Pekka Lahdenne, Susan Nielsen, Bjørn Straume and Marite Rygg for the Nordic Study Group of Pediatric Rheumatology. Arthritis Rheum 2011;63(9):2809-18.

- In this study 500 children was included, 440 (88.0%) of these had repeated visits, with the last visit occurring at least 7 years after disease onset (median 98 months, range 84–147 months).
- Changes in the International League of Associations for Rheumatology (ILAR) category during the disease course were observed in 10.8% of the children, and, in addition, extended oligoarthritis developed in 34.7% of the group with oligoarticular JIA.
- During the observation period, 58.0% of the children were treated with disease-modifying antirheumatic drugs, including biologic medications.
- JIA-related damage developed in 22.9% of the children.
- Ongoing disease activity was mostly mild, as shown by low median scores of disease activity measures at the final study visit, although considerable variation was found.
- At the last followup visit 4.8% of the children reported absence from school or work for >5 days during the previous 2 months, and 76.7% of the school-age children participated fully in physical education, while 17.2% participated partly and 6.0% did not participate.
- At the last followup visit, remission off medication was observed in 42.4% of the children, 8.9% were in remission on medication, and 48.7% were not in remission.
- The highest rates of remission were observed in patients with persistent oligoarthritis and in those with systemic JIA.

Paper II

Validity and predictive ability of the Juvenile Arthritis Disease Activity Score (JADAS) based on C-reactive protein in a population-based Nordic cohort of juvenile idiopathic arthritis.

Ellen Nordal, Marek Zak, Kristiina Aalto, Lillemor Berntson, Anders Fasth, Troels Herlin, Pekka Lahdenne, Susan Nielsen, Suvi Pältoniemi, Bjørn Straume and Marite Rygg for the Nordic Study Group of Pediatric Rheumatology. Ann Rheum Dis 2011; (accepted for publication).

- Of 389 children with available JADAS score at the first study visit, the correlation between JADAS27 based on CRP and JADAS27 based on ESR was r = 0.99, whereas the correlation between CRP and ESR was r = 0.57.
- Children with higher JADAS scores had increased risk of concomitant pain, physical disability and use of disease-modifying antirheumatic drugs (DMARD).
- Higher JADAS score at a study visit the first year after onset of disease significantly predicted physical disability, damage, and no remission off medication at the final study visit (median 8 years after disease onset). This early high JADAS score also predicted use of DMARD during the disease course.
- Sensitivity to change, demonstrated as change in JADAS score compared to the American College of Rheumatology paediatric measures of improvement criteria, showed mostly excellent classification ability.

Paper III

Biomarkers of chronic uveitis in juvenile idiopathic arthritis: predictive value of antihistone antibodies and antinuclear antibodies.

Ellen Nordal, Nils T. Songstad, Lillemor Berntson, Torolv Moen, Bjørn Straume and Marite Rygg. J Rheumatol 2009;36(8):1737-43.

- Chronic uveitis developed in 16 of 100 children with JIA, and acute uveitis in two children.
- Chronic uveitis developed in 14 of 68 children with positive immunofluorescence titer of ANA ≥80, and in 13 of 44 children with antihistone antibodies ≥8 U/ml.
- Antihistone antibodies were found in higher proportions in children with uveitis (mean 12.4 U/ml), than in those with JIA and no uveitis (mean 6.9 U/ml) or in healthy controls (mean 4.3 U/ml).
- All children with chronic uveitis had either a positive immunofluorescence titer of ANA ≥80 and/or positive antihistone antibodies ≥8 U/ml.
- Young age at onset of arthritis, presence of IF-ANA titer ≥320, and antihistone antibodies ≥30 U/ml were significantly associated with development of uveitis, but there were no association to female gender or oligoarticular onset of JIA.
- Antinuclear antibodies (ANA) tested by ELISA-technique was positive in four of the 100 sera from children with JIA, and was not associated with uveitis.

5 GENERAL DISCUSSION

The present study contributes to the current understanding of JIA by describing disease outcome the first eight years of disease course in a population-based setting. The change in disease categories over time challenges the present ILAR classification criteria. A low level of disease activity was found eight years after onset, although there was a considerable range in functional disability, pain and general impact of the disease. The composite disease activity measure JADAS can be an important clinical tool and was shown valid in a population-based setting. ANA method is important in predicting uveitis development in JIA. Our findings on a high rate of non-remission support the understanding of JIA as a long-standing chronic disease, and a significant proportion of the children in our cohort had some disease-related damage.

5.1 Strengths and limitations

The population-based setting is a major strength of the study. The cohort is derived from a defined population, which enables extrapolation of the results beyond our study group. Our cohort is prospectively collected and followed longitudinally over many years. Heredity and a broad range of detailed clinical information were thoroughly registered to ensure a well-characterized cohort. Recently developed disease activity, damage and remission measures were used.

A limitation in our material is a small number of patients in some of the disease categories. This should be kept in mind when interpreting findings in the systemic, the polyarticular RF-positive and the psoriatic arthritis category. The first study visit often took place after the initial peak of disease activity, which may be a limitation for prognosis studies on baseline predictors. The first study visit was timed approximately six months after disease onset, when data to assess JIA category were available, since the study initially focused on incidence and classification issues. However, clinical information at the first registration was then collected for the whole initial period of

the disease. Because cases were collected at referral centers, the mildest cases may not have been included, inflicting a risk of selection bias towards more severe disease.

5.2 Methodological considerations

5.2.1 Choice of study design

Methodological differences are a major obstacle when comparing information on incidence, disease course and outcome of JIA from different studies. NoSPeR has chosen to perform a longitudinal population-based cohort study in the Nordic countries. The strengths of a longitudinal cohort study are the possibilities to identify baseline predictors of certain outcomes such as development of uveitis or severe disease activity and damage. In order to collect the full spectrum of the disease and precisely describe incidence, course and outcome, the population-based approach is necessary (158).

Traditionally many studies on JIA have been case series or cross-sectional, usually retrospective studies from tertiary referral centers, collecting only the most serious cases. Selection bias has clearly been a problem. Milder clinical cases might never be referred to a pediatric rheumatologist and will be lost in referral-based retrospective studies. There is a bias towards lower rates of the milder oligoarticular disease and higher rates of seriously ill systemic JIA in the literature, especially in older studies (296). The uniform organization of health care system in the Nordic countries provides unique opportunities to minimize the problem of selection bias, and epidemiologic studies of the incidence and natural history of JIA in a geographically defined population can be performed (24, 44, 122).

5.2.2 Population-based approach

We have tried to be as population-based as possible. But is our study truly population-based? A population-based study must be able to define and characterize its study population. In the geographic areas of our study, baseline demographic data as total number of inhabitants, age and gender distribution are available. A critical question is if all eligible children in these areas were included? Possible reasons for missing cases is that; 1) cases are undiagnosed or not referred, 2) cases are referred to other specialists than the participating centers, 3) cases are not correctly diagnosed at the participating center (most centers are general pediatric departments with pediatric rheumatologists in the staff), and 4) cases are refusing to participate.

Undiagnosed cases are probably few, because the Nordic health care systems include regular checkups at a child health centre. Health care facilities at school, the general practitioner and specialist care are easily available, mostly governmental and all free of charge for children. Most children with a long-standing complaint will probably be found and referred. From a previous study of JIA in the region of Northern Norway, the prevalence show overlap with the 95% CI of truly population-based prevalence studies in Australian and Belgian school children, indicating that at least in this region most of the JIA cases are probably referred (102, 159, 163, 164). The possibility of missing milder cases can still not be excluded, as long as all children in the area were not examined by a pediatric rheumatologist.

Referral of all eligible cases to the study centers were our aim. Measures were taken to include only geographical areas where the centers had a tradition over many years to diagnose and treat all patients with suspected rheumatic diseases in their catchment area. As previously described, all the collaborating departments, general practitioners and all private specialist clinics in the regions received repeated written information on the ongoing JIA study. Some regions (Nord-Trøndelag, Møre- og Romsdal, East Denmark) had the experience that a few incident cases from their region were referred to other hospitals outside the study centre. The main outcomes of the subgroup from

these centers were analyzed separately without significant differences in rates of oligoarticular category or remission status.

In order to diagnose correctly case ascertainment was done by 20 experienced pediatric rheumatologists conducting the study, using uniform inclusion and assessment criteria. Efforts were taken to standardize clinical assessments to avoid misclassification, by meetings in the study group, comprising ten of these pediatric rheumatologists. Definitions were discussed to reduce inter-observer variations that might have influenced the quality of the data. Refusal to participate was not a major problem, because only three eligible patients did not wish to be included in the study, and 12 stated that they did not wish to continue in the followup study.

The population-based setting is clearly important for validity of the outcome data of study I. This also applies for the study on biomarkers for uveitis in study III, but the children took part only if there were an available blood sample and an informed consent for this particular study. No statistically significant differences in the rate of uveitis or oligoarticular category were however found between the total Norwegian cohort and the participants in study III. In the JADAS validation study we considered the advantage of having more visits to analyze more important than the drawback of not keeping a strict population-based approach. This is because the correlations, predictive value and responsiveness to change of JADAS are validated against outcomes within the group. The inclusion period was therefore prolonged for study II to include all participants in the data base, also from time periods when the centers were not convinced that all eligible children with JIA were included. Nine tenths of the participants in Study II originate from the population-based cohort, so the study still is unique in its population-based approach compared to validations of JADAS in therapeutic trial settings.

5.2.3 Lost to followup

Even though only 12% of the cases are lost to followup, they represent a risk of selection bias to our results. The group lost to followup has a higher age at onset, which may explain the higher presence of RF and the lower presence of ANA and uveitis. Study adherence is more difficult to achieve after transfer to adult rheumatology for the oldest patients, which is a problem also in other studies (63).

5.2.4 Followup telephone interview

Another limitation is that 14.5% of the children answered a telephone interview on their present health status, instead of a complete examination by a pediatric rheumatologist. However, the telephone interviews gave valuable information on the proportion of children that do not meet to clinical examination, and otherwise would be lost to followup. Telephone interviews were mainly performed in participants more than 16 years old. Studies on RA in adults have shown that the correlation is moderate to high between patient-reported swollen and tender joint count and a joint count performed by a rheumatologist (297).

5.2.5 Data quality and data handling

To what extent is our data accurate? At each visit clinical data from the examination, self-reported measures, and course since last study visit was recorded. When there is a long time span of more than 1-2 years since the last visit, data on disease course may be less trustworthy. Data handling from the study database via Excel to statistical software can be a potential source of systematic or random errors. For each participant a summary of all the study visits were made in Excel and manually updated based on all the registered visits. For each visit assessment, the JIA category was decided after consideration of all disease descriptors. Random errors may have occurred in this time-consuming work. However, JIA categories showed very consistent results, when compared to the JIA categories assessed by another researcher in our Nordic group

(Lillemor Berntson) working separately on data from the original 4D database two years earlier.

5.3 Clinical implications of the results

5.3.1 Changing categories and classification issues (study I and III)

Stable homogeneous disease categories are a goal of a clinically useful and biologically relevant JIA classification (18, 31, 37). In line with other studies, we found that approximately a third of the children with initial oligoarticular disease developed an extended course with more than four joints involved (Study I) (39, 144, 253). This change is implicit in the structure of the JIA classification (18). Oligoarticular persistent and oligoarticular extended categories are defined as two separate groups in JIA, and the former are shown to have a better prognosis both regarding remission rates and disease activity measures in many studies, including our study I (37, 41). This continuous change makes it impossible to give early prognostic information based on disease onset category in the large group with oligoarticular onset. There is therefore an ongoing search for early predictors of extended disease among children with oligoarticular disease the first six months (41, 298, 299).

In addition to the children developing oligoarticular extended disease, JIA categories changed in 10.8% of the remaining children in our study. There is reason to believe that further change will occur over time, as change was observed throughout the observation period, and onset of psoriasis, enthesitis or related determinants in the children or their relatives may appear at any age. Biology is dynamic by nature, and the full clinical picture of a disease category may need time to develop (300). This a major challenge for a classification system based on clinical descriptors. Whether subdividing JIA according to psoriasis is worthwhile or not have been questioned (301).The enthesitis-related group has also been a special classification challenge (302). The proportion of children with enthesitis-related arthritis (ERA) increased from 7.7% six months after onset to 11.1% at the final study visit in our cohort. Flatø

et al described that the juvenile spondyloarthropathy (JSpA) group increased from 11.1% to 26.4% in their cohort of 72 children reviewed after ten years (44). Andersson Gäre et al showed that the juvenile ankylosing spondylitis (JAS) group increased from 4.8% to 12.1% over a seven-year period in a population-based study (137). These numbers may indicate that the present JIA classification possibly performs better in defining ERA at an early stage than the previous criteria of JSpA in JRA, and JAS in JCA.

An early finding in our Nordic JIA cohort was a very high proportion of undifferentiated arthritis, and in almost half of these cases heredity for psoriasis in a second degree relative was the reason for exclusion from other categories (35). Heredity in second degree relatives is also difficult to ascertain, and this exclusion criterion was removed in the revised 2001 Edmonton criteria (18). In study I undifferentiated arthritis is still found in more than one of ten children, when heredity and disease descriptors have been carefully considered. In many clinical studies the undifferentiated category is not mentioned (42, 221, 237, 240, 252). This category is usually not part of therapeutic trials (183, 197). The complex exclusion criteria and the undifferentiated arthritis category are limitations in clinical use of the ILAR classification.

How can classification of chronic childhood arthritis be improved, given the weaknesses pointed out above? In a search for a better classification of JIA, biomarkers are sought such as genetic associations or autoantibodies defining homogeneous groups. ANA is suggested as a determinant in classification by Ravelli et al, showing that ANA positive patients are a rather homogeneous group sharing many disease characteristics (303, 304). In study I we could not find that ANA was associated with any particular outcome pattern. We have later argued that ANA is not a suitable determinant, because it is a very unspecific immunologic marker; the sub-specificity of ANA in JIA is mostly unknown, and reproducibility is a problem because there are several different methods of detection (Study III) (75, 79, 305). The immunofluoresence ANA test is operator-dependent and uniform cut-off values does

not exist (78, 79, 305). Martini et al suggest systemic arthritis, rheumatoid factor-positive polyarthritis, enthesitis-related arthritis, and early-onset ANA-positive oligoarthritis as the more well-defined categories of JIA (37, 38). Less well-defined categories discussed are ANA-negative and/ or late-onset oligoarthritis, rheumatoid factor-negative polyarthritis and psoriatic arthritis (38).

The ILAR classification has been criticized for being too complicated for regular clinical use (156). In adults new classification criteria for rheumatoid arthritis (RA) are recently agreed upon with a quite different focus (306). The main aim is to early diagnose and start DMARD treatment in those with risk of erosive arthritis. Rheumatoid arthritis is less heterogeneous than JIA, but is still called a "disease construct" (306). Also in JIA there is some evidence for benefit of early treatment. The recently published ACR treatment recommendations also suggest five JIA treatment groups; oligoarthritis, polyarthritis, sacroileitis and systemic JIA with or without active systemic features. The stated reason for this approach is that minimal evidence support differential treatment for many of the ILAR category distinctions (46). Multiple correspondence and cluster analyses of clinically well-characterized large cohorts of JIA may give valuable clues in elaborating a more homogeneous and biologically relevant JIA classification (303).

Changing categories remains a problem, because JIA category at onset is used to guide therapeutic decisions and information on prognosis to the children and parents (51, 307). Clearly, the existing JIA classification still does not provide biologically meaningful, easily identifiable and stable classification criteria. How to improve classification of JIA remains a difficult task, but a prerequisite is high-quality clinical studies to describe in detail disease characteristics, course and outcome.

5.3.2 Disease activity and functional ability (Study I and II)

At the final study visit the disease activity measures in our cohort showed generally low scores, with median values mostly within the normal range, in line with other long-term studies (Study I) (39, 44, 47, 63, 237). Oen et al reported recently similar outcomes in a Canadian JIA inception cohort assessed within 18 months after the first disease onset (64).

In the Nordic population-based setting JADAS was shown to be feasible and valid compared with other measures of disease activity not included in the score (Study II). Previous validations have mostly been done in more homogeneous cohorts with polyarthritis and high levels of disease activity, enrolled mostly from specialized tertiary pediatric rheumatology centers (257, 308). The Nordic JIA cohort was collected consecutively, and validation was performed in a heterogeneous group with all categories of JIA. Our cohort is dominated by children with low ongoing disease activity, representative of what we see in daily clinical work, and presumably relevant for many other pediatric rheumatology centers.

In the clinic CRP may be a more easily available test than ESR. A blood sample can be taken from the finger tip instead of venopuncture in small children, results are rapidly available, and costs are comparable. The feasibility of JADAS increases when either CRP or ESR can be used. The close correlation of JADAS based on CRP and ESR, and the overall very close performance of the two measures, show validity of both measures. Our results indicate that the two measures also can be used interchangeable in the followup of the individual patient. This finding, however, should be confirmed in other studies before it can be generally recommended to use JADAS based on CRP and ESR alternating in the same patient to guide treatment decisions. A simplified JADAS version without inflammatory markers may be worth elaborating and validating, because an inflammatory marker is not always available in a clinical setting (257).

In the present and earlier studies, there have been minimal differences between the JADAS versions regarding validity and feasibility (Study II) (257, 308). For retrospective studies the JADAS based on maximum 10 joints may be preferred. It is possible to use also if the number of active joints, but not the exact joint is recorded. JADAS71 is a comprehensive score based on all 71 joints counted. JADAS27 is somewhat simpler and less tedious by counting fewer joints, but the clinician must have an easy system to be able to register if the involved joint is among the 27 joints counting in the score. For practical reasons agreement on which joint count to use should be standardized so that different studies can be compared, and we suggest JADAS27-CRP to be used as the standard version.

5.3.2 Patient-reported outcome measures (Study I and II)

The outcome measures that are most relevant to the patient's own experience of health must have high priority in research (309). Several patient-reported outcome measures were used in Study 1 and II. Visual analogue scales were used for ratings of impact of the disease on overall well-being and pain in the previous week. Children's ratings of pain are found to agree only moderately with ratings of their parents, whereas the ratings of fathers and mothers agree at a good level (310, 311). The standardized approach at all centers that these ratings were done by the children if aged more than nine years and by the parents in younger children, may therefore be important for validity of the data.

Global assessment of the impact of the disease on overall well-being scored by the child/ parent and the physician's rating of disease severity are two different concepts. The patient may have another perspective than the care-giver. In spite of these differences, patients' and physicians' global assessment VAS showed very similar median and interquartile scores at the final study visit in the total cohort.

In study I we chose to present the numbers of children with CHAQ >0, pain VAS >0, child/parents and physicians global VAS >0 and CHQ physical summary score <40 (-1 SD of the mean score in a healthy reference population). The clinical significance of such low thresholds can be discussed, and CHAQ scores >0.5 may be a more meaningful measure of physical disability. Other measures of high disease activity such as JADAS27, present DMARD use, pain, and active joint counts showed however similar pattern in the different JIA categories (study I). Zero as a threshold for these measures has also been used in other outcome studies (49). CHAQ has also been criticized for having a ceiling effect and not being sensitive enough for the physical difficulties usually found in JIA (312).

Approximately half of the patients in our cohort reported pain from the disease and that the disease had some impact on their daily life at the last study visit. These figures demonstrate that even though objective activity measures are low, many patients experience pain and less well-being. This important finding points to a clear impact of the disease and disease-related pain in daily living for these young people. In a Swedish population-based study Andersson Gäre et al found slightly higher median pain scores (0.1 for boys and 0.8 for girls, range 0-10) seven years after onset (47), and Minden et al found median pain score 1.0 (iqr 0-3.0) in their 16.5 year followup of a partly population-based, partly referral-based cohort (39). Advances in medical treatment may partly explain the lower scores in our cohort. Chronic pain is not restricted to children with JIA or other chronic diseases. Recent studies on pain in healthy adolescents show the prevalence of self-reported chronic musculoskeletal pain to be 33.4% (313). The children with JIA is however asked to rate pain related to their articular disease during the preceding week, and the pain scores show a close correlation with other measures of disease activity such as active joints, DMARD use and continuously active disease (Study I and II).

Several authors report that disease activity explains only a modest proportion of pain experience in children with JIA (239, 314, 315). Thastum et al has shown that health beliefs and pain-coping strategies are associated to disease-related pain in JIA (238,

315, 316). They also found that children with high pain ratings in disproportion with other disease activity measures, compared to other children with JIA, perceived themselves as more disabled, expressed that pain signified more damage and that exercise therefore had to be restricted (315). Schanberg et al found parent and familial pain history to be prevalent and to influence pain experiences in children with JIA (317, 318). Pain sensitizing may be a mechanism explaining lower pain thresholds in children with JIA compared to healthy peers (239). Increasing pain is reported in both JIA and in healthy children with increasing age in girls (239, 313). Assessment of pain and also pain-specific beliefs may be important in optimal management of children with JIA in order to identify and offer behavioral intervention to the subgroup of children whose pain experience is in discordance with the actual disease activity (238).

5.3.3 Treatment (Study I and II)

Intraarticular corticosteroids (IACS) were used in three of four children in our cohort, and the maximum number of injections in one child was 70 (Study I). Solari et al report a similarly high rate of children receiving IACS (79%), while most other studies report much lower rates (63, 237). IACS may be a valuable tool with limited side effects in reaching the goal of inducing early inactive disease, and the use is in line with present recommendations (46). The total number of 32.3% using systemic glucocorticoids may reflect short-term use, because the 1.1% presently using at the last followup is low compared to other followup studies (3.2-13%) (63, 64, 237).

There are indications that early DMARD treatment may change the disease course. Totally 58.0% of the children in our study had ever used DMARD and 30.5% were using DMARD at the final study visit. These numbers are higher than older studies and in fact most other outcome studies except for Solari et al and Flatø et al reporting outcomes from tertiary center samples (44, 48, 63, 64, 237). MTX is recommended as the first choice DMARD in JIA, and it is the most commonly used systemic drug in our cohort (46, 192). Oen et al found in their retrospective cohort that use of methotrexate more than quadrupled between those diagnosed in the 1990's compared

to the 1970's (63). In the study of Flatø et al hydroxychloroquine was the most commonly used DMARD during the 1980's (44). There are no firm evidence of efficacy of hydroxychloroquine as monotherapy in JIA, and this drug is not often used in our study (205). However, a recent Finnish RCT showed combination therapy of hydroxychloroquine, salazopyrine and MTX to be superior to MTX alone, but inferior to infliximab and MTX (204). Present use of DMARD is in our study chosen as a marker of severe disease. The use of biologic agents in pediatric rheumatology represents the beginning of a new era in medical treatment of JIA, and etanercept was introduced at the same time as our study started (183). Indications and approvals have been widened as efficacy and safety data on biologic agents in children have emerged (183, 209, 319). The use of biologic medication was increasingly used during the study period. In case of unsatisfactory response to MTX, early use of biologic agents is presently recommended (46).

In 2008 the FDA issued a "black box warning" on increased risk of cancer in children with inflammatory bowel disease or JIA treated with TNF-blocking agents (REF). Half of the malignancies were lymphomas, and most cases had received concomitant immunosuppressive treatment (321). The background risk of malignancies in JIA has not been known until Simard et al reported findings in a case-control study of 9027 cases of JIA in a Swedish population (248). Patients with JIA identified before 1987 were not at increased risk of cancer, whereas JIA identified in 1987 and thereafter was significantly associated with lymphoproliferative malignancies and overall cancer. The overall risk is low, but still this is a striking finding of increased cancer risk in the period when MTX was the dominating DMARD, with no change the last decade after introduction of biologic agents (248). A large international long-term surveillance study is started to clarify whether this is related to the disease per se or to the treatment with methotrexate, biologics or other antiinflammatory agents (249).

5.3.4 Remission rates and prognosis (Study I and II)

The first question from parents of children with newly diagnosed JIA is often "will my child get well?" Up to the 1990's a prevailing notion was that 80% of the children would "out-grow" their disease (208). Our study showed that less than half of the children are in remission off medication eight years after disease onset. According to a retrospective study by Wallace et al, even fewer children had continuous inactive disease when assessed during longer observation periods (42). Recent followup studies have shown that JIA has a chronic course in the majority of children, with fluctuating disease activity resulting in cycles of active and inactive periods (45, 63, 236, 322). As mentioned there are indications that early treatment may modify the disease course in a milder direction (176, 323, 324). The question to what extent earlier effective treatment may lead to longer periods of inactive disease still remains largely unanswered. If this presumption can be verified, there is an urgent need for robust baseline predictors of an ongoing disease course to identify children in need of early aggressive treatment. The baseline JADAS score is shown to be associated with remission status at the last study visit (Study II).

The remission rates of the children in our study showed considerable differences depending on JIA category at the final study visit (Study I). In the oligoarticular extended group only 21.3% were in remission. In fact, there was a trend that children in this category had the most severe prognosis in terms of pain and global assessment of disease impact in daily life according to the patient or parent. This finding is in line with other studies, and emphasizes the need for early predictors of extended or persisting oligoarticular course, because less aggressive treatment has usually been recommended upfront in initially oligoarticular disease (45, 46, 192, 196). Barnes et al showed in recent onset arthritis that gene expression profiles of peripheral blood mononuclear cells of oligoarticular persistent patients have a characteristic pattern (325). Similar biologic differences predicting extended oligoarticular disease were reported by Hunter et al, examining early samples of synovial fluid cellular composition and gene expression (41). A timely question is if DMARD are started too late in extended oligoarthritis due to a false presumption of a better prognosis in

oligoarticular onset? In this way the early "window of opportunity" to modify the disease course might be missed.

A surprisingly high remission rate of 83.3% was found in our cohort of systemic JIA (Study I). Similar results are also found in some other followup studies (45, 64). Persistent arthritis in systemic JIA can be very resistant to treatment, and a severe prognosis is reported from many tertiary care centers seeing the most difficult cases (196, 326, 327). This high remission rate of systemic JIA in a population-based setting, also in children not treated with biologic agents, should be kept in mind when interpreting data from newer studies with biologic agents as first-line therapy (193).

5.3.5 Damage (Study I and Study II)

Inducing early remission and avoiding damage are the main goals of JIA treatment (172). Damage in JIA can be defined as disease-related long-term/ irreversible conditions or sequelae (243). There are few reports on damage in JIA according to JADI, because the damage index is recently developed (245). Available reports from the Italian validation study, a Brazilian cohort of oligoarticular JIA, a Serbian and an Indian study showed that between 37 - 61% of the children had damage according to the JADI (237, 243-245, 328). JADI measures a broad range of damage from serious visual impairment or joint replacements, to less serious leg length discrepancies or subcutaneous atrophies. Summary scores of such varied sequelae should be interpreted cautiously. In our cohort higher JADAS score at the first visit was shown to predict damage, and more than one in five children developed some JIA-related damage (Study I and II). A clinical implication is that more aggressive treatment may be needed in children with higher baseline JADAS score, not only to treat the arthritis, but also to avoid long-term damage.

5.3.6 Predictors (Study I, II and III)

The diverging clinical spectrum of disease course in JIA and the potent treatment possibilities implies a strong need for robust predictive baseline factors. The predictive value of JADAS regarding outcome measures as physical disability, pain, DMARD treatment, and remission was shown in the validation study (Study II). In addition to assessing JADAS validity, this shows that early disease activity is predictive of disease course and outcome in a longer term. Myeloid-related protein (MRP)-8/ MRP-14 (also called calprotectin) is a biomarker shown to predict the risk of flare after methotrexate withdrawal, and has been studied as a baseline predictor of severe disease course (329, 330). JADAS and MRP8/ MRP14 may simply both be indirect measures of high level of inflammation, predicting severe ongoing disease. A higher percentage of active disease in the first two years is shown to be related to an unremitting disease course the following three years (40, 177). Other studies have shown that CRP, ESR, RF, early radiographic erosions, and hip arthritis are predictors of severe disease (44, 46, 49). The newest treatment recommendations for JIA are based on early assessment of such risk factors from the different treatment groups (46).

Biomarkers of uveitis were studied in the Norwegian cohort of children with JIA (Study III), because early diagnosis and initiation of treatment in this potential sight-threatening complication is crucial (135). Minden et al reports that among the 14% with uveitis in their JIA cohort, half of the patients developed complications and of these 80% had visual impairment (39). In line with other studies we found that early-onset arthritis was an important risk factor of chronic uveitis. In our study ELISA ANA is not associated with uveitis development in JIA. A change in ANA method of analyses in the laboratory may not be considered important by the clinician. In the case of ANA a change from immunofluoresence to ELISA analyses will result in increased frequency of negative ANA for children with JIA. A negative ANA implies less frequent eye examinations, according to most screening guidelines (150). This message has important clinical implications, which must be emphasized for clinicians interpreting an ANA result to avoid delayed diagnosis of uveitis. Given the weaknesses of ANA immunofluoresence analyses regarding reproducibility, ELISA

antihistone antibodies may be an alternative biomarker of development of chronic uveitis. The combinations of positive antihistone antibodies and IF-ANA are an interesting option that identified all children developing uveitis in our study. This result needs confirmation in further studies.

In relation to the suggestion from Martini and Ravelli et al on ANA identifying a homogeneous subset of children with JIA, the presence of IF-ANA was not associated to remission status in our study. However, fewer children with young age at disease onset achieved disease remission off medication compared with children with late-onset disease, independent of ILAR categories (Study I).

6 CONCLUSION

Outcome in terms of disease activity and remission rates are reported in this population-based longitudinal cohort study. Our findings challenge the present classification criteria for JIA in several ways; 1) substantial change in the categories is shown to occur during the disease course, 2) more than one of ten children are classified to have undifferentiated arthritis, and 3) extended oligoarthritis and RF-negative polyarthritis have very similar outcome.

Almost one third of the children were still using regular medication and 58.0% had used DMARD during the disease course. One of five children had some JIA-related damage. The chronicity of JIA is shown as 57.6% of the children were not in remission off medication eight years after disease onset.

The composite disease activity measure JADAS were found feasible and valid in this population-based setting. JADAS based on CRP correlate closely with JADAS based on ESR, and both measures can be used to quantify disease activity in JIA.

Biomarkers and early predictors of uveitis were evaluated. The main findings were that antihistone antibodies ≥8 U/ml tested by ELISA and ANA titer ≥80 tested by immunofluorescence have similar test properties as significant predictors of uveitis development. Early-onset arthritis was also a significant predictor of uveitis. ANA performed by ELISA analysis was not associated with uveitis

This study underlines the chronicity of JIA and the need for long-term followup into adulthood in order to avoid damage and further improve outcome.

7 FUTURE STUDIES

In our cohort there are several further possibilities for research in JIA. The length of a longitudinal outcome study can always be even longer, and plans are already made for the next followup study of the 500 participants included at baseline. The main challenge will be to avoid a high rate of participants lost to followup, as years pass by and many participants may move or become busy with education and work in early adulthood.

Potential predictors of disease outcome regarding extended or persistent course in oligoarthritis and remission status will be explored, using the collected biologic material. The aim is to find robust biomarkers to propose groups for tailored treatment.

Potential predictors or descriptors in JIA classification such as young age, ANA positivity and specific joint involvement may be investigated in our cohort. Defined cut-offs of JADAS for different levels of disease activity and inactive disease should be elaborated, and would be useful in monitoring treatment. A disease activity measure without an inflammatory marker may also be clinically useful, because blood sampling is not always performed at visits. There are few population-based studies on uveitis in JIA, and we would like to further study the development and implications of uveitis. Patient-reported outcome and quality of life according to the different clinical characteristics can also be explored in this longitudinal population-based setting.

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