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Prediction of unfavorable outcome in Juvenile Idiopathic Arthritis (JIA) and assessment of the long-term outcomes in JIA-associated uveitis

A prospective Nordic multicenter study of JIA from childhood to adulthood

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This thesis is mainly based on the Nordic juvenile idiopathic arthritis (JIA) cohort, which started recruiting newly diagnosed children with JIA in 1997-2000. The cohort is a result of a unique collaboration between pediatric rheumatologists from Finland, Sweden, Denmark, and Norway for more than two decades. I want to thank the children and parents who participated in the study; we could not have conducted the study without them. I am thankful to the NoSPeR researchers; Anders Fasth, Marite Rygg, Troels Herlin, Lillemor Berntson, Kristiina Aalto, Susan Nielsen, Marek Zak, Ellen D Arnstad, and Mia Glerup, and hope for further productive collaborations in the years to come. I am grateful to my main supervisor Ellen Nordal for excellent supervision and productive collaborations. Thanks to all the co-authors of the four papers that make up this Ph.D. thesis, especially to Jaime Guzman for providing us with the possibility of validating our prediction model in the Canadian cohort. I look forward to our future project plans.

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ABBREVIATIONS

ACR: American College of Rheumatology

ANA: Antinuclear antibodies

AUC: Area under the curve

BCVA: Best corrected visual acuity

Biologic DMARDs: biologic disease modifying anti-rheumatic drugs

CHQ-PF50: Child Health Questionnaire Parent form

CHAQ: Childhood Health Assessment Questionnaire

CI: Confidence interval

C-index: Concordance index

CRP: C-reactive protein

DMARDs: Disease modifying anti-rheumatic drugs

ERA: Enthesitis-related arthritis

ESR: Erythrocyte sedimentation rate

GA: Global assessment

HLA-B27: Human leucocyte antigen B27

IOP: Intraocular pressure

ILAR: International League of Association for Rheumatology

IQR: Interquartile range

JADAS: Juvenile arthritis disease activity score

JADI: Juvenile arthritis damage index

JIA: Juvenile idiopathic arthritis

JIA-U: Juvenile idiopathic arthritis associated uveitis

NoSPeR: Nordic Study Group of Pediatric Rheumatology

NSAIDs: Non-steroidal anti-inflammatory drugs

OR: Odds ratio

Patient´s GA: Patient/parent self-reported global assessment of well-being on a VAS

Patient´s Pain: Patient self-reported pain on a VAS

Physician´s GA: Physician global assessment of disease activity on a VAS

PhS: Physical summary score derived from CHQ-PF50

PsS: Psychological summary score derived from CHQ-PF50

PROMs: Patient-reported outcome measures

P-value: Probability value

RA: Rheumatoid arthritis

ReACCh-Out: Research in Arthritis in Canadian Children Emphasizing Outcomes

RF: Rheumatoid factor

ROC: Receiver operating characteristic

SUN: Standardization of Uveitis Nomenclature

Synthetic DMARDs: synthetic disease modifying anti-rheumatic drugs

TNF: Tumor necrosis factor

TRIPOD: Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis

VA: Visual acuity

VAS: Visual analogue scale

WHO: World Health Organization

ABSTRACT

Background and main aims

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children. The hallmark is a chronic inflammation affecting the joints and in some cases in the uvea of the eyes.[2] Prognostication of the disease course is challenging due to the heterogeneity of JIA. It is still of great importance since early aggressive treatment in children with poor prognosis may modify and improve the disease course.[3-5] In *paper I*, we aimed to develop clinically applicable tools for prediction of unfavorable disease outcomes to guide early treatment decisions in JIA. Our second objective was to validate the prediction models in an independent cohort to verify the general predictive ability. In collaboration with the Canadian ReACCh-Out investigators, we aimed to validate their Canadian prediction model to see how well it predicted *severe disease course* among the Nordic children with JIA (*paper II*). We further hypothesized that the Nordic prediction model for *non-achievement of remission off medication* would perform well when externally validated in the independent Canadian ReACCh-Out cohort (*paper III*). The models' predictive abilities were also tested on the outcome that they originally were not designed for (*paper II and III*). The overall goal of *papers I-III* was to obtain validated prediction models for use in clinical practice.

Uveitis is the most common extra-articular manifestation in JIA. There are sparse long-term prospective studies on the consequences of having JIA-associated uveitis. We aimed to assess and describe the long-term outcomes of uveitis in a Nordic JIA-cohort. The aim of *paper IV* was further to gather clinical information relevant for the screening and treatment strategies in JIA-associated uveitis, and identify predictors and targets for the prediction of unfavorable outcomes in JIA-associated uveitis.

Methods

In the Nordic prospective, population-based, multicenter, JIA cohort, we constructed four multivariate logistic regression models. The primary outcome to predict was *non-achievement of remission*, and the secondary outcomes were functional disability and articular damage, eight years after disease onset *(paper I*). External validation of the Nordic prediction models was performed in the Canadian ReACCh-Out cohort with 513 children and a 3-year follow-up. In parallel, the Canadian model was externally validated in the Nordic JIA cohort with 440 children and an 8-year follow up. The models were evaluated as published and then

evaluated after repeated fine-tuning of the logistic regression coefficients in training cohorts before testing in disjoint validation cohorts. Predictive ability was assessed with the area under (AUC) the receiver operating characteristic (ROC) curve and C-indices, considering C-index or AUC values >0.7 to be helpful for prediction (*paper I, II and III*).

In the Nordic JIA cohort 18 years after the onset of JIA, a total of 434 patients were assessed. Data on clinical characteristics, disease activity, ocular complications, and visual outcome were collected and analyzed. Long-term outcome and predictors associated with uveitis complications were identified (*paper IV*).

Main results

The model for prediction of the primary outcome *non-achievement of remission* comprised of eight clinical variables: the cumulative active joint count, ESR mm/h, CRP >10 mg/l, morning stiffness >15 minutes, physician´s GA, presence of ANA, presence of HLA-B27 and ankle joint arthritis. The model performed well with AUC equal to 0.78 (IQR 0.72–0.82) in internal validation (*paper I*). The Canadian prediction model had excellent predictive ability for *severe disease course* in external validation in the Nordic JIA cohort, yielding a C-index 0.85 (0.80–0.89). The Canadian model could not predict *non-achievement of remission* with an acceptable C-index level (*paper II*). The Nordic model for predicting *non-achievement of remission* performed acceptable with a C-index of 0.73 (0.66-0.80), and after fine-tuning with a C-index of 0.76 (0.69-0.83). For prediction of *severe disease course,* the Nordic model achieved a C-index of 0.79 (0.68–0.91) in the Canadian JIA cohort (*paper III*).

We found a high cumulative incidence of uveitis (96 of 434 (22%) patients) in the Nordic JIA cohort. Complications were present in 38.8% of the young adults with JIA-associated uveitis. Predictors associated with the development of ocular complications were short duration between the onset of JIA, and the diagnosis of uveitis, a diagnosis of uveitis before the onset of JIA, and presence of ANA (*paper IV*).

Main conclusions

A well-performing prediction model can help assess the risk of ongoing severe disease and guide early therapeutic decisions. We concluded that it is possible to develop prediction models with acceptable predictive ability for long-term unfavorable outcome in the heterogenous disease of JIA. External validation of the Nordic and Canadian models yielded a

good predictive ability for *severe disease course* confirming their applicability for this outcome. In all tests the C-indices for prediction of *severe disease course* were higher than for *non-achievement of remission*. The results imply that a prediction model's performance also largely depends on which outcome you aim to predict. Prediction of a *severe disease course* was more precise than prediction of *non-achievement remission* (*paper I-III*).

In the Nordic JIA cohort, more than 1 in 5 children developed uveitis. Long-term follow-up of JIA-associated uveitis shows that a considerable proportion of patients develop sight-threatening complications in early adulthood. Our findings emphasize the need for interdisciplinary care, with timely systemic immunosuppressive treatment in high-risk patients to minimize the risk of visual damage and reduced quality of life in young adults with JIA (*paper IV*).

LIST OF ORIGINAL ARTICLES

Paper I

Rypdal V, Arnstad E. D, Aalto K, Berntson L, Ekelund M, Fasth A, Glerup M, Herlin T, Nielsen S, Peltoniemi S, Zak M, Rygg M, Rypdal M, Nordal E and for the Nordic Study Group of Pediatric Rheumatology (NoSPeR). Predicting unfavorable long-term outcome in juvenile idiopathic arthritis: results from the Nordic cohort study. Arthritis Research & Therapy 2018, 20(1): 91. https://doi.org/10.1186/s13075-018-1571-6. Published.

Paper II

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Paper III

Henrey A, Rypdal V, Rypdal M, Loughin T, Nordal E, Guzman J and for the ReACCh-Out and NoSPeR Investigators. Validation of prediction models of severe disease course and non-achievement of remission in juvenile idiopathic arthritis part 2: results of the Nordic model in the Canadian cohort. Arthritis Research & Therapy 2020, 22(1): 10. https://doi.org/10.1186/s13075-019-2091-8. Published.

Paper IV

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1 Introduction

The work in this thesis is based on data from the Nordic JIA cohort, which consist of children with JIA included between 1997-2000. The children were followed prospectively until the last follow-up 18-years after disease onset. The Nordic Study Group of Pediatric Rheumatology (NoSPeR) conducted the study from each respective pediatric and ophthalmology center in the participating countries. Regular meetings in the NoSPeR group were held twice a year while planning the study and during data collection and the analysis phase.

We use data from the baseline study visit, the 8-year follow-up, and the 18-year follow-up in this thesis. I collected data for the participants in Northern Norway at the 18-year follow-up, and wrote the research papers, and the thesis, while in a 50% PhD-position from September 2015 to December 2020. I combined the research work with clinical work at the Department of Pediatrics at the University Hospital of North Norway and completed my pediatrics specialization in August 2020.

In *paper I*, we used data from the Nordic JIA cohort to build models for predicting long-term unfavorable outcomes in JIA based on clinical characteristics early in the disease course. We tested the model's predictive ability using internal cross-validation, i.e., applying the model in a subset of the Nordic JIA cohort different from the subset used to develop this model. The next step after internal validation was to test the model's predictive ability in another independent cohort. A collaboration with the Canadian ReAACh-out investigators, a research group that had also developed a prediction model for prediction of *severe disease course*, provided the possibility of external validation. In *paper II,* we externally validated the Canadian JIA model in the Nordic JIA cohort. In *paper III,* we externally validated the Nordic JIA prediction model in the Canadian ReAACh-out JIA cohort.

Uveitis is the most common manifestation of JIA outside the joints. Uveitis is an inflammation of the uvea in the eye which may result in sight-threatening complications. In *paper IV*, we present the long-term outcomes for the children with JIA that developed uveitis. We identified demographic, clinical, and laboratory predictors for developing uveitis-related complications in the Nordic JIA population.

2 Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) encompasses arthritis of unknown origin that develops before age 16 years, with a duration over six weeks. JIA is not *one* disease but rather a group of chronic rheumatic diseases characterized by arthritis where infections and other reasons for arthritis are excluded.[2, 6] Arthritis is an inflammation of the joint defined clinically by a swollen joint or a joint with limitation of movement, accompanied by joint pain or tenderness.[1] Children with JIA have a diverse genetic background, pathophysiology, clinical presentation, disease severity, and prognosis.[6] The course and outcome in JIA may vary considerably, with disease severity spanning from inflammation in one joint of limited duration to unremitting widespread disabling arthritis.[1] Extra-articular manifestations such as serositis and inflammation of the uveal tract of the eye (uveitis) may also present.[2]

2.1 Epidemiology

The reported incidence of JIA is between 2-22 children per 100 000 per year. The prevalence also varies greatly in different parts of the world, from 15 to 150 per 100 000.[7] Even higher prevalence has been reported from a population-based study in Australia.[8] There are numerous reasons for the variation in reported incidence and prevalence. Changing classification criteria used through the years, different study designs, different follow-up times, genetic factors, and ethnicity may all contribute to the differences reported in epidemiologic studies.[9]

There are also geographic differences in the distribution of children belonging to each JIA category (Table 1). For instance, oligoarthritis is the most common category in the northern countries, while systemic JIA is rare. In contrast, systemic JIA is more common in Asia and Africa, where oligoarthritis is infrequent. This suggests a genetic disposition for different phenotypes of JIA.[9] Overall, reports on the incidence of JIA in the Nordic countries are in the higher ranges. In our Nordic population-based study, the incidence was 15 per 100 000 <16 years per year.[10] A retrospective study from Northern Norway found a cumulative incidence of 22%.[11] A recent study from Sweden reported an incidence of 12.8 per 100 000 children <16 years per year, confirming similar incidence in the Nordic countries.[12]

2.2 Classification criteria

In order to group the children with JIA into more homogeneous disease groups, JIA has been divided into seven categories based on clinical characteristics and laboratory findings, including; the number of joints involved, family history, presence or absence of extraarticular manifestations, presence or absence of rheumatoid factor (RF) and human leucocyte antigen B27 (HLA-B27) during the first six months after the onset of JIA.[1] The partition in categories is used for defining homogeneous groups both in research and for establishing prognosis and treatment strategies in clinical practice. Further modifications of the category definitions are recently suggested and under validation in order to define even more similar groups of children with JIA.[13]

The currently used classification criteria are the International League of Association for Rheumatology (ILAR) classification criteria (Table 1).[1] The ILAR criteria defines JIA as arthritis that begins before the age of sixteen, with a duration of at least six weeks where the etiology is unknown.[1]

Table 1. The different JIA categories according to the ILAR classification criteria[1]

Systemic arthritis

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

Exclusion: a,b,c,d

Oligoarthritis

Arthritis affecting 1 to 4 joints during the first 6 months of disease. Two subcategories are recognized:
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.

Exclusion: a,b,c,d,e

Polyarthritis RF negative

Arthritis affecting 5 or more joints during the first 6 months of disease; a test for RF is negative.

Exclusion: 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.

Exclusion: a,b,c,e

Psoriatic arthritis

Arthritis and psoriasis, or arthritis and at least 2 of the following:
1. Dactylitis
2. Nail pitting or onycholysis
3. Psoriasis in a first-degree relative

Exclusion: b,c,d,e

Enthesitis-related arthritis

Arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following:
1. 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.

Exclusion: a,d,e

Undifferentiated arthritis

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

a. Psoriasis or a history of psoriasis in the patient or first-degree relative.

b. Arthritis in an HLA-B27 positive male beginning after the 6th birthday.

c. Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis, or a history of one of these disorders in a first-degree relative.

d. The presence of IgM rheumatoid factor on at least 2 occasions at least 3 months apart.

e. The presence of systemic JIA in the patient.

2.3 Etiology and pathogenesis

In general, JIA is considered to be an autoimmune disease with disruption of the immune system mechanisms to establish and keep tolerance to self.[14] Both the innate and the adaptive immune systems contribute to an erroneous immune response against self-antigens driving a chronic inflammation process.[14] The etiology is largely unknown, but the disease is thought to arise in a genetically predisposed child after exposure to one or several environmental triggers. [2, 15, 16] Studies on environmental triggers in JIA, such as smoking, viruses, bacteria and vaccination are inconsistent in both the direction and magnitude of the effects and have yet to be confirmed.[2, 17, 18]

The common pathophysiological feature in the different JIA categories is the joint inflammation, characterized by infiltration of neutrophils, plasma cells, and activated T cells, macrophages, and dendritic cells.[19] The Th1 CD4+ cells seem to drive the inflammation, causing production of cytokines. The sustaining inflammatory process results in hypertrophy of the synovium and new vascularization. Furthermore, it may lead to the formation of pannus together with damage of cartilage and/or bone tissue.[20]

JIA mostly occurs sporadic, but the relative risk of developing JIA has been reported to be in the range of 15-30 among siblings.[21] Studies of monozygotic twins show a concordant rate of 20-40%. This higher risk of developing JIA, suggest that genetic factors plays a part in predisposing for the disease, but do not explain fully the etiology.[21, 22] Interestingly, studies have shown that siblings with JIA often have a similar disease course and disease onset time.[21, 23]

Both human leukocyte antigen (HLA), which plays a role in the antigen presentation to autoreactive T cells, and non-HLA susceptibility loci are found in JIA patients.[15, 16, 24, 25] There are associations between HLA polymorphisms and JIA categories, although the findings vary between studies. [15, 16, 24] The oligoarticular category is associated with the following human leucocyte antigens; HLA DRB1:11, HLA DRB1:08, HLA DPB1:02.[25] An association is also found between the antinuclear antibody (ANA) against intracellular nuclear antigens, and early onset oligoarthritis.[26] RF-negative polyarticular JIA is associated with HLA DRB1:11, HLA DRB1:08 and HLA DRB1:13.[25] Oligoarthritis and RF-negative polyarthritis share common HLA-associations, and these categories may be more similar than previously thought.[25] RF-positive polyarticular JIA is associated with HLA DRB1:01 and HLA DRB1:04. The children in the RF-positive category may also have anti-citrullinated protein antibodies (anti-CCP) against the modified amino-acid citrulline. Anti-CCP is associated with a more severe prognosis and a disease course similar to adult rheumatoid arthritis.[25, 27, 28] Enthesitis-related arthritis is associated with HLA B27 and HLA DRB1:01.[29]

There are also associations between JIA and non-HLA genes resulting in dysregulation of cytokines such as TNF-α, interleukine-6 (IL-6), interleukine-8 (IL-8), interleukine-1 (IL-1) and interleukine-18 (IL-18).[17, 30]

There are no known autoantibodies associated with systemic JIA, but there is an association with HLA DRB1:11, which is considered a risk factor for systemic JIA.[31] The main feature of the pathogenesis in systemic JIA is a highly activated innate immune system with an imbalance in cytokine regulation driving the inflammation.[32] The pro-inflammatory cytokines IL-6, IL-1, and IL-18 play an essential role in the inflammatory process of systemic JIA. Treatment strategies with anti-IL-6-antibody and anti-IL-1-antagonist have been proven effective in systemic JIA, confirming the role of these interleukins in the pathogenesis of systemic JIA.[33]

Genetic information may possibly be used to group JIA patients into more homogenous categories,[1, 25] and used as predictors in prediction tools, perhaps improving prognostication.

2.4 Current treatment strategies

The primary treatment goal in JIA is clinical remission or inactive disease. If the primary treatment goal is not achievable the alternative option is minimal disease activity.[34]
There is increasing evidence that early aggressive treatment with synthetic and biologic disease-modifying anti-rheumatic drugs (DMARDs) may modify the disease course and improves outcome in selected JIA categories. The discovery of the prompt treatment benefit led to the concept of starting treatment early during the "window of opportunity"[3-5, 35]

A treat-to-target treatment strategy has emerged in JIA. The strategy was first introduced in adult rheumatology for rheumatoid arthritis (RA) and has shown to be superior to standard clinical care.[36-38] The focus in treat-to-target strategy is prompt control of inflammation by stepping up treatment aiming for inactive disease. During this period, the disease activity is frequently assessed, and if progress is not made, treatment is adjusted.[34, 39] Prompt initiation of appropriate therapy is important in order to prevent joint damage and improving the long-term outcomes.[3-5] The combination of early diagnosis, an increasingly number of available efficient drugs, early aggressive treatment and treat-to-target strategy pose a challenge for physicians who need to decide whether and how to start initial treatment, and when to step-up systemic treatment.

The American College of Rheumatology (ACR) has published treatment guidelines in JIA.[40-43] The commonly used drugs in JIA are non-steroidal anti-inflammatory drugs (NSAIDs),

intraarticular and systemic glucocorticoids, synthetic and biologic DMARDs. Synthetic and biologic DMARDs are indicated to achieve the treatment goals in children with moderate to high disease activity.

The most commonly used synthetic DMARD is methotrexate, a chemotherapeutic agent that in modest doses suppresses the immune system.[44, 45] When methotrexate is not enough, or not tolerated, biologic DMARDs is an increasingly used treatment option. In JIA, this has become the cornerstone in the combined "early aggressive-treatment and treat-to-target strategy." These drugs function by modulating specific immune systems pathways, such as TNF-α, IL-1, and IL-6 signaling or lymphocyte activation or function. Biologics agents became available around two decades ago. Their introduction and increased availability have improved patient outcomes tremendously. The proportion of children entering adulthood without joint damage or complications from JIA-associated uveitis has increased compared with the pre-biologic era.[46, 47] The most commonly prescribed biologics agents are the TNF-inhibitors: etanercept, adalimumab, and infliximab. Other targeted biologic drugs are abatacept (a T-cell co-stimulatory modulator), anakinra (an IL-1 receptor antagonist), canakinumab (an IL-1β inhibitor), and tocilizumab (an anti-IL-6 pathway inhibitor). The interleukin inhibitors are considered first-line biologic therapy for systemic JIA.[43] A recent study estimate that approximately 20% of the children with JIA start biologic DMARDs within the first three years after diagnosis. Among these one in five later switch to a second biologic.[48, 49] However, studies reporting treatment failure before the current treat-to-target approach, may have a higher proportion of non-responders.

Intraarticular glucocorticoid injections combined with NSAIDs may be sufficient in treating active arthritis in patients with e.g., oligoarthritis or as a bridging therapy while waiting for the full effect of DMARDs. Systemic glucocorticoid use has decreased after the introduction of biologic agents but may still have a place as bridging therapy, and in the treatment in systemic JIA.[40, 50]

2.5 Disease outcomes

Due the heterogeneous nature of JIA, there is no single outcome measure comprising the overall disease outcome. Several measures of disease activity and remission, functional ability, and damage are developed and validated for JIA. These are mostly based on

combinations of clinical findings, laboratory tests and patient-reported outcomes (PROMs). Among the PROMs questionnaires, there are both generic tools developed to assess general child and adolescent health and disease specific tools designed for JIA.

2.5.1 Measures of remission and disease activity

JIA researchers and patients are generally interested in outcomes assessing disease activity, remission, functional ability, quality of life, joint damage, pain, extraarticular complications, and treatment response. In JIA, the ultimate goal of treatment and the outcome to strive for, is disease remission over time. Remission is defined as clinical remission on medication when there is an inactive disease on medication for six successive months, and clinical remission off medication when inactive disease for at least 12 consecutive months without medication.[51, 52] According to the 2004 Wallace preliminary criteria,[51] inactive disease is defined as 1) No joints with active arthritis meaning no swelling or no movement limitation with pain or tenderness. 2) Absence of systemic features such as serositis, splenomegaly, generalized lymphadenopathy, fever, or rash. 3) No active uveitis. 4) Normal erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). 5) Physician´s GA of disease activity assessed as no disease activity present.

As new therapeutic alternatives emerged over the last decades, it became clear that we need explicit and objective criteria to describe disease status.[53-56] The 2004 Wallace's preliminary criteria were developed by a consensus formation approach. This was a collaboration between The Childhood Arthritis and Rheumatology Research Alliance (CARRA), The Pediatric Rheumatology International Trials Organization (PRINTO), and The Pediatric Rheumatology Collaborative Study Group (PRCSG). The criteria were applicable for the oligoarticular, polyarticular, and systemic JIA categories. However, in clinical practice and research, the Wallace criteria are also used to evaluate disease activity for patients with ERA, psoriatic arthritis, and undifferentiated arthritis. The Wallace preliminary criteria were validated in 2011.[52] The revised version is known as the American College of Rheumatology (ACR) 2011 provisional criteria. There were three main changes in the revision: 1) The definition of abnormal ESR and CRP. The new definition does not take elevated ESR and CRP into account if it is not attributable to JIA. 2) The definition of uveitis according to the SUN working group.[57] 3) Morning stiffness less than 15 minutes duration was added as a criterion for inactive disease.

Recent studies have shown that studies using different criteria for defining clinical inactive disease cannot be compared directly. Even if the different definitions use mostly the same variables they may capture different patients.[58] Clinical inactive disease within the first year after onset of JIA has been reported to be between 25-45% in recent years.[58, 59] Long-term studies report remission-off-medication rates in the range of 35-60%,[60, 61] with considerable variation between the different JIA categories. Glerup et al. found that 33% of the patients with JIA were in clinical remission off medication for at least 12 months, and that 46% had active disease according to the ACR 2011 provisional criteria 18 years after disease onset.[61] Another long-term prospective study, carried out before the biologic era reported that 59% were in clinical remission and 34% had active disease at the 30-year follow-up.[60]

For assessing JIA disease activity in everyday practice, the composite Juvenile Arthritis Disease Activity Scores (JADAS) is easier to use.[62] JADAS is the main composite measure of disease activity currently used. Composite measures have been found to be more robust than individual variables for assessment of disease activity.[62, 63] Indeed, the heterogeneity of JIA favors a composite assessment of disease activity. By grouping together information on different aspects of the disease, such as the number of active joints, patient's/parent's GA, physician's GA of disease activity and acute phase reactants (ESR or CRP) a score is obtained. Several versions of JADAS have been developed. The main difference between the versions is the number of active joints evaluated (10, 27 or 71 joints), and whether blood tests are included or not. There are different JADAS cut-off thresholds for defining inactive disease, minimal and severe disease activity.[62, 64, 65] Both the ACR 2011 and the JADAS criteria include the core variables active joint count and physician global assessment. Other variables, such as patient-reported outcome, acute phase reactants, systemic clinical features, uveitis, and morning stiffness, are included in some JADAS scores. Clinical JADAS (cJADAS) does not include acute phase reactants but captures disease activity just as well as JADAS.

There is evidence that the Wallace criteria and the JADAS are inconsistent with respect to identification of clinically inactive disease. This inconsistency may be due to some of the variables included, especially the patient/parent GA of well-being, which is included in JADAS but not in the Wallace criteria, and also the physician GA of disease activity. The physicians tend not to mark zero on the physician GA of disease activity, even if the child is

in remission. The child will then be evaluated as having an active disease. This effect is smaller by using JADAS with cut-off values for defining disease activity status.[66]

2.5.2 Measures of physical and psychosocial function and damage

The Childhood Health Assessment Questionnaire (CHAQ) is a standard and validated disease-specific instrument for measuring functional disability in JIA. CHAQ gives a comprehensive evaluation of functional ability in different activities of everyday life.[67] CHAQ is completed by children of age >9 years, or otherwise by their parents. In adults >18 years, the corresponding Health Assessment Questionnaires (HAQ) is used. The scores range from zero to three, where zero is no functional disability, and three worst possible.[67] The CHAQ is a JIA-specific and frequently used patient-reported outcome measurement.

The Child Health Questionnaire (CHQ) is also used to assess functional disability, but in contrast to CHAQ, it is a generic patient-reported measurement tool that is also used for children with other chronic conditions such as asthma and attention deficit disorder. In addition to scoring the physical function, it also assesses psychosocial functioning to achieve a broader evaluation of daily functioning. The CHQ-PF50 (parents form) consists of 50 items and 12 domains, yielding a physical summary score (PhS) and a psychological summary score (PsS). The scores range from 0 to 100, with a higher score indicating better function.[67, 68]

The Juvenile Arthritis Damage Index (JADI) is a validated disease-specific tool for measuring articular and extraarticular permanent damage due to JIA. Physicians fill in a standardized form to assess accumulated damage. Articular damage (JADI-A) is scored from 0 (indicating no damage) to a maximum of 72, where 36 joints or joint groups are scored 0 for no damage, 1 for partial damage, or 2 for severe damage. Extraarticular damage (JADI-E) is scored from 0 to 17.[69]

2.6 Prediction of disease outcome

A prognosis is a prediction of the course of disease following its onset. Prediction of disease outcome in JIA is challenging due to the heterogeneous nature of the disease, even within the same JIA category. To enable physicians to answer parents' and children's questions regarding long-term prognosis, physicians have had information on prognosis available only on a group

level, not individually. Moreover, early prediction of disease course for the individual child can facilitate tailored personalized treatment. Hence, JIA researchers are increasingly interested in methods for determining whether a child will respond well to therapy, grow up with an active or inactive disease and achieve remission or not.[3, 70-73] Several studies have presented predictors in terms of clinical features associated with an unfavorable outcome at the group level, but few studies have demonstrated individual predictors.[74-76] More recent studies have aimed to identify predictors that can be used to predict outcomes for individuals.[77-81]

2.7 Clinical predictors

To guide early treatment decisions, predictions of disease outcomes have to make optimal use of information that is collected early in the disease. Variables suitable for prediction of disease outcomes may be patient and disease characteristics, imaging results, laboratory tests and other relevant variables. Identifying variables that have an association with the outcome is, however, only the first step towards a model that can guide treatment. The second step is to understand how the combination of predictors as a whole, can determine the most likely disease course. This second step is of particular importance in JIA, since there is increasing evidence that early aggressive treatment modifies disease course.[4, 5]

In 2005 Adib et al.[71, 82] reviewed outcomes and predictors used at the time. They found that patients with an oligoarticular JIA had the best prognosis. The worst prognosis was seen in systemic and polyarticular JIA. Female gender, symmetric joint involvement, elevated inflammatory markers, and RF positivity were also predictors of an unfavorable outcome. However, the reviewed studies were frequently inconsistent with large variability in the data. The authors also pointed out the large variability of outcomes used and called for unified remission criteria.

A more recent systematic review article by Van Dijkhuizen et al.[72] evaluated early characteristics predicting validated outcomes of disease activity, joint damage, functional ability, and quality of life. Most of the reviewed studies were retrospective, assessing mainly clinical and laboratory variables. The polyarticular and systemic categories were associated with the worst outcomes, consistent with Adib et al. Van Dijkhuizen et al. also found that a delay in JIA diagnosis was associated with an unfavorable outcome.[74, 75] A polyarticular onset

of JIA had the worst prognosis regarding joint damage, and patterns of symmetric joint involvement and higher disease activity parameters were predictors of a worse functional ability.[74, 76, 83] The results were difficult to generalize since different methods for determining disease activity were used, as well as different study designs, and a large variation in the variables assessed.

Recent studies confirm what is previously reported. The polyarticular and enthesitis-related arthritis (ERA) categories have poorer outcomes than children with oligoarthritis.[61, 84-86] Interestingly, the children with systemic JIA seem to have a better long-term prognosis than previously reported,[87] possibly because of the specific treatment with interleukin antagonists and inhibitors that are now available. Symmetric joint arthritis and arthritis in specific joints such as the ankle, wrist, fingers, and the cervical spine are reported to have a worse prognosis. This may, however, mainly reflect that many cumulative active joints are affected, and a polyarticular course, more than the specific joint involvement.[79, 81, 86, 88, 89] The predictive value is not straightforward to establish since these variables correlate with other disease activity measures, and sometimes also with the JIA category. The effect of confounding factors must be kept in mind when developing prediction tools. The different variables assessing disease activity cannot be pooled together in prediction models before considering their correlation and their individual predictive capability.

Inconsistencies in reported predictors over time may be explained by the absence of standardized classification systems, outcome definitions, evolving therapeutic approaches, and statistical methods. Prospective evaluation using validated outcome measures is required to generate robust disease outcomes and prediction models.

2.8 Prediction models in JIA

Recent prediction-model studies are presented in Table 2. The predictive performance of a prediction model is often reported as AUC of the ROC, or as a C-index. The AUC of the ROC is the same as concordance probability (C-index) for binary outcomes. In the following section, the two terminologies are used.

Bulatovic et al.[80] developed a prediction model that included clinical and genetic variables to identify patients with JIA that do not respond to methotrexate treatment. The AUC of the

ROC curve was 0.65. The model classified 72% of patients correctly in the development cohort, but only 65% in the validation cohort. In 2017 Guzman et al.[77] developed a clinical prediction model for predicting *severe disease course*, an outcome constructed from data to identify the most severely affected children with JIA. The model performed excellently in both development and validation cohorts. However, the model was complex, and the outcome was not an established and validated outcome measure. Van Dijkhuizen et al. published in 2015, a model for predicting methotrexate intolerance. The authors showed that this model had a moderate predictive ability, and suggested further validation in an independent cohort. They also proposed updating the model with new predictors before it could be recommended as a clinical tool.[90] In 2018, Van Dijkhuizen et al.[81] published models to predict inactive disease within two years of diagnosis. The model combined clinical characteristics, Luminex technology to identify biomarkers and microbiota data. The AUC statistic of the model was only 0.65 for the whole cohort, but the model performed better in selected subgroups. Mo et al.[91] used machine learning methods for prediction of treatment response within three months after starting methotrexate. The two models (Table 2) used both clinical and laboratory variables, and performed excellently. Guzman et al.[86] published in 2019, a model that used clinical and laboratory features to predict early remission on treatment within one year of diagnosis. The model did not achieve AUC >0.70, which is usually considered the threshold for acceptable for prediction. The Table 2 in this thesis is adapted from Table 3 in the review of Guzman et al.[78]

Table 2. Recent prediction modeling studies in JIA

Author (country)	Study and model construction	Predictors in the prediction model	Outcome to predict	Main results Model performance*
Bulatovic et al 2012, The Netherlands	Retrospective JIA cohort. N=183 patients for model development. Prospective JIA cohort. N=104 patients for model validation. Multivariable logistic regression model.	ESR and gene SNPs (MDR-1/ABCB, MRP-1/ABCC1, PCFT) involved in the mechanism of action of MTX.	Non-response to MTX according the ACR ped. 70 criteria during the first year of treatment.	AUC=0.72 (95% CI:0.63-0.81). In internal validation: AUC=0.65 (95% CI:0.54-0.77). Prediction model transformed into risk score (range 0-11). At a cut-off of ≥3: Sensitivity=78%. Specificity=49%. PPV=83%. NPV=41%.
Van Dijkhuizen et al 2015, The Netherlands	Prospective JIA cohort. Total N=152 patients. Multivariable logistic regression model.	JIA category, ANA, parent/patient assessment of pain, JADAS-27, thrombocytes, ALT, creatinine and SNPs determined at MTX start.	Prediction of MTX intolerance at 6 or 12 months after MTX start.	C-index=0.78. In internal validation: C-index=0.67. Prediction model transformed into a risk score (range 0-17). At a cut-off of ≥6: Sensitivity=82.0%. Specificity=56.1%. PPV=58.7%. NPV=80.4%.
Guzman et al 2017, Canada	Prospective JIA cohort. Total N=1087 patients. Four distinct courses were identified in 609 patients. 75% of cohort for model development. 25% of cohort for model validation. Multivariable logistic regression model performed best.	Active joint count, psoriatic arthritis, oligoarthritis, RF-negative polyarthritis, upper limb joint involvement, symmetric joint involvement, RF-positive, subtalar joint involvement, finger joint involvement, cervical spine involvement, ankle joint involvement, hip joint involvement, TMJ involvement, mid-foot involvement, enthesitis, morning stiffness.	Severe disease course. Four distinct disease courses identified by cluster analysis. The union of the two worst were the severe disease course.	C-index=0.87. In internal validation: Mean C-index=0.85. 91% of children in the highest decile of risk experienced a severe disease course, and 5% in the lowest decile of risk experienced a severe disease course.
Van Dijkhuizen et al 2018, Italy and The Netherlands	Prospective JIA cohort. Total N=152 patients. 75% of cohort for model development. 25% of cohort for model validation. Multivariable logistic regression model.	Sub-groups models: Oligoarthritis: JADAS at baseline, mogibacteriaceae in stool, time since baseline. ANA positive patients: shorter time with morning stiffness, higher hemoglobin, treatment with biologics, time since baseline. Polyarthritis: RF-neg., shorter time with morning stiffness, higher hemoglobin, CXCL-9 level, treatment with biologics.	Inactive disease according to Wallace criteria at 6-month intervals within the first 2 years.	In internal validation. All patients: AUC=0.65. Oligoarthritis: AUC=0.69. ANA positive: AUC=0.72. Polyarthritis: AUC=0.69.

Mo et al 2019, China	Retrospective JIA cohort. N=362 patients. Extreme gradient boosting (XGBoost), support vector machine, random forest, and logistic regression machine learning algorithms. 80% of cohort for model development. 20% of cohort for model validation. The XGBoost established the best models.	Pre-MTX administration prediction model: CRP, CD3+Abs, RF-IgG, tender joint count, total bilirubin, indirect bilirubin, APTT, PT, TT, and fibrinogen. Mix-variables model (collected within 3 months, before and after MTX administration): CRP, CD3+CD4+, CD3+CD8, RF-IgG, total bilirubin, and fibrinogen near 3 months after administration.	Prediction of the response to MTX defined as a significant change of disease activity scores from baseline to 3 months after starting MTX.	For the pre-MTX administration prediction model: AUC=0.97. Accuracy=92%. Sensitivity=91%. Specificity=93%. For the mix-variables model: AUC=0.99. Accuracy=95%. Sensitivity=95%. Specificity=93%.
Guzman et al 2019, Canada	Prospective JIA cohort. Total N=1087 patients. 75% of the cohort for development. 25% of cohort for model validation. Best performing model: cox-logistic regression model.	Physician GA, time onset to diagnosis, RF-pos. polyarthritis, sJIA, wrist involvement, subtalar joint involvement, symmetric joint involvement, upper limb involvement, lower limb involvement, enthesitis, number of enthesitis sites, pain VAS, parent´s GA, French ethnicity, history of joint swelling, HLA B27, ANA, RF.	Inactive disease for ≥ 6 months within 1 year of diagnosis in patients who did not receive early biologic agents or DMARDs.	C-index=0.69 (95% CI:0.67-0.71). Sensitivity=71%. Specificity=57%.

*The predictive performance of a prediction model is often reported as AUC of the ROC or as C-index. The AUC of the ROC is the same as concordance probability (C-index) for binary outcomes. ESR, Erythrocyte sedimentation rate; MDR-1/ABCB1, methionine synthase reductase, multidrug resistance 1; MRP-1/ABCC1, multidrug resistance protein 1; PCFT, proton-coupled folate transporter; MTX, methotrexate; SNPs, single nucleotide polymorphisms; PPV, positive predictive value; NPV, negative predictive value; ALT, alanine aminotransferase; TMJ, temporomandibular joint; GA, global assessment; CXCL-9, Chemokine C-X-C motif ligand 9; APTT, Active partial thrombin time; PT, Prothrombin time; TT, Thrombin time; ACR, American College of Rheumatology; ANA, antinuclear antibody; AUC, area under the Receiver Operating Characteristic Curve; C-index, concordance index; CI, confidence interval; JADAS, Juvenile Arthritis Disease Activity Score; sJIA, systemic JIA; VAS, Visual Analogue Scale.
The table is adapted from the review of Guzman et al 2019, Predicting disease severity and remission in juvenile idiopathic arthritis: are we getting closer?

2.8.1 Modeling studies in medicine

Prediction-model building is a relatively new branch of JIA research.[77-81, 90, 92] In other fields of medicine there are several well-known prediction rules applied in clinical practice, such as the Framingham Risk Score used to estimate cardiovascular risk of an individual,[93, 94] and the FRAX model for osteoporosis risk.[95] There are also examples in pediatrics,[96] such as the recently published prediction rule for identification of febrile infants at low risk of serious bacterial infections.[97]

Prediction models in medicine should be accurate for the outcome in question for each patient. Besides accuracy, a clinically relevant prediction model needs to be simple. Simplicity may be challenging to achieve since more complex models, that make use of more

information, may perform better. A simple model may be easier to construct for homogenous outcomes, but in JIA disease heterogeneity presents a challenge. In JIA, disease heterogeneity presents a challenge. Therefore, very simplified prediction models may not be realistic. An alternative approach may be to develop separate models for different JIA categories.

2.8.2 Development and validation of prediction models

The optimal design for prognostic research is a longitudinal cohort study. The guideline "Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD)" present norms for developing and validating prediction models.[98-100] Prediction models, also called prediction rules, combine several predictors and the contribution of each predictor is weighted. From the weighted rule, a risk score for the assessed outcome is obtained.[101] The outcome is often binary, i.e., the prediction model gives the probability of a given outcome or not.

In developing a prediction model, different procedures for selecting predictors may be used. Logistic regression or Cox regression models are the most commonly used in medicine.[100, 102] In multivariable logistic regression model-building, one approach is to remove predictors based on *p*-values or their regression coefficients. Alternatively, clinical judgment or a literature review can be used to decide if specific variables should be used in the model. One can also give preference to variables with few missing data. It is also common to avoid variables that significantly overlap or correlate with variables that are already included. Selecting predictor variables is not an easy task; for instance, with many potential predictors, there is an increased risk of choosing uninformative variables and, in this way, overfitting the model. Overfitting is a modeling error that may improve the model's performance in the training cohort, but decreases its predictive ability in the test cohort. Overfitting is common if the number of predictor variables is high compared to how often the predicted outcome occurs. This is a particular concern when the sample size is small. Underfitting occurs if essential and informative variables are not included in the model.[103]

For a realistic evaluation of a model's predictive ability, it is not enough to quantify the predictive ability in the total cohort used for building the model. This approach will result in an overestimation of predictive power, and is not recommended.[98] Every prediction model should at least undergo internal validation, which may be done by resampling, e.g.,

bootstrapping or cross-validation, to evaluate the model's performance more realistically. Another option is to randomly split the data into two parts: one for development often called a training set, and another for model performance evaluation. The latter is often called the validation set. The data set may also be evaluated at different time points. In this case the data is split by time or location into one part for development and the other for testing of the model. In this way, one tests the model in a set of patients whose information has not been used to develop the model. This will be the case when the model is applied to future patients. When testing is done in the same cohort, it is called internal validation. The splitting of the cohort in training and testing cohort needs to be done several times to obtain confidence intervals for the model's predictive ability.[98] If the model's predictive ability is not tested, and the presented accuracy of the model is the one for the whole cohort, the predictive ability will most likely be over-optimistic.

Before prediction models can be recommended for general use in clinical practice, the predictive performance, reliability, and accuracy across different populations need to be assessed to avoid overestimating the model's predictive performance. External validation refers to testing a prediction model in a cohort separate to the one used to build the model, or to evaluation of an already published model on separate data.

If a model predicts a given outcome, what is the probability that this prediction becomes true? This question is answered by the C-index (equal to the AUC). In a logistic regression model, the C-statistic measures the goodness of fit: the probability that a randomly selected patient who experienced the outcome had a higher risk score than a patient who did not experience the predicted outcome. The value ranges from 0.5 to 1.0. An AUC value of 1.0 is equal to perfect prediction; the model can separate the patients experiencing the outcome perfectly from those who do not experience the outcome. In general, a value above 0.7 is considered helpful for prediction. In contrast, a value of 0.5 is equal to chance alone, while a model with a predictive performance above 0.8 has excellent predictive ability.[104]

Clinical prediction models may improve outcomes. For the patients where predictions are carried out, measures can be implemented to improve the predicted outcome. One example is initiation of early potent treatment in JIA. The ultimate test of a prediction model's usefulness would be a randomized controlled trial using a prediction model to guide treatment decisions

as a part of clinical care versus standard clinical care. Only then, we will know whether outcomes can be significantly improved.

2.8.3 From modelling to clinical applicable prediction tools

A clinical prediction tool (a risk calculator) allows physicians to feed models with the required information, e.g., clinical features and laboratory findings. In this way, physicians can receive objective probability-based risk scores for a given outcome. For a patient in the early stages of the disease course, the required input can be entered into a software tool that may be implemented as an online calculator or a mobile app. If the prediction model is a multivariable logistic regression model, the different variables are multiplied by their respective coefficients and summed up. The output obtained is a prediction score, which can be translated into the probability of an unfavorable outcome. Figure 1 shows a mobile app developed by our group.[79]

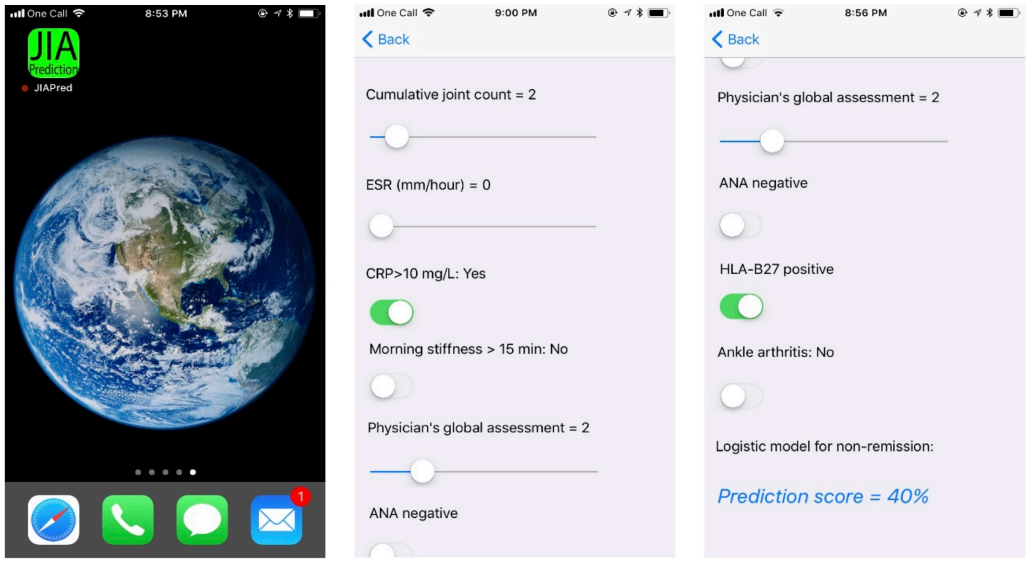

Figure 1. Screenshots of the JIA prediction app.

3 Uveitis in JIA

3.1 General aspects and epidemiology

Although the main feature of JIA is arthritis, several extraarticular manifestations may arise with potentially higher morbidity than the joint disease. Uveitis is the most common extraarticular manifestation. It is characterized by an inflammation of the uvea in the eye, affecting the iris, ciliary body, and the choroid.[2] In the majority of studies, the cumulative incidence of juvenile idiopathic arthritis-associated uveitis (JIA-U) is found to be between 4-24%, but both lower and higher rates have also been reported.[105-111] Differences in study design, patient accrual, and geographic and ethnic variations are likely reasons for the variation in reported uveitis rates.[105, 111] Reports have shown clear differences in uveitis rates across different parts of the world. JIA-U is more common in Northern Europe than in Asia and South America, and it has been suggested that children of European descent, especially with Nordic descent, have higher risk of JIA-U.[105, 106, 112, 113]

In contrast to intraocular inflammation in adults, children with JIA-U are often asymptomatic and therefore dependent on physicians' awareness and vigilance of the disease to be discovered. Chronic anterior uveitis is the most frequent type of uveitis associated with JIA, affecting both eyes in the majority of children. This type of uveitis onset goes unnoticed by the children or parents in more than 85% of the cases.[111, 114] Approximately 80-90% are diagnosed with uveitis within four years of JIA onset. However, there are children who develop uveitis before JIA and later on in life, with the risk of delayed diagnosis.[106, 114, 115] Since chronic anterior uveitis often is asymptomatic until ocular complications occur, children with JIA should undergo ophthalmologic screening regularly. Early identification and treatment of uveitis is necessary to prevent complications that may lead to visual impairment. Effective screening by slit lamp examination is necessary.[116, 117]

Acute anterior uveitis is another type of uveitis associated with JIA. This type is associated with human leukocyte antigen B27 (HLA-B27), and is more common among children with ERA and psoriatic arthritis. Acute anterior uveitis is usually symptomatic, unilateral, and is often more episodic. Children with acute uveitis often present with a painful red eye. They are promptly examined and treated by the ophthalmologist. Consequently, they have a lower risk of developing ocular complications.[41, 118]

All children with suspected or confirmed JIA need to be examined by an ophthalmologist at regular intervals according to their risk profile. Different screening programs have been suggested.[114, 116] According to the recent 2019 ACR recommendations regarding screening in JIA-U the following children with JIA are considered to be at high risk of uveitis: Those with oligoarthritis, RF negative polyarthritis, psoriatic arthritis, and undifferentiated arthritis who are ANA positive, younger than seven years at JIA onset, and have a duration of their uveitis of four years or less. These children should be screened every three months.[41] Children with low to moderate risk of JIA-U should be screened every 6-12 months. These are children that are ANA negative but in the high-risk JIA categories, and who develop JIA after the age of seven, or have had JIA for more than four years. The low to moderate risk group also include the RF positive polyarthritis, systemic JIA and ERA not mentioned in the high-risk group.[41]

3.2 Classification of JIA-associated uveitis

The International Standardization of Uveitis Nomenclature (SUN) working group[57] developed standardized classification criteria for uveitis. Uveitis in children can be idiopathic or associated with other diseases than JIA such as e.g., reactive arthritis, inflammatory bowel disease, Behcet´s disease and vasculitis. The SUN-criteria categorizes uveitis according to the anatomic localization of inflammation.[57] In addition uveitis is classified according to the onset type, duration and clinical course of uveitis. In JIA-U, the most typically finding is an anterior localization, with a chronic or recurrent course.[105] The SUN working group also established criteria for assessing the degree of inflammation in the eye, and the occurrence of ocular complications.[57] The ACR 2011 criteria for inactive JIA disease include the assessment of uveitis activity. In order to have inactive JIA disease,[52] no active uveitis defined as <1 cell in field sizes of 1x1mm slit beam should be found.[57] The SUN working group also defined criteria for assessing the degree of improvement of inflammation. Uveitis is registered as inactive if no cells are found in the anterior chamber, in remission if inactive disease is present for three months or more, after stopping uveitis treatment. Worsening is defined as a two-step increase in the level of inflammation or increase in grade from 3+ to 4+. Improved uveitis activity is present if there is a two-step decrease in the level of inflammation, or decrease to inactive uveitis.[57]

3.3 Etiology and pathogenesis of JIA-associated uveitis

The cause of uveitis in JIA is still unknown. As in JIA, uveitis is thought to be an autoimmune disorder.[119] The pathogenesis of JIA-U is probably similar to the pathogenesis in JIA, influenced by both environmental and genetic factors.[119] The adaptive immune system with both T cells, mostly CD4+ cells, and B lymphocytes, plays a role in the response towards ocular self-antigens, producing cytokines and driving the ocular inflammation.[119] Recent studies have found an association between HLA-DRB1*11 and HLA-DRB1*13, and an increased risk of JIA-U.[120]

Hep2-ANA positivity is reported to be more frequent among the JIA-U patients than in JIA patients without uveitis, raising the question of whether this antibody plays a role in the pathophysiology of uveitis.[107, 112, 121] Although antibody binding to ocular components have been found in children with JIA-U, no antigen as the target for ANA has been found.[122]

3.4 Current treatment strategies in JIA-associated uveitis

The goal in treatment of JIA-U is inactive disease. The treatment strategy of uveitis is similar to the stepping-up treatment strategies for arthritis.[41, 123]A combination of regularly ophthalmological screening and prompt treatment, with repeated assessments of treatment results and continuous evaluation of the need for early systemic treatment is crucial in order to gain control of the uveitis. The aim is quiescence of inflammation in order to avoid complications endangering vision. The care of patients with JIA-U should be interdisciplinary, involving both ophthalmologists and pediatric rheumatologists. Local treatment with topical glucocorticoid eye drops is the first choice if active uveitis is present. The decision to step up treatment depends on the degree of inflammation, the local glucocorticoid dose, flare-ups despite local treatment, development of complications, or not achieving inactive disease. Synthetic or biologic DMARDs should be considered if local treatment cannot be stepped down within three months.[41, 123] Methotrexate is often the first choice of systemic treatment. If severe inflammation is present, both methotrexate and an TNF inhibitor such as adalimumab may be needed.[124, 125] Etanercept was not found effective in the treatment of uveitis in an RCT, and should be avoided in JIA if the indication for starting biologics is mainly or partly due to uveitis.[126] Topical glucocorticoids have an adverse potential for causing glaucoma and cataract, and is therefore recommended only for shorter

periods.[41, 127] If the child is in need of topical glucocorticoids despite systemic therapy, the treatment should be intensified or switched to another TNF inhibitor. Alternative biologic DMARDs for JIA-U are abatacept or tocilizumab, or synthetic DMARDs such as mycophenolate or leflunomide.[128, 129] After the treatment goal is achieved, the recommendation is to continue systemic treatment for a minimum of two years before tapering. As for treatment of arthritis in JIA, systemic glucocorticoids are not recommended, other than as a possible bridging therapy awaiting the effect of DMARDs.[41, 50]

3.5 Ocular complications in JIA-associated uveitis

The frequency of ocular complications due to longstanding chronic anterior uveitis in JIA has decreased in the last decade. Two or more decades ago, up to 90% of the patients with JIA-U developed ocular complications.[130-132] The most severe consequence of ocular complications is impaired vison and in worst case blindness. Cataract and glaucoma are the most common ocular complications threatening the sight in children with JIA-U.[117, 133, 134] Cataract is a clouding of the normally clear lens of the eye, and glaucoma is when damage of the optic nerve is caused by high pressure in the eye. The reported cataract rate in JIA-U is 20-80%, and for glaucoma 10-40%.[135-137] These numbers vary greatly depending on the time period, study design, and the cohort composition in the studies. In JIA-U, the percentage with ocular complications have decreased the past years. This decrease is most likely a result of tight screening programs and earlier initiation of synthetic and biologic DMARDs in JIA.[138, 139] More restrictive use of local glucocorticoids may also be beneficial, since they are known to have an adverse effect of inducing glaucoma and cataract as mentioned above.[41] Other sight threatening complications are synechiae which often develops as the result of severe inflammation resulting in adherence between the lens and iris. Band keratopathy, macular edema, and phthisis bulbi may also occur.[114, 135, 140] Figure 2 shows the eye of a young boy with JIA-U. He has synechiae, early cataract formation, and band keratopathy on slit lamp examination.

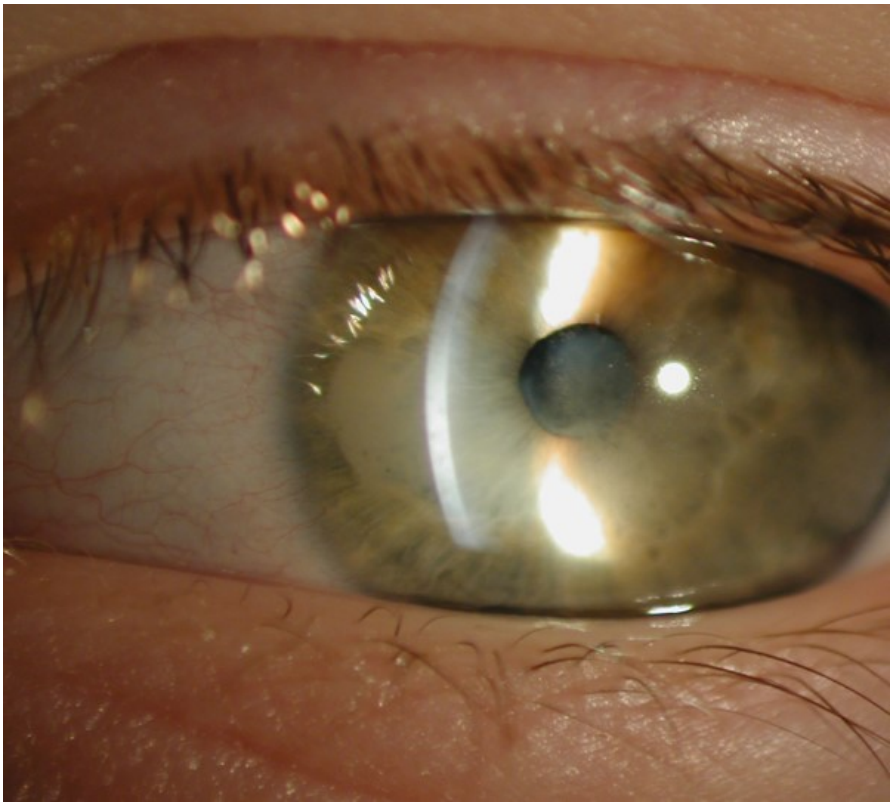

Figure 2. Slit lamp photo from a patient with JIA-associated uveitis. A grayish area with band keratopathy is seen to the left from the slit light on the cornea. Posterior synechiae are visible at the pupillary border. The lens does not seem to be completely clear as seen with incipient cataract of the lens. Photo by Terje Christioffersen

3.6 Predictors of uveitis and uveitis-related complications

Young age at the onset of JIA, as well as belonging to the oligoarthritis and RF- negative polyarthritis categories, are considered to be predictors associated with an increased risk of developing uveitis.[107, 114, 117] Presence of ANA and HLA-B27 are associated with chronic and acute uveitis, respectively.[108, 111] In contrast, uveitis is rarely seen in the systemic JIA and RF positive polyarthritis categories.[105, 111]

Predictors associated with the occurrence of ocular complication are: the presence of ocular complications at baseline, severe inflammation in the uvea, the onset of uveitis before arthritis, and a short interval between the onset of JIA and the onset of uveitis.[117, 133, 138, 141] Even though males are underrepresented among patients with JIA-U, males are reported to be more prone to develop ocular complications.[142] Some studies have shown that female gender, persistent oligoarthritis, and presence of ANA are significant predictors of ocular complications.[133, 143] However, there are discrepancies between studies, and most reports find

no significant associations between ocular complications and JIA subtype, ANA nor female gender.

In Table 3, selected studies from 2007-2020 reporting on predictors of ocular complications and the rates of complications in JIA-U. The JIA onsets in these studies span from the 1980s to the present.[84, 108, 113-115, 133, 137-139, 141, 142, 144-147] The proportion of JIA-U patients that developed ocular complications range from approximately 20% to 60%. A recent study from a large German inception cohort reported a rate of complications in the lower end of this range.[138] In a Finish study, the rate of complications decreased from 35% for patients enrolled in the year 1990, to 21% for patients enrolled in the year 2000.[139] Before the year 2000, few patients with JIA were treated with biologics agents, compared to today. Biologic treatment targets specific parts of the immune system involved in inflammation. The treatment can be highly effective when uveitis is refractory to local steroids or synthetic DMARDs.[41] A German study on JIA-U reported that 29% had complications of their uveitis. This rate is lower than the complication rates reported from the pre-biologic era.[138] Another reason for the lower rate of ocular complications in the recent years may be the increased use of standardized uveitis screening guidelines.[116] A known risk factor for developing ocular complications is the onset of uveitis before arthritis, and most uveitis develops in the first few years after JIA diagnosis. Therefore, early and regular eye screening at a short intervals in the beginning of the disease course is essential to avoid long-term ocular complications.[115] The studies presented in Table 3 originate from Europe and North America, and only one study analyzed predictors associated with complications for different ethnicities.[108] The largest studies from multi-center cohorts are performed in Germany[114, 138], the USA,[108, 133, 141] and Canada.[107, 142]

Table 3. Predictors associated with development of uveitis-related complications

Author (country)	Patients N	Uveitis N (%)	Study design	Predictors of complications and vison loss	Complications, vison loss and uveitis activity %
Heiligenhaus et al 2007, Germany	3271 JIA.	406 (12%)	Prospective. National database. Mean follow-up 5.6 years.	Complications at first visit. Uveitis before arthritis.	Complications: 56% of JIA-U patients.
Woreta et al 2007, USA	75 JIA-U.	75	Retrospective. Cross-sectional. Patients evaluated between the years 1984-2005.	Presence of ≥1+ anterior chamber flare. Positive ANA. Shorter duration between the diagnosis of arthritis and uveitis.	Complications: 64% of JIA-U patients. 67% of eyes of JIA-U. VA in affected eyes: 20/50 or worse: 36%. 20/200 or worse: 24%.
Thorne et al 2007, USA	75 JIA-U.	75	Retrospective. Median follow-up 3-years. Patients evaluated between the years 1984-2005.	Presence of posterior synechiae. Presence of anterior chamber flare ≥1+. Abnormal IOP. Inflammation ≥0.5+ cells.	Any ocular complication: 0.33/EY. VA: 11% VA loss. 20/50 or worse: 10/EY. 20/200 or worse: 0.08/EY.
Saurenmann et al 2007, Canada	1081 JIA.	142 (13%)	Inception cohort. Tertiary center. Mean follow-up 6.9 years. Ophthalmologists' records of JIA-U patients collected.	Synechiae and cataract associated with abnormal vision.	Complications: 37.3% of JIA-U patients. 4.9% of total JIA cohort.
Reininga et al 2008, The Netherlands	153 JIA.	27 (18%)	Retrospective. Evaluation of medical records. Referral center. 7-years follow-up.	Not reported.	Complications: 48% of JIA-U patients. VA: 21 of 25 patients had VA ≥0.1. 4 patients had VA <0.05.
Sabri et al 2008, Canada	1081 JIA.	142 (13%)	Retrospective chart review. Mean follow-up 6.9 years. To be included: minimum of 1-year follow-up.	Short time from diagnosis of JIA to uveitis. Higher use of oral prednisone. Ocular surgery.	Complications: 37.3% of JIA-U patients. 32.5% of eyes of JIA-U. Impaired VA in 6 eyes: 3.4%. Blindness in 10 eyes: 5.7%.
Skarin et al 2009, Sweden	350 JIA.	55 (16%)	Retrospective. Examined at 7 and 24 years after onset of JIA-U. Tertiary center.	Not reported.	Complications: 58% of JIA-U patients. 7 years after JIA-U onset: Cataract 42%, Glaucoma 5%. 24 years after JIA-U onset: Cataract 51%, Glaucoma 22%. Active uveitis: 49%.

Hoeve et al 2012, The Netherlands	62 JIA-U.	62	Retrospective. 2-years follow-up.	Female gender, but male gender for hypotony.	Not reported.
Angeles-Han et al 2013, USA	4983 JIA.	459 (12%)	Registry study. Retrospective.	Not reported.	Not reported.
Gregory et al 2013, USA	327 JIA-U.	327	Multicenter. Retrospective.	Posterior synechiae. Active uveitis. Intraocular surgery. Increasing uveitis activity was associated with increased risk of vision loss.	Complications: 60.2% eyes of JIA-U. Incidence of developing at least 1 new ocular complication over follow-up was 0.15/EY. VA at presentation: 20/50 or worse: 240 eyes (40.3%). 20/200 or worse: 144 eyes (24.2%).
Kotaniemi et al 2014, Finland	Years: 1990-1993: 239 JIA. 2000-2003: 240 JIA.	(25%) (18%)	Retrospective. Comparison between two cohorts separated by 10 years.	Not reported.	Complications: 1990-1993: 35% of JIA-U patients. 2000-2003: 21% of JIA-U patients.
Paroli et al 2015, Italy	69 JIA-U.	69	Retrospective. Tertiary uveitis clinic.	ANA positivity. Hypotony. Anterior chamber flare >1.	Complications: 30% of eyes of JIA-U. At baseline: Post. synechiae: 52%. Band keratopathy: 38%. Cataract:12%. VA: 20/50 or worse: 0.04/EY. 20/200 or worse: 0.02/EY.
Tappeiner et al 2015, Germany	18555 JIA. Years: 2002: 2013:	(13%) (11.6%)	Prospective cross-sectional study. Years 2002-2013.	Not reported.	Complications: 33.6% of JIA-U patients in 2002. 23.9% of JIA-U patients in 2013. Uveitis activity: 69.4% in 2002. 34.7% in 2013.
Haasnoot et al 2016, The Netherlands	67 JIA-U.	67	Retrospective. Assessed during 18th, 22nd and 30th year of life.	Uveitis before arthritis.	Complications: 54% of JIA-U patients. Uveitis activity 18th life year: 54%. Visual impairment or legal blindness 18th life year: Bilateral: 4%. Unilateral: 33%.
Dimopoulou et al 2017, Greece	102 JIA.	11 (11%)	Retrospective. 17-years follow-up.	Not reported.	Complications: 46% of JIA-U patients.
Papadopoulou et al 2017, Sweden	299 JIA.	32 (11%)	Retrospective. 7-years follow-up.	Not reported.	Complications: 47% of JIA-U patients. 46% of eyes of JIA-U.

Heiligenhaus et al 2019, Germany	954 JIA.	106 (11%)	Prospective. 2-years follow-up.	At first uveitis: Older age at JIA onset. Short duration between JIA and uveitis onset. Higher anterior chamber cell grades. Poor visual acuity. Corticosteroids eye drops.	Complications: At first uveitis: 29.8%. 1-year follow-up: 30.7%. 2-year follow-up: 32.8%. Uveitis activity: 1-year follow-up: 18.2%. 2-year follow-up: 20%.
JIA, Juvenile idiopathic arthritis; JIA-U, JIA-associated uveitis; ANA, anti-nuclear antibody; VA, visual acuity; IOP, intraocular pressure; EY, eyes per year.					

The ultimate treatment goal in JIA and JIA-U is inactive disease, with no signs of arthritis or active uveitis. The treatment strategies are in general costly and come with potential serious side effects. Identifying the patients at high risk of high disease activity and need for early aggressive treatment is therefore an aim.

4 Aims of the study

The overall aim was to develop clinically useful prediction tools relevant for guiding early treatment decisions in JIA. Further, to provide new insight in long-term outcome of JIA-associated uveitis, and to assess predictors of ocular complications.

Specific aims are listed below.

4.1 Paper I:

- Develop a prediction model based on baseline clinical characteristics in the Nordic JIA cohort to assess the probability of the main outcome *non-achievement of remission off medication* for each child with JIA.

- Develop a prediction model based on baseline clinical characteristics in the Nordic JIA cohort to assess the probability of *functional disability* in different activities of everyday life, and the probability of *joint damage* for each child with JIA using the following validated outcome measures: CHAQ, CHQ-PF50 (PhS) and JADI-A.

- Develop a clinical tool to assist in decision-making for early treatment strategies in JIA as software for mobile devices (iOS) and online applications to ensure convenience for use in clinical practice.

- Test the predictive ability of the Canadian prediction model developed in the Canadian ReACCh-Out cohort[77] for the following outcomes: *non-achievement of remission off medication, functional disability*, and *joint damage* in the Nordic JIA cohort.

4.2 Paper II and Paper III:

We aimed to validate each prediction model in a different cohort than the one used for building the model.

4.2.1 Paper II: Part 1 – External validation of the Canadian prediction model in the Nordic JIA cohort

- Test the Canadian prediction model's ability to predict the outcome it was constructed to predict, *severe disease course* (Canadian outcome) in Nordic patients with JIA.

- Test the Canadian prediction model's ability to predict *non-achievement of remission off medication* (the Nordic outcome) in Nordic patients with JIA.

- Test the Nordic prediction model's ability (developed in *paper I*) to predict *severe disease course* (Canadian outcome) in Nordic patients with JIA.

4.2.2 Paper III: Part 2 – External validation of the Nordic prediction models in the ReACCh-Out cohort

- Test the Nordic prediction model's ability to predict the outcome it was constructed to predict, *non-achievement of remission off medication* and *functional disability* (Nordic outcomes) in Canadian patients with JIA.

- Test the Nordic prediction model's ability to predict *severe disease course* (Canadian outcome) in Canadian patients with JIA.

4.3 Paper IV:

- Assess the long-term outcome of uveitis in JIA in terms of cumulative incidence, clinical characteristics, disease activity, ocular complications, and visual outcome.

- Identify predictors for development of uveitis-related complications that may further be used in individual prognostication.

5 Materials and methods

5.1 Study design and population

5.1.1 The Nordic JIA cohort

The population-based, longitudinal, prospective, multicenter study on JIA in the Nordic countries was initiated and run by The Nordic Study Group of Pediatric Rheumatology (NoSPeR). The central part of the thesis is based on data from the Nordic JIA cohort. We studied consecutive new JIA cases included from January 1997 to June 2000 from 12 participating centers from defined geographical areas of Denmark, Finland, Norway, and Sweden. The Nordic countries' health care system is mostly free of charge for children under 16 years of age, making it feasible to conduct a population-based study. During the inclusion period, letters were repeatedly sent to primary health care providers, child health centers, orthopedic, pediatric, and rheumatology specialists in the catchment areas to ensure all eligible patients' referral to collect a population-based cohort.[148]

The included patients were followed prospectively for 18 years. The first visit was the baseline study visit with 500 patients, approximately six months after onset of JIA. Besides the baseline visit, there were two other major visits, the 8-year visit with 440 patients and the 18-year visit with 434 patients (Figure 3).

The children were followed at regular intervals, with two visits in the first year, and after that, 1-to-3-year intervals up to the 8-year visit.[148] During this observation period, the children were also screened for uveitis by an ophthalmologist at each center. In the first two years, the ophthalmologic examinations were scheduled every 2-3 months; after that, longer intervals depending on the time since onset of JIA and the JIA category.

5.1.2 The ReACCh-Out cohort

We used the Canadian ReACCh-Out cohort for the validation of the Nordic JIA prediction model. The Research in Arthritis in Canadian Children Emphasizing Outcomes (ReACCh-Out) cohort is a prospective and multicenter cohort. Initially 1497 children with JIA were included from 16 pediatric rheumatology centers across Canada between January 2005 and December 2010. The first visit occurred as soon as possible after diagnosis, but could be up to

one year after diagnosis. Follow-up visits were scheduled every six months during the first two years, and then yearly up to 5 years, or until May 2012.[59, 74]

5.2 Inclusion criteria

For the studies based on the Nordic JIA cohort, the inclusion occurred between January 1st, 1997, and June 30th, 2000. Children or adolescents <16 years of age with newly diagnosed JIA according to the ILAR criteria were included in the study.[1] To continue in the study a minimum of two study visits was required, one of them being the baseline visit.

For the study based on the Canadian ReACCh-Out cohort, the inclusion period was from January 2005 to December 2010. Children or adolescents <16 years of age with newly diagnosed JIA according to the ILAR criteria were included in the study.
In the Nordic prediction model development study (*paper I*) 423 of 500 (85%) children in the Nordic JIA cohort met the inclusion criteria of having a baseline study visit, an 8-year-follow-up visit, and not belonging to the systemic JIA category.[79] In the validation study of the Canadian prediction model (*paper II*), all children in the cohort with 8-year follow-up were included. These were 440 of 500 (88%), including those with systemic JIA (Figure 3).[149]

For the validation of the Nordic prediction model in the Canadian ReACCh-Out cohort (*paper III*), Canadian children recruited within three months of diagnosis who had enough information at the 3-year visit to ascertain the outcomes were included. Data from 513 children attending the 3-year visit in the ReACCh-Out cohort study were used.[150]

The inclusion criteria for the study on JIA-associated uveitis (*paper IV*) were all children in the Nordic JIA cohort with a baseline visit and an 18-year follow-up visit. In all, 434 of 500 (86.8%) patients were followed for 18 years. Among these, 329 of 434 (75.8%) attended the study visit at the department of pediatrics, and 273 of 329 (83.0%) attended the study visit at the department of ophthalmology. The remaining 105 (24.2%) patients participated in the 18-year follow-up study through a standardized telephone interview as shown in Figure 3.

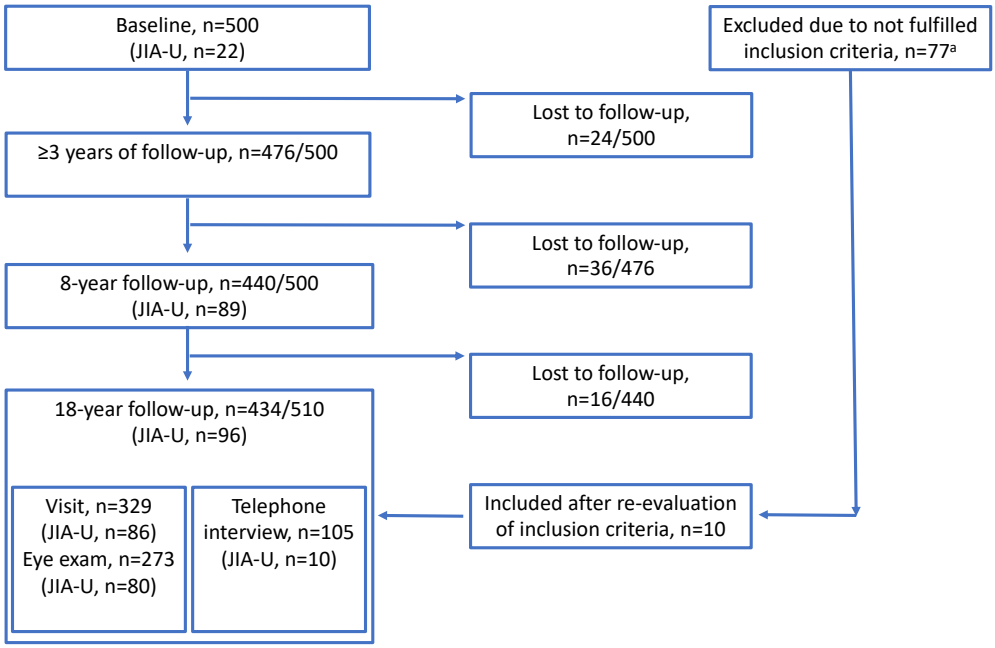

Figure 3. Flow chart of the Nordic JIA cohort from baseline to the 18-year follow-up. The number of patients that physically attended the study visit at the pediatric rheumatologist and ophthalmologist at the 18-year follow-up is presented. [a]10 of 77 excluded patients fulfilled the inclusion criteria after re-evaluation.

5.3 Data collection

A thorough registration of medical and family history, symptoms, and clinical findings including complete joint counts, patient/parent-completed health assessment measures, and laboratory parameters. This was performed every six months during the first year. Then new visits were performed every 1-3 years during the first eight years after disease onset, at the 8-year follow-up and finally at the 18-year follow-up. Information from all study visits was prospectively registered in a specifically designed database (4th Dimension) at all centers. Local biobanks of serum and full blood specimens were sampled at baseline, 8-years, and 18-years. At the 18-year follow-up, the patients were also examined by an ophthalmologist and comprehensive clinical information on uveitis was collected. The data from the 18-year visit was stored in a new database (SurveyXact). The core variables from baseline and 8-year were merged with the latest data set in SurveyXact.

Data registered at baseline (approximately six months after disease onset)

- Demographics including age, date of onset of JIA, family history, medication, and information about progress in school and physical education
- General physical examination including joint assessment

- Uveitis-related clinical data
- Assessment of disease activity measures and disease course
- Classification according to ILAR and EULAR criteria
- Serum and EDTA whole blood sampled and stored
- Registration of results of laboratory tests such as ANA, rheumatoid factor, HLA-B27, and the inflammatory parameters CRP and ESR
- Patient/parent-reported questionnaires: CHAQ

Data registered at the 1-3-year interval after disease onset

- General physical examination including joint assessment
- Uveitis-related clinical data
- Assessment of disease activity measures and disease course
- Classification according to ILAR and EULAR criteria
- Routine blood samples
- Patient/parent reported questionnaires: CHAQ

Data registered at the 8-year follow-up

- Update on demographics and family history, medication, and information about education/employment
- General physical examination including joint assessment
- Serum and EDTA whole blood sampled and stored
- Registration of results of ANA, rheumatoid factor, HLA-B27, and the inflammatory parameters CRP and ESR
- Extended information on uveitis-related clinical data
- Assessment of disease activity measures and disease course: JADAS
- Assessment of joint damage: JADI-A and JADI-E
- Patient/parent-reported questionnaires: CHAQ, HAQ, CHQ-PF50, SF-36

Data registered at the 18-year follow-up

- Update on demographics and family history, medication, and information on education/employment
- General physical examination including joint assessment, and registration of height and weight

- Ophthalmology visit for eye status and registration of uveitis-related clinical data
- Dental visit for temporomandibular joint status and oral examination data, including a full-face cone-beam computed tomography (CBCT)
- Serum and EDTA whole blood sampled and stored
- Assessment of disease activity measures and disease course: JADAS and DAS
- Assessment of joint damage: JADI-A and JADI-E
- Patient-reported questionnaires: HAQ, SF-36, FSS

5.4 Predictor variables and outcomes assessed

In *paper I*, several clinical variables were screened as potential predictor variables. Five clinical variables were included *a priori* in the four prediction models. These variables were the cumulative active joint count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), morning stiffness, and physician's global assessment of disease activity (Physician's GA). According to the provisional Wallace 2004 criteria, these four variables are assessed when evaluating if the patient is in remission.[51] We considered to include whether the patient had active uveitis or not, but since the patients with uveitis were a subgroup of the total cohort, this variable was not included in the prediction model. Other key variables were included by the model-building procedure described in the statistics section. As a result of this procedure, the set of included variables were different for each of the four outcomes.

The primary outcome assessed in *paper I* was *non-achievement of remission off medication*; this included active disease, inactive disease of fewer than 12 months of duration, and clinical remission on medication according to the preliminary Wallace criteria.[51] The secondary outcomes were functional disability assessed by CHAQ and CHQ-PF50 (only PhS was assessed), and joint damage assessed by JADI-A. In the model for prediction of *non-achievement of remission off medication*, ANA, HLA-B27, and ankle joint arthritis entered the model as predictors in addition to the five *a priori* variables. Figure 4 shows the resulting multivariable logistic regression model for prediction of *non-achievement of remission off medication*. In the model for predicting functional disability assessed by CHAQ, finger joint arthritis and pain VAS were added by the modeling building procedure. For the prediction of functional disability assessed by PhS, pain reports on a VAS were entered as an additional

variable in the model. Finger joint arthritis and older age at disease onset were the extra predictor variables in the model predicting joint damage assessed by JADI-A.

In *paper II*, we evaluated the Canadians' prediction model's validity. The Canadian model uses 16 predictor variables (active joint count at baseline, psoriatic arthritis, oligoarthritis, RF negative polyarthritis, upper limb joint involvement, symmetric joint involvement, RF positivity, subtalar joint involvement, finger joint involvement, cervical spine involvement, ankle joint involvement, presence of morning stiffness, hip involvement, temporal mandibular joint involvement, mid-foot involvement, and presence of enthesitis). The multivariable logistic regression prediction model is shown in Figure 4. The model was tested in the Nordic cohort using the outcomes *non-achievement of remission off medication* (Nordic outcome) and *severe disease course* (Canadian outcome). In the Nordic cohort, the *severe disease course* outcome was constructed on the basis of the variables cumulative active joint count, remission status, CHAQ and the PhS derived from CHQ-PF50 form. We also constructed an alternative version including pain reports on VAS at the 8-year visit. The outcome construction is described in detail in the section on statistical methods.

In *paper III*, the Nordic prediction model developed in *paper I* was tested in the ReACCh-Out cohort. For Canadian children, we used the eight variables in the model for prediction of *non-achievement of remission off medication* (stated above) to predict the outcomes *severe disease course* and *non-achievement of remission off medication* at the 3-year visit. The exact same definition of the *non-achievement of remission* used in the original Nordic study, was not possible to use in the ReACCh-Out cohort due to differences in the frequency of visits and other differences between the two cohorts. The outcome *severe disease course* was originally constructed in the ReACCh-Out cohort with a cluster procedure based on changes in pain, health related quality of life, number of active joints, medication requirements, and medication side effects over five years.[77]

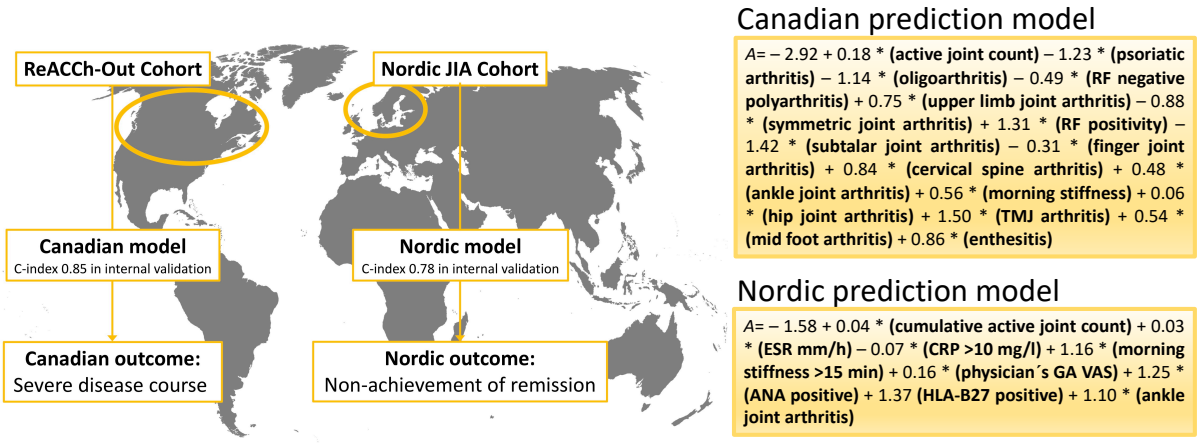

Figure 4. Illustration of the Canadian and Nordic multivariable logistic regression models. The yellow boxes present the included predictor variables and coefficients. C-indices in internal validation were 0.85 for the Canadian model and 0.78 for the Nordic model.

In *paper IV*, we identified the following predictors associated with the outcome ocular complications: short time interval between the onset of JIA and uveitis, onset of uveitis before JIA, and positive ANA test. Other variables explored as possible predictors of developing ocular complications were: gender, young age at diagnosis of uveitis, young age at diagnosis of JIA, oligoarthritis and RF negative polyarthritis categories, and HLA-B 27. These are variables previously reported to be associated with increased risk of uveitis. An association with uveitis-related ocular complications was, however, not found.[105, 107, 112]

5.5 Statistical methods

The analyses were performed using the software packages STATA version 14, and Wolfram Mathematica version 11.1.1.0, and R software. Conventional descriptive statistics such as absolute numbers, median, interquartile range (IQR; 1st and 3rd quartile), and percentages were used to describe demographics and clinical characteristics in *paper I-IV*. In the following sections the methods used for developing models, validation of models, and construction of clusters and heat-maps will be presented in more detail.

5.5.1 Prediction model building

In *paper I*, we performed univariate logistic regression as a screening procedure to assess baseline variables as potential predictors for the four outcomes. Variables with a p <0.05 in the univariate analysis were considered candidates for a prediction model. The variables'

dependencies were assessed by Spearman correlation, and if two variables had strong correlations, only one was included. Models were constructed based on the predefined variables selected *a priori*, and the additional variables selected using a forward stepwise method where the criterion for inclusion was that a variable contributed to the multivariable model with p <0.05, when included. For each predictor variable, the model coefficients were estimated by multivariable logistic regression. The probability of the predicted outcome is computed according to the formula

$$P = 1/(1 + e^{-A}), \text{ with } A = \beta_0 + \beta_1 x_1 + \cdots + \beta_n x_n \,, \quad (1)$$

where $\beta_1, \ldots, \beta_n$ are the model coefficients for each predictor variable x_i.

5.5.2 Validation of prediction models

In *paper I*, internal cross-validation was performed by randomly dividing the cohort 100 times in a training cohort and a validation cohort. Prediction models were constructed in the training cohort to find variables and estimate model coefficients in each realization. In the validation cohort, the multivariable logistic regression model provided a probability of each of the patients' outcome. The receiver operating characteristic (ROC) curve was computed by comparing the predicted probability of unfavorable outcome with the actual outcome at the 8-year visit, and the area under the curve (AUC) estimated.

In *paper II*, we needed to construct a version of the *severe disease course* (Canadian outcome) in the Nordic JIA cohort. The K-medoids clustering algorithm was used to divide patients into mild, moderate, severe controlled, and severe persistent disease courses, in this way, grouping patients with similar characteristics together. The union of the two worst groups constituted the *severe disease course* outcome. The identified patients in the Nordic cohort were compared to the patients identified in the ReACCh-Out cohort. The percentage of patients with *severe disease course*, and their clinical characteristics were similar in both cohorts. External validation of the Canadian model was first done without fine-tuning, meaning that we tested the model exactly as it was published, and afterwards with fine-tuning. The fine-tuning was done by re-estimating coefficients in 500 repeated random splits. For each random split, we used 75% of the cohort for training and 25% of the cohort for testing the model. Internal validation of the Nordic model for prediction of *severe disease course* was also

performed. Uncertainty was measured by bootstrapping (resampling) and reported as the IQR. The results were presented with C-indices, equivalent to the area under the Receiver Operating Characteristic curve (AUC).

In *paper III*, we performed validation of the Nordic model in the ReACCh-Out cohort. Missing information on baseline predictor variables were imputed by multiple imputation by chained equations (MICE) in 20 data sets.[151] The Nordic prediction model (exactly as published in *paper I*) was applied to 100% of the data within each of 20 imputed datasets. The C-index and the standard error (SE) of the C-index were computed from each data set. The fine-tuned Nordic model, with re-estimated coefficients and intercept, was tested by multiple splits of the ReACCh-Out cohort. For a given imputed dataset, the average C-index was estimated using the Leave-One-Out Cross-Validation (LOOCV) error method. Standard errors were estimated by nested cross-validation bootstrapping with 25 bootstrap samples, with a total of 500 fits. The C-index and standard deviation (SD) of all predicted values were computed.

5.5.3 Cluster analysis

We had to construct a version of *severe disease course* in the Nordic cohort. To do this we used four variables collected at the 8-year follow-up. These variables were the cumulative active joint count, the remission status, the Childhood Health Assessment Questionnaire disability index (CHAQ), and the Physical Summary Score (PhS) derived from the Child Health Questionnaire Parent form (CHQ-PF50). We used multiple imputation of missing data using a principal component algorithm. On the imputed and normalized data, we used the K-means clustering algorithm to group patients. The K-means method groups observations, in this case, patients, so that each one belongs to the cluster whose mean is closest. This analysis was carried out in Wolfram Mathematica version 11.3.0.0.

We decided to group the cohort into four clusters, the same number of clusters chosen by Guzman et al.[77] The clinical characteristics of each of the four groups were analyzed using standard descriptive statistics. The result of this investigation clearly showed that two of the clusters were associated with more serious disease, which combined made up 22% of the cohort. We also considered an alternative construction of *severe disease course* that included pain VAS as a fifth variable. To make the relative size of this version correspond to those

found in the Canadian study, we used the *K*-medoids algorithm. This algorithm is similar to the K-means method except for the use of real observations (medoids) instead of means to represent the center of clusters.

5.5.4 Hierarchical clustering and heat-maps

In *paper IV*, we used hierarchical clustering to make two heat maps to analyze uveitis in the Nordic JIA cohort. One heat map was to illustrate the association between predictors and complications. The other heat map to illustrate how complications are distributed between the different uveitis characteristics.

The heat map for predictors and uveitis complications was constructed starting from a matrix where the horizontal position represented patients with uveitis. The vertical positions represented complications (glaucoma, cataract, synechiae, epiretinal membrane, hypotony, phthisis, macular edema, and band keratopathy). An entry in the matrix was assigned the value 0 if the given patient did not have the given complication. The value was 0.5 if the patient had the complication in one eye, and the value was 1 if the patient had the complication in both eyes. The agglomerative clustering algorithm was applied to patients and complications, and the rows and columns were reordered according to the hierarchical clustering. After the reordering, patients with similar complications were placed next to each other, and complications that were distributed similarly in the cohort were placed next to each other. The heat map was annotated with predictors.

The second heat map was constructed in the same way. The aim was to illustrate uveitis characteristics according to SUN criteria, and we therefor clustered eyes instead of patients. Vertical positions represented different uveitis characteristics. The characteristics were 0 or 1 variables, except for one variable which took three values (acute=1, recurrent=0.5, and chronic=0). After hierarchical clustering and reordering, the heat map was annotated with uveitis complications.

5.6 Ethical approval

Approvals from medical research ethics committees and data protection authorities were granted according to each participating country's regulations and in accordance with the

Declaration of Helsinki. Sweden; Dnr 2014/413-31, Denmark; 1-10-72-280-13, Norway; REK 2012/2051, and Finland; 174/13/03/03/2014. Written informed consent was obtained from parents of children aged <16 years and from the children themselves if aged ≥16 years of age.

6 Summary of main results

The main results from the four papers constituting the thesis are presented in this section. For further details see the published papers attached.

6.1 Paper I

Predicting unfavorable long-term outcome in juvenile idiopathic arthritis: results from the Nordic cohort study

Study cohort

- In the Nordic JIA cohort 423 patients were included after 17 patients with systemic JIA were excluded. The outcome was assessed eight years after disease onset.

- Among the included patients, we had data for 410 of 423 (96.9%) for assessment of remission status, 340 of 423 (80.4%) for CHAQ scores, 199 of 423 (47.0%) for CHQ-PF50 (PhS) scores, and 216 of 423 (51.1%) for JADI-A data at the 8-year follow-up.

Predictor variables

- We found moderate to strong correlations (Spearman correlation coefficients ≥ 0.50) between the cumulative active joint count, joint-specific variables, and polyarthritis RF-negative category. Moderate to strong correlations was also found between physician's GA and PROMs.

- Predictor variables significantly associated with *non-achievement of remission off medication* in univariate logistic regression were: higher cumulative active joint count, higher physician's GA, polyarthrits RF-negative category, ankle joint arthritis, tarsal joint arthritis, subtalar joint arthritis, wrist joint arthritis, finger joint arthritis, upper

limb joint arthritis, symmetric ankle joint arthritis, symmetric finger joints arthritis, higher patients/parents GA, higher CHAQ-score, higher pain VAS, morning stiffness >15 min, higher ESR, CRP >10, and positive HLA B27.

- The five selected *a priori* variables were: cumulative joint count within six months of JIA onset, ESR, CRP, morning stiffness and physician GA.

Prediction of the main outcome non-achievement of remission off medication

- 244 of 410 (59.5%) patients did not achieve remission off medication at the 8-year follow-up visit.

- The multivariable logistic regression prediction model for prediction of *non-achievement of remission off medication* eight years after JIA onset was given by Equation (1), with:

$$A = -1.58 + 0.04 \times (\text{cumulative joint count within 6 months of onset}) + 0.03 \times (\text{ESR mm/h}) - 0.07 \times (\text{CRP>10mg/L}) + 1.16 \times (\text{morning stiffness >15 min}) + 0.16 \times (\text{physician GA}) + 1.25 \times (\text{ANA positive}) + 1.37 \times (\text{HLA B27 positive}) + 1.10 \times (\text{ankle joint arthritis})$$

- The model predictive ability presented with AUC was 0.84 for the total cohort. In internal validation the AUC was 0.78 (IQR 0.72–0.82) for the model including laboratory parameters (ESR, CRP, ANA, and HLA B27). When we excluded the laboratory parameters, we achieved an AUC of 0.76 (IQR 0.72–0.80).

Prediction of the functional disability and joint damage

- 111 of 340 (32.7%) patients had functional disability defined as a CHAQ >0, and 40 of 199 (20.1%) had functional disability defined as a PhS <40, at the 8-year follow-up visit.

- 29 of 216 (13.4%) patients had joint damage defined as JADI-A >0, at the 8-year follow-up visit.

- The multivariable logistic regression model for prediction of CHAQ >0 included the following two variables in addition to the five a priori variables: ***finger joint arthritis (β_6=1.21)*** *and* ***pain VAS (β_7=0.77)***.

- The model for predicting CHAQ >0 achieved an AUC of 0.79 for the total cohort. In internal validation the AUC was 0.73 (IQR 0.67–0.76).

- The multivariable logistic regression model for prediction of PhS <40 included ***pain VAS (β_6=1.30)*** in addition to the five a priori variables.

- The model for predicting PhS <40 achieved an AUC of 0.90 for the total cohort. In internal validation the AUC was 0.74 (IQR 0.65–0.80).

- The multivariable logistic regression model for prediction of JADI-A >0 included the following two variables in addition to the five a priori variables: ***finger joint arthritis (β_6=1.84)*** and ***older age at disease onset (years) (β_7=0.16)***.

- The model for predicting JADI-A >0 achieved an AUC of 0.84 for the total cohort. In internal validation the AUC was 0.73 (IQR 0.63–0.76).

Testing the Canadian prediction model on the Nordic outcomes

- The Canadian model was applied directly as published[77] on the children in the Nordic JIA cohort, and yielded an AUC of 0.69 to predict *non-achievement of remission off medication*. The AUCs were 0.68 for CHAQ >0, 0.69 for PhS <40, and 0.71 for JADI-A >0.

6.2 Paper II

Validation of prediction models of severe disease course and non-achievement of remission in juvenile idiopathic arthritis: part 1—results of the Canadian model in the Nordic cohort

Study cohort

- In the Nordic JIA cohort 440 patients were included, also the patients with systemic JIA. The outcome was assessed eight years after the onset of JIA.

- Our cluster analysis identified 98 of 440 (22%) as having a *severe disease course* in the Nordic validation cohort, compared to 125 of 609 (21%) identified by the cluster analysis in the ReACCh-Out development cohort.

- 246 of 427 (58%) patients did *not achieve remission off medication* at the 8-year visit.

- The patients identified to have a *severe disease course* had similar disease characteristics in the ReACCh-Out development cohort and the Nordic validation cohort. In general, the *severe disease course* in the Nordic cohort and the *severe disease course* in the ReACCh-Out cohort had the following similar characteristics: The patients were older at JIA onset, longer time from disease onset to diagnosis, they had higher cumulative affected joint count with the neck, finger joints, and ankle joints frequently affected, higher reports on pain and CHAQ scores, and a higher percentage used synthetic DMARDs at baseline in the *severe disease course* groups.

Prediction model validation

- External validation of the Canadian model (without fine-tuning) for predicting *severe disease course* (the Canadian outcome, constructed in the Nordic cohort) yielded an excellent predictive performance with a C-index of 0.85 (IQR 0.83-0.87).

- When the model was fine-tuned to the Nordic patients by re-estimation of parameters, the predictive performance remained at the same level as without fine-tuning (C-index of 0.85 (IQR 0.81-0.89)).

- The Canadian model did not achieve acceptable predictive performance when applied to predict *non-achievement of remission off medication* (the Nordic outcome) with a C-index of 0.66 (IQR 0.63-0.68). When the model was fine-tuned to the Nordic patients with, the predictive performance improved slightly (C-index of 0.69 (IQR 0.65-0.73)).

- The Nordic model (developed in *paper I*) performed excellently when applied to predict *severe disease course* (the Canadian outcome), which was not the outcome it was constructed to predict. The result was a C-index of 0.90 (IQR 0.86-0.92) in the Nordic cohort.

6.3 Paper III

Validation of prediction models of severe disease course and non-achievement of remission in juvenile idiopathic arthritis part 2: results of the Nordic model in the Canadian cohort

Study cohort

- In the ReACCh-Out cohort 513 patients were included, and the outcome was assessed at a mean of 3.75 years (3-year follow-up visit) after the onset of JIA.

- 408 of 506 (81%) patients with data to assess remission status did *not achieve remission off medication* at the 3-year follow-up in the ReACCh-Out cohort.

- 53 of 354 (15%) were identified to have a *severe disease course* at the 3-year follow-up in the ReACCh-Out cohort.

- 137 of 361 (38%) reported functional disability with a CHAQ >0 at the 3-year follow-up in the ReACCh-Out cohort.

- The patients who did not achieve *remission off medication* had similar characteristics in the Nordic development cohort and the ReACCh-Out validation cohort. The following characteristics were similar: Younger age at disease onset, both had the highest percentage from the RF-polyarthritis category, the active joint count was higher, ankle and finger joints frequently affected, the scores in PROMs and physician GA were higher, and also the use of synthetic DMARDs at baseline was higher in the non-remission groups.

Prediction model validation

- External validation of the Nordic model (without fine-tuning) for prediction of *non-achievement of remission off medication* (the Nordic outcome, in the ReACCh-Out cohort) resulted in a lower C-index than in internal validation in the Nordic development cohort. In the external validation we found the C-index to be 0.68 (95% CI 0.62-0.74). Excluding patients with systemic JIA, as done in the Nordic development cohort, improved the predictive performance to a C-index of 0.73 (0.66-0.80) i.e., an acceptable predictive ability.

- When the Nordic model was fine-tuned to the Canadian patients, with re-estimation of coefficients, the predictive performance for *non-achievement of remission off medication* improved to a C-index of 0.74 (0.67-0.80), and 0.76 (0.69-0.83) if systemic JIA patients were excluded. The fine-tuned version with no laboratory parameters had a C-index of 0.74 (CI 0.67–0.81), which is the same predictive performance as with the laboratory parameters. This model has the advantage of being simpler.

- The Nordic model applied to predict *severe disease course* (the Canadian outcome) yielded a C-index of 0.69 (CI 0.61-0.78) when applied directly, a C-index of 0.79 (0.68-0.91) after fine-tuning, and a C-index of 0.79 (CI 0.69-0.89) without laboratory parameters. The fine-tuned Nordic model predicted well *severe disease course*, an outcome it originally was not developed to predict.

- The Nordic prediction model for functional disability (CHAQ >0) did not achieve a C-index >0.7 when tested in the ReACCh-Out cohort.

6.4 Paper IV

Uveitis in Juvenile Idiopathic Arthritis – 18-Year Outcome in the Population-based Nordic Cohort Study

Study cohort, disease activity and treatment

- In the Nordic JIA cohort, 434 patients with JIA were followed for 18 years. Of these, 96 patients developed JIA-U.

- We found the cumulative incidence of uveitis to be 22.1%, and 2.8% developed uveitis late (between the 8-year and the 18-year follow-up).

- The majority of patients with JIA-U had bilateral and anterior uveitis. Patients with JIA-U were significantly younger at JIA onset than the patients without uveitis. The median time from onset of JIA to the uveitis diagnosis was 1.6 years (IQR 0.4-5.0 years).

- At the 18-year follow-up visit, active uveitis was found in 24.4%. Active JIA disease was significantly higher among patients with JIA-U than those without uveitis. The percentage of patients in medication-free remission was lower among those with JIA-U.

- There was a significantly higher use of synthetic and biologic DMARDs among the patients with JIA-U over the 18-years period compared to the patients without uveitis. This difference was also present at the 18-year follow-up visit. At the visit, a significantly higher percentage of patients with JIA-U used synthetic and biologic DMARDs compared to the patients without uveitis.

Ocular complications

- One or more ocular complications was found in 31 of 80 (38.8%) examined patients with uveitis at the 18-year follow-up visit. The most frequent ocular complications were cataract and glaucoma. Among the 31 patients who developed complications, the majority did so during the first 8-years after uveitis onset.

- Although the rate of ocular complications was relatively high, the visual acuity was good with binocular best-corrected visual acuity (BCVA) <6/12 in only 5.0% of the patients with JIA-U.

Predictor variables associated with ocular complications

- Onset of uveitis before JIA, a short interval between the onset of JIA and the diagnosis of uveitis, and the presence of ANA positivity are significant predictors associated with the development of ocular complications. The eight children diagnosed with

uveitis before JIA developed cataract, and seven also glaucoma. These results emphasize the need for tight screening of uveitis and stepping up treatment early until inactive uveitis is achieved.

7 Discussion

The studies presented in this thesis provide new insight into the prediction of disease outcome in JIA, the challenges regarding disease outcome measures, and summarizes the long-term outcome in JIA-associated uveitis.

Our Nordic prediction model uses easily available clinical variables and performed well in predicting *non-achievement of remission off medication* in both internal and external validation. We discovered that the model performed equally well without laboratory variables. This makes it possible to simplify the model even more, enabling it for clinical use. We externally validated the Canadian prediction model, yielding an excellent performance for predicting *severe disease course* outcome in the Nordic JIA cohort. We learned that the choice of outcome strongly influences the predictive ability of a model. Our simplified Nordic prediction model had an excellent predictive performance for the Canadian *severe disease course* outcome. In contrast, the Canadian model did not achieve acceptable predictive performance for *non-achievement of remission*. Hence, it is essential to define optimal, clinically relevant prediction outcomes, validated across different JIA cohorts, before individualized prediction can be generally recommended.

Our uveitis study is, to our knowledge, the only population-based study following JIA-U patients prospectively for almost two decades. We found a high cumulative incidence of uveitis and ocular complications almost two decades after JIA onset. Our findings support most previous conclusions, especially that children who develop uveitis before JIA or near after, are at high risk of ocular complications. We also found that uveitis may develop several years after JIA onset. This finding raises important questions about how many years after disease onset regular eye screening is beneficial. The predictors associated with ocular complications in uveitis may serve as key variables in further efforts to develop prediction models for unfavorable outcome in JIA-associated uveitis.

7.1 General strengths and limitations

The Nordic JIA cohort study is unique in JIA research because of the multicenter longitudinal, prospective population-based study design. The long follow-up time makes it suitable for assessment of long-term outcomes. The study has collected a broad range of demographic, clinical and patient-reported information throughout the study period. Validated outcome measures are used, and despite the long-follow up time, we had a low rate (15%) of patients lost to follow-up.[51, 52, 60, 62, 69]

In addition to the study design and conductance, the model development study's main strengths in the Nordic cohort (*paper I*) are the use of validated outcome measures, the simplicity of the models, and the strict internal cross-validations. A strength of the two validation papers *(paper II and III*) is the use of the strict TRIPOD[100] guidelines for performing external validations and critical evaluations of the models before recommendation. These studies are the first external validations published on prediction models in JIA. The uveitis paper (*paper IV*) is the only long-term prospective population-based study on JIA-U, as far as we are aware of. However, differences in health care systems, socioeconomic conditions, and differences in the JIA cohorts, genetics, and ethnicity need to be kept in mind when generalizing the results. We have reliable ophthalmologic data for 83% of the patients with uveitis after almost two decades, and this represents a major strength of our study. The study was conducted using established criteria for the classification of JIA[1], validated outcome measures and classification of uveitis according to the SUN criteria. This makes it possible to compare results with other cohorts.[57]

One of several study limitations is that the baseline study visit took place six months after disease onset and was not necessarily the first clinical visit. Most likely many children with high disease activity had therefore already started treatment. When predictor variables were assessed at the study visit at approximately six months, the disease activity was most likely milder than at the first clinical visit. Also, the treatment at baseline and during the disease course may have altered the disease outcome. Treatment strategies have evolved rapidly. There is now earlier and more aggressive treatment strategies than in the beginning of the Nordic JIA study. Hence, it is not straightforward to make assumptions about the effects of treatment.[4, 40, 43, 53]

For the uveitis paper (*paper IV)*, a limitation is that we do not have information on the precise timepoints when patients started topical corticosteroids. We could therefore not assess the association between the use of topical steroids and uveitis-related complications. The exact time point for start of systemic treatment and whether this was treatment primary for uveitis or arthritis is also unknown. The study started at the beginning of the biologic era when early aggressive treatment strategies were not established. Compared to other studies, this may have caused a higher incidence of uveitis and accompanying complications.[139, 146] Emerging research shows a significant reduction in uveitis occurrence coinciding with the increased use of synthetic and biologic DMARDs.[146, 152] During the 18-year follow-up in our cohort, we saw a significant increase in the use of these drugs. At approximately 12 months after onset of JIA, 36.7% of the cohort used synthetic DMARDs, while only 1.8% used biologic DMARDs. During the total period of 18 years, 60% had used synthetic DMARDs, and 30% had used biologics at some point.[61]

The primary outcome in *paper I*, *non-achievement of remission off medication*, is defined as inactive disease for more than 12 months and does not necessarily reflect the disease course during the whole study period. Between the eight and the 18-year follow-up we have ten years without study data. For instance, the exact time points for development of uveitis-associated complications and alterations in treatment are not reported. Another issue is the chosen cut-off thresholds used for the secondary outcomes in *paper I* (CHAQ >0, PhS <40 and JADI-E >0). Results may have been different if we used a higher cut-off for significant functional disability and joint damage. It is also possible that this would have given better predictive abilities. Missing information was another limitation of the secondary outcomes, with possible implications for predictive performance.

There were few patients with systemic JIA, RF-positive polyarthritis and psoriatic arthritis. This was one of the reasons why we excluded the systemic JIA patients from the model development study (*paper I*). Another reason is the very different clinical features of this category. By removing the systemic JIA, we were trying to make the cohort more homogenous. There is still considerable diversity among the other categories, and perhaps different models are needed for different categories. Such a study will be difficult to perform because of the need for a very large cohort. Otherwise, the sample size when assessing subgroups of JIA will be too small. We have also previously shown in the Nordic JIA cohort that categories may change during disease course for individual patients.[148] The small number

of patients with RF positive polyarthritis may have caused this category not to enter the model as a predictor variable through the model-building procedure. On the other hand, with increased sample size, the category would most likely correlate strongly with the cumulative active joint count and would have been removed regardless. In the validation studies (*paper II and III*), the distribution of categories within the *severe disease course* cluster differed somewhat between the Canadian and Nordic constructions. Compared to the Canadian cohort, the Nordic cohort had fewer with RF-positive polyarthritis and systemic JIA.

7.2 Methodological considerations

7.2.1 Study design and the population-based approach

The NoSPeR researchers decided to conduct a population-based, prospective longitudinal JIA cohort study. This design was chosen with the purpose of collecting the whole range of disease severity and explore the characteristics of the disease course. The Nordic JIA cohort provides a unique possibility to identify associations between baseline predictors and outcomes in JIA, and assess the long term-outcomes from child to adulthood.

Population-based studies capture the full disease spectrum, from mild oligoarthritis cases to severe polyarticular or systemic JIA. The feasibility of conducting a population-based study is rare in most parts of the world. In the Nordic countries, all health care systems for children are free of charge, and a broad range of measures was taken to strive for a population-based study. During the inclusion period, letters were repeatedly sent to primary healthcare providers, child health centers, orthopedic, pediatric, and rheumatology specialists in the catchment areas to ensure all eligible patients' referral.[148] Nevertheless, there is a risk of missing children with JIA due to undiagnosed or misdiagnosed patients, not referring eligible patients, referral to other than the participating centers' and children/parent's own decision not to participate. In the way the Nordic health care system is organized, most children with a longstanding arthritis will be referred from the primary health care to the pediatric rheumatologist. The study centers also had the primary responsibility for diagnosing and treating all children with suspected rheumatic diseases in their catchment area. Only three individuals declined to participate in the study, and only 12 did not want to participate further at some point in the follow-up study.

The advantage of a population-based study is the possibility of generalization of results. The estimated incidences and prevalence of the disease are thought to be representative for the region. When the study population is followed longitudinally, it is suitable for assessment of the relationship between exposure or predictors and the postulated outcome.[153, 154]

Several studies on JIA are registry-based or tertiary center studies. Most prospective studies in JIA have few years of follow-up time. Tertiary-center-based studies and cross-sectional assessments may underreport the milder forms of JIA, while the more severely affected patients may be overrepresented. This may not give a realistic picture of the distribution of JIA categories and disease course in the population.

Different study designs and follow-up times may make the comparison of results across different studies challenging, or even wrong. The use of different outcomes can also affect the possibility of comparison. Direct comparison across studies is hampered when validated outcome measures are not used.

7.2.2 Lost to follow-up and follow-up by telephone interview

During the observation period of 18 years, 15% of the participants were lost to follow-up. The loss to follow-up in our long-term study is low compared to others.[60, 155] After such a long follow-up time, those who did not attend the visit may be the ones that have been in remission for a long time. We found no significant differences in age at onset, gender, JIA category, and number of active joints among the patients lost to follow-up and the patients still included. Five patients with uveitis were lost to follow-up between the 8-year and the 18-year visit.

Some of the patients included in the study participated only through a telephone interview. This rate was 14.5% at the 8-year follow-up and 24.2% at the 18-year follow-up. Among the patients who participated through a telephone interview at the 18-year follow-up we had access to medical records for 91%. The medical records were used to check unclear issues or missing responses. At the 18-year follow-up, 10 of 96 patients with JIA-U participated through the telephone interview. Data collected per telephone are not as robust as the data collected at clinical visits. For the results on JIA and uveitis disease activity, only patients attending a visit at the pediatric rheumatologist and ophthalmologist were included.

7.2.3 Data quality and handling

In the Nordic JIA cohort, the collected data were plotted into the data bases 4th dimension up to the 8-year visit, and SurveyXact for the 18-year visit. In case of missing data or any inconsistencies, we cross-checked by asking the physician that examined the patients. We also had the possibility of cross-checking the medical records in the vast majority of cases. Data were then exported via Excel to the researchers' preferred statistical package.

7.2.4 Considerations concerning prediction model development

Due to past evidence of poor quality of reporting in prediction model studies in medicine, the TRIPOD initiative developed a recommendations for studies developing, validating, and updating prediction models.[100] We have followed these recommendations.

In the model-building part there is a sequence of choices to be made. In *paper I* we decided to include five predefined key variables (the cumulative active joint count, ESR, CRP, physician's GA, and morning stiffness) before entering additional predictor variables. This choice was based on clinical judgment and criteria for defining inactive disease and clinical remission.[51, 52] Studies have shown that the same child can be classified as either having active disease or inactive disease depending on which set of criteria is used.[58] At the moment there are no recommendations for optimal treat-to-target strategies, and therefore no established outcome for assessing this strategy. [52, 58, 66, 156] Besides the *a priori* variables mentioned above, additional variables were included by the model-building procedure. For the main outcome, *non-achievement of remission*, the additional predictor variables were ankle joint arthritis, HLA B27, and ANA.

In the process of building a logistic regression model, several clinical variables are usually screened as potential predictor variables. In this process, there is a risk of selecting uninformative predictors and overfitting the model. One measure to avoid overfitting a model is performing internal cross-validation by randomly splitting the cohort into a development cohort and a validation cohort. This was done for both the Nordic and the Canadian models in their respective development cohorts. Both models performed well in internal cross-validations. This approach may be problematic if there is a small sample size or limited data, in which case one risks a lack of power in each set.[157-159] An alternative method is to split the

data into time-periods so that development and testing of the model can be done for different time points. This strategy could be a more robust way of evaluating model performance when sample sizes are limited and the same cohort is used.[160, 161]

It is not easy to compare our modelling results in JIA with other studies because there are sparse reports on this topic in JIA research. Most of the prediction-modeling studies in JIA have focused on response/non-response to methotrexate treatment.[80, 86, 90] The most relevant comparison is with the model of Guzman et al. which performed excellently for *severe disease course* in internal and external validation.[77] The Canadian prediction model contains 16 predictor variables. The combination of a specific data-driven constructed outcome together with many predictor variables may have caused overestimation of the predictive ability in internal validation.[77, 79, 86] The performance was lower for the other unfavorable outcomes; *non-achievement of remission off medication*, CHAQ >0, PhS <40, and JADI-A >0 (*paper I and paper II*). In contrast, the Nordic model performed well when applied to the Canadian outcome *severe disease course (paper II and III)* but had a lower predictive ability for *non-achievement of remission* in external validation. This lower predictive ability may be due to the distribution of this outcome, which is almost half and half (favorable versus unfavorable outcome). The proportion of Nordic children that did not obtain remission off medication was 59.5% at the 8-year follow-up visit. *Non-remission* is more difficult to predict compared to the outcome *severe disease course* which identifies a more distinct group, namely the 20% of patients with the most severe illness.

7.2.5 Construction of the severe disease course outcome

One of the methodological challenges in *paper II* was to define an outcome in the Nordic cohort that corresponded to what Guzman et al. had termed *severe disease course*. This outcome is not based on distinct predefined criteria, and it was not obvious how to decide which children in the Nordic cohort should be included in this group. One approach could have been to specify a set of objective criteria to apply in the Nordic cohort. These criteria would have had to be tuned so that the clinical characteristics were consistent with the Canadian cohort's *severe disease course* group. We used the alternative approach of a data-driven construction similar to Guzman et al.

In the Canadian cohort, Guzman et al. formed four different disease courses using a clustering algorithm based on the following variables: participant-defined quality of life and pain reports (both assessed on a 10-cm VAS), active joint count, medication requirements, and medication side effects. The *severe disease course* was the union of the two worst groups, severe controlled course and severe persistent course.[77] We decided to construct clusters of patients based on four variables collected at the 8-year follow-up in the Nordic cohort. The four variables used were the cumulative active joint count, remission status, CHAQ, and the PhS derived from the CHQ- PF50. The reason for choosing different variables for cluster analysis was that we did not have Nordic data on the same variables used in the Canadian cohort. Different clinical characteristics may, however, identify the same group of patients, those with the highest disease burden. In the Nordic cohort, 22% were identified as having a *severe disease course*. This percentage was 21% in the Canadian cohort. We analyzed 440 patients, and after imputation, we had 1760 data points. The Canadian study used five variables with values from at least 6 of 8 visits for 609 patients, which gave 24 360 data points. The main difference in the construction was that Guzman et al. used data collected from at least six visits and we used only the 8-year visit. The Canadian construction may better identify temporal structure in the disease trajectories, but this has not been seen in the results. Missing data were imputed for the outcome variables. The results were the same with and without imputation suggesting that imputation was not a source of bias.

Guzman et al. compared several different clustering algorithms (K-Means, K-Medoids, Agglomerative Clustering, and Divisive clustering) to consider the different choices for the number of clusters to construct. The constructions were compared with silhouette values and R^2. They also carried out a stability analysis for their clusters. In the Nordic cohort, this analysis was not relevant since our aim was not to demonstrate the existence of clusters but rather to replicate the *severe disease course* group found in the Canadian cohort in order to test prediction models for this outcome. We deliberately made a series of choices to achieve outcome results that were similar to the *severe disease course* group of Guzman et al.[77]

7.3 Clinical implications of the results

7.3.1 Prediction of unfavorable disease outcome in JIA

Previous assumptions that JIA is a disease that the child would outgrow are not accurate. The course of JIA is often chronic with fluctuating disease activity.[76, 162, 163] In the Nordic cohort at the 8-year follow-up 40.5% were in remission without the use of medication, and at the 18-year follow-up remission off medication was seen in 32.8% of the patients.[61, 148] Since the clinical heterogeneity is considerable, predicting disease course and outcome is challenging.[78]

In recent years, the implementation of prediction models in medicine has been of great interest with the goals of cost-effective treatment strategies, informed decision-making, and improved patient outcomes.[164, 165] Currently, there are no clinical established used statistical prediction models in JIA. As a result of the treat-to-target treatment strategy and the concept of "window of opportunity" there is an increased interest in prediction models to identify children with a high probability of an unfavorable outcome.[3, 5, 36-39] Prediction of the long-term outcome based on early clinical characteristics and robust disease activity measures would be especially beneficial in JIA. By feeding models with early clinical characteristics, physicians may receive objective probability-based assessments to aid treatment decisions. The aim was therefore to develop rules to predict long-term unfavorable outcomes to guide early treatment decisions in children with JIA onset. In the Nordic cohort we developed four prediction models (*paper I*). The four models all achieved AUCs >0.7, which is considered helpful in prediction.[104]

To generalize the use of prediction models, we need to validate the model in an independent cohort and report details on the development and validation so that other research groups can replicate and verify the results.[157] External validation of the Canadian model applied precisely as published in the Nordic cohort (*paper II*), yielded a C-index of 0.85 (IQR 0.83–0.87) for prediction of *severe disease course* and a C-index of 0.66 (0.63–0.68) for prediction of *non-achievement of remission*. The performance was slightly better for prediction of *non-achievement of remission* after fine-tuning, with a median C-index of 0.69 (0.65–0.73. The Nordic model performed excellently with a median C-index of 0.90 (0.86–0.92) for *severe disease course* in internal valdiation.[149]

The purpose of *paper III* was to externally validate the Nordic prediction models in Canadian patients with JIA to predict the main outcome *non-achievement of remission*, *severe disease course*, and CHAQ >0. The Nordic models were evaluated as published and after fine-tuning of coefficients. The fine-tuned Nordic model without the blood tests (active joint count, physician global assessment of disease activity, morning stiffness, and ankle involvement) predicted well *non-achievement of remission* and *severe disease course* in Canadian patients with C-indices of 0.74 (0.67–0.80) and 0.79 (0.68–0.91), respectively. A possible reason for this effect was the shorter follow-up time in the Canadian cohort. The last study visit was approximately three years after inclusion in order to have sufficient outcome data, which is significantly earlier than the eight years follow-up in the Nordic cohort. Fewer patients have probably *achieved remission off medication* at three years than at eight years after onset. In time, the percentage of patients achieving remission off medication tend to increase, compared to early in the disease course where fluctuating disease activity is more common.[61, 163] [60, 166] This may have contributed to the Nordic prediction model's reduced predictive performance for *non-remission off medication* in Canadian patients.

Surprisingly, the Nordic model performed better in predicting the Canadian outcome *severe disease course*. This result is consistent with our findings in *paper II* and further highlights the importance of the outcome in prediction studies. Which outcome one aims to predict will likely influence the overall accuracy and the predictive performance.[149, 150] It is possible to construct a data-driven outcome for which we can obtain excellent prediction performance. Still, if this outcome is difficult to replicate in other JIA populations, the purpose of the model vanishes, and the research becomes technical and non-applicable in clinical practice. Hence, the outcome needs to be standardized and easy to replicate across studies and populations.

In assessing disease activity and remission status, it may be better to predict an overall course of JIA, at least for an estimated period, rather than the outcome at a single point in time. We should be cautious in screening too many predictor variables, and we should carefully assess the dependency among them. For instance, the dependence among clinical characteristics of disease activity, such as the number of active joints, the physician's GA, the parent/patient GA, CHAQ score, and joint involvement patterns may lead to confounding bias. Involvement of specific joints may also have a relationship with the outcome, e.g., finger joints are more frequently affected in the polyarticular categories, which is known to be associated with a more severe disease course.[2, 73]

A good prediction model should be simple and have sufficient predictive accuracy for clinical purposes.[100] The exclusion of ESR, CRP, ANA, and HLA B27 had a negligible impact on the Nordic model accuracy both in internal validation (*paper II*) and external validation (*paper III)*. This result is very interesting and comparable to results on clinical JADAS, where removing acute phase reactants in JADAS (clinical JADAS) did not reduce the accuracy in identifying patients with similar disease activity.[167, 168]

Our findings indicate that the Nordic prediction model without blood tests and the data-driven outcome *severe disease course* outcome could be an optimal combination obtaining an excellent predictive performance while keeping the model simple to use. The challenge remains to identify a proxy for *severe disease course* based on already established validated outcome measures in JIA to facilitate comparison and validation across different cohorts.

7.3.2 Long-term outcome in uveitis - what have we learned?

The current prevalence of uveitis, ocular complications and visual impairment seems to have decreased compared to earlier reports.[111, 139, 146, 152] This may be due to a combination of tight screening programs, and more aggressive early treat-to-target strategies in JIA. Early stepping up treatment to synthetic and biologic DMARDs seems to prevent development of uveitis and complications.[145-147, 169]

In *paper IV* we found a high cumulative incidence of uveitis and uveitis-related complications 18-years after onset of JIA.[115] One possible reason for this finding is the study design, with prospective long-term follow-up capturing more uveitis cases and development of ocular complications. Another reason for the higher prevalence of uveitis in the Nordic countries may be the genetic background. Through the years, studies in the Nordic countries have reported a higher incidence of uveitis compared to other populations. Inherent genetic risk for developing uveitis may contribute to the higher incidences in these countries.[11, 105, 106, 108, 112, 113, 132] Another factor is the that the study began very early in the biologic era. In our study, 26% of the children with uveitis were treated with synthetic DMARDs approximately six months after onset of JIA. This rate increased to 53% up to the 1-year visit, and 75% up to the 8-year visit. None of the patients with JIA-U used biologic DMARDs at the six months visit. Eight were treated with biologic DMARDs at the 1-year visit, of whom three were diagnosed

with uveitis before JIA.[41] Timely start of systemic treatment may reduce the risk of complications. In a recent German study with two years follow-up, they found a significant reduced risk of developing uveitis in 1 year among children with JIA that were treated with methotrexate, or TNF inhibitors, or a combination of both.[152] Tappeiner et al. also showed in another large German study a reduction in uveitis point prevalence between 2002 and 2013. The majority of children develop their uveitis within the first 4 years after onset of JIA.[107] In our study we found that children developing uveitis before or near after the onset of JIA had increased risk of ocular complications.[115, 135, 137] These results emphasize the need for early treatment strategies.

After the year 2000 the reported proportion of uveitis related complications have been in the range 25-50%.[133, 145, 170] In our study, we found that 38.8% of the patients had ocular complications 18 years after the onset of JIA. This is in the higher end of the range of what has been previously reported. The findings may have severe implications for the young adults in our study (median age at visit of 22 years). Since JIA-U is mostly asymptomatic and the start of early treatment may prevent complications, early and frequent ophthalmologic screening is important. Several screening guidelines have been published and modified throughout the years.[114, 116, 123, 171] In 2019, The ACR foundation published recommendations for screening of children with JIA and management and treatment of established uveitis in JIA.[41] Both the uveitis inflammation and corticosteroid treatment can lead to ocular complications, and the consequence may be visual impairment. The rate of visual impairment in JIA-U varies but is often reported between 10-20%.[133, 170] In our cohort, 5% had BCVA <6/12, which is comparable to the study by Carvounis et al.[111] who found a bilateral VA <20/40 in 9% of the patients with JIA-U. Skarin et al. performed a retrospective 24-year study in the pre-biologic era. In their JIA cohort, 16% developed uveitis. Among the JIA-U patients, 51% had cataract, and 22% glaucoma after 24 years.[135] In our prospective study, 31% developed cataract and 28% glaucoma after 18 years of follow-up. Cataract, glaucoma, and synechiae were the most common ocular complications. This result is in line with other studies.[135]

How do we know which children are at high risk of uveitis, and when should these children start synthetic DMARDs? We have previously published a study on predictors for the development of uveitis,[112] and in line with several other studies, we found that young age at JIA onset, and the presence of Hep2-ANA were predictors of chronic uveitis.[107, 114] In the

current study we analyzed predictors for developing ocular complications in children with uveitis. We found that short duration between the onset of JIA and the diagnosis of uveitis was a predictor for developing ocular complications, together with a diagnosis of uveitis before the onset of JIA. Presence of Hep2-ANA was also associated with developing one or more complications. In 2019, Heiligenhaus et al. found that older age at JIA onset, short interval between JIA and the onset of uveitis, higher anterior chamber cell grades, poor visual acuity, and the use of topical corticosteroid at first documentation of uveitis were associated with uveitis-related complications. In contrast, JIA onset after the age of five years, no use of topical corticosteroids, and adalimumab treatment were associated with inactive uveitis for at least 6 months.[138] A recent study presenting a multivariable prediction model for estimating the probability of developing uveitis in children with JIA. The model achieved a median AUC of 0.75 after internal validation. The prediction model used the following predictor variables: age at JIA onset, JIA category and ANA positivity.[172] Haasnoot et al published in 2019 a review regarding biomarkers measured at JIA-onset. The purpose was to identify biomarkers with potential for prediction of uveitis in order to develop clinical prediction tools for improving early diagnosis of uveitis and aid treatment decisions. Among the possible biomarkers were: ESR, S100A12 protein, HLA-DRB1-YST-motif, and ANA. The predictive ability to identify children with high risk of uveitis should be tested with both internal and external validation.[92] This may be done in long-term prospective studies. We are not aware of studies reporting on prediction models for uveitis-related ocular complications.

8 Concluding remarks

This thesis provides new knowledge on prediction modeling in JIA, and new insight into the long-term consequences of uveitis in JIA.

- We have demonstrated that it is possible to develop models for prediction of long-term unfavorable outcome in JIA based on early clinical predictors. The prediction models have acceptable performance and require only easily available baseline variables. The models are easy to use as online calculators or a mobile device (iOS), and may be valuable tools to aid early treatment decisions after validation in other JIA cohorts.

- Based on clinical characteristics from the baseline visit, approximately six months after JIA onset we can calculate a probability of *not achieving remission off*

medication eight years ahead in time. This probability score can support decisions of when to start or step-up treatment.

- Outcomes and predictors need to be carefully assessed in model construction. The work presented in this thesis suggests that we should aim for simple models and validated outcomes.

- We found an excellent predictive performance of the Canadian model (median C-index of 0.85) for *severe disease course* when externally validated in the Nordic JIA cohort. The Nordic model also achieved an excellent performance in predicting *severe disease course,* with a C-index of 0.90 in internal validation.

- The Nordic model performed well in predicting *non-achievement of remission off medication* (median C-index of 0.73) when externally validated in the Canadian cohort (excluding systemic JIA).

- The fine-tuned Nordic model predicted well *non-achievement of remission off medication* (median C-index 0.76) and *severe disease course* (median C-index 0.79) when externally validated in Canadian patients with JIA (excluding systemic JIA). The simple model, without laboratory parameters, combining active joint count, physician´s GA, morning stiffness and ankle involvement, preformed just as well as the model with laboratory parameters.

- In all tests the C-indices for prediction of *severe disease course* were higher than for *non-achievement of remission off medication*. This shows that prediction of long-term remission is more challenging than prediction of severe disease course.

- We identified some key points after performing the validation studies:

    1. The choice of outcome to be predicted is essential for predictive performance, and perhaps more important than model design. It is easier to predict a severe outcome than, e.g., achievement of remission.

2. Data-driven outcomes may be highly valuable. However, remission according to the 2004 Wallace criteria, and the revised 2011 ACR criteria, for inactive disease are validated outcome measures, and hence more accessible for use and evaluation in other cohorts.

3. In prediction studies the outcome needs to be practical for clinical use. Therefore, identifying a clinical useful validated prediction outcome is an important future task.

4. Prediction models based on a few key variables may have similar predictive ability as more complex models. Carefully evaluating the predictors is necessary for satisfactory model development.

- We found a high cumulative incidence of uveitis in the Nordic JIA cohort. A considerable proportion of patients with JIA-U that develop sight-threatening complications in young adulthood. Close interdisciplinary collaborations between pediatric rheumatologists and ophthalmologist are necessary in order to start early synthetic and or biologic DMARDs in patients with high risk of complications.

- Predictors associated with the development of uveitis-related ocular complications are: onset of uveitis before JIA or closely after the onset of JIA, and ANA positivity.

- Our study underlines the importance of immediate and frequent screening by an ophthalmologist if JIA is suspected or confirmed. In addition, we recommend increased awareness in young adults with JIA based on our finding of asymptomatic late-onset uveitis.

9 Futures perspectives

- Future studies should focus on determining improved clinical disease-outcome definitions in JIA to facilitate more accurate validation across cohorts. A treat-to-target strategy requires validated outcome measures. These outcomes should preferably not be data-driven, but if data-driven outcomes are necessary, they must be simple and easy to reproduce.

- Future work will aim to further simplify prediction models making them easier to use in clinical practice.

- We need to identify an objective clinical definition of a severe disease course. In that context, explore whether JADAS scores early in the disease are a robust measure to identify patients with a high probability of severe disease course.

- Once improved outcomes and models are in place, we can test models in a third and independent cohort. The ultimate step in assessing of whether prediction models improve outcome in JIA or not is a randomized controlled trial.

- Our future work will also aim to develop prediction models for severe uveitis. This will enable targeted screening and treatment strategies adapted to high-risk subgroups.

- We also plan to describe predictors associated with active uveitis and early development of ocular complications in a recent Norwegian 2-year prospective follow-up cohort. We will compare incidence of uveitis in this cohort with our long-term cohort to assess the impact of synthetic and biologic DMARD use.

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PAPER I

Predicting unfavorable long-term outcome in juvenile idiopathic arthritis: results from the Nordic cohort study

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Predicting unfavorable long-term outcome in juvenile idiopathic arthritis: results from the Nordic cohort study

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Abstract

Background: The aim was to develop prediction rules that may guide early treatment decisions based on baseline clinical predictors of long-term unfavorable outcome in juvenile idiopathic arthritis (JIA).

Methods: In the Nordic JIA cohort, we assessed baseline disease characteristics as predictors of the following outcomes 8 years after disease onset. Non-achievement of remission off medication according to the preliminary Wallace criteria, functional disability assessed by Childhood Health Assessment Questionnaire (CHAQ) and Physical Summary Score (PhS) of the Child Health Questionnaire, and articular damage assessed by the Juvenile Arthritis Damage Index-Articular (JADI-A). Multivariable models were constructed, and cross-validations were performed by repeated partitioning of the cohort into training sets for developing prediction models and validation sets to test predictive ability.

Results: The total cohort constituted 423 children. Remission status was available in 410 children: 244 (59.5%) of these did not achieve remission off medication at the final study visit. Functional disability was present in 111/340 (32.7%) children assessed by CHAQ and 40/199 (20.1%) by PhS, and joint damage was found in 29/216 (13.4%). Model performance was acceptable for making predictions of long-term outcome. In validation sets, the area under the curves (AUCs) in the receiver operating characteristic (ROC) curves were 0.78 (IQR 0.72–0.82) for non-achievement of remission off medication, 0.73 (IQR 0.67–0.76) for functional disability assessed by CHAQ, 0.74 (IQR 0.65–0.80) for functional disability assessed by PhS, and 0.73 (IQR 0.63–0.76) for joint damage using JADI-A.

Conclusion: The feasibility of making long-term predictions of JIA outcome based on early clinical assessment is demonstrated. The prediction models have acceptable precision and require only readily available baseline variables. Further testing in other cohorts is warranted.

Keywords: Juvenile idiopathic arthritis, Disease activity, Prediction, Outcome research

Background

Juvenile idiopathic arthritis (JIA) is a heterogeneous childhood disease, with chronic joint inflammation as the common feature. The JIA categories differ by the number of joints affected, and the presence of extra-articular involvement [1]. Disease course and prognosis differ between JIA categories, but there is also large variability within each category [2, 3]. Therefore, efforts have been made to discern baseline clinical prognostic factors that can predict the severity, course, and long-term outcome of the disease [4, 5].

The primary goal of JIA treatment is to achieve remission [6]. Early prediction of the disease course for the individual child can facilitate tailored treatment. There is increasing evidence for the concept of "the window of therapeutic opportunity" in JIA, where early aggressive treatment with biologic agents and/or other disease-modifying anti-rheumatic drugs (DMARDs) may modify the disease course and improve long-term prognosis [7–9]. On the other hand, it is

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also essential to avoid unnecessary, costly, and potentially toxic treatment in children with a favorable prognosis.

Guzman et al. have recently presented a model for prediction of severe disease course, with outcomes developed specifically for their study [10]. In a systematic literature review, Dijkhuizen and Wulffraat state the need for prospective longitudinal studies of baseline clinical predictors using standardized validated outcome measures [4]. In the Nordic JIA cohort, we studied prediction of four established and validated outcomes, and aimed to construct prediction models that may aid decision on early aggressive treatment.

Methods

Study population

The initial prospective longitudinal multicenter Nordic JIA cohort consisted of consecutive children with incident JIA from 12 participating centers in defined geographical areas of Denmark, Finland, Norway and Sweden. All children in these areas with newly diagnosed JIA and disease onset in the study periods between 1 January 1997 and 30 June 2000 were included. The study was designed to be as close to population-based as possible, as previously reported [11].

In the current study, 440 children met the criteria of having a baseline study visit and a final study visit 8 years after disease onset. Out of these, 17 patients with systemic JIA were excluded, because systemic JIA is considered to have autoinflammatory rather than autoimmune disease mechanisms, and the clinical characteristics of predominantly fever, rash and serositis differs from other JIA-categories [12].

The baseline study visit was planned 6 months after disease onset. At this visit, disease activity variables, complete joint count, physician's global assessment of disease activity (physician's GA) on a 10-cm visual analogue scale (VAS), patient's/parent's global assessment (GA), medication and blood tests were registered [13]. Disease onset was defined as the time of presentation of symptoms of active arthritis, and the JIA categories were determined according to the International League of Associations for Rheumatology (ILAR) criteria [14].

Outcomes

At follow up, we evaluated 4 outcomes: (1) the main outcome was non-achievement of remission off medication, chosen as the best available validated measure of an adverse disease state over time. This included active disease, inactive disease of less than 12 months of duration, and clinical remission on medication (according to the preliminary Wallace criteria) [15, 16]. For the remainder of the paper, not in remission or non-achievement of remission refers to non-achievement of remission off medication unless otherwise specified; (2) and (3) functional disability was evaluated using the Childhood Health Assessment Questionnaire (CHAQ), and the Child Health Questionnaire Parent form (CHQ-PF50), aiming to achieve a broad evaluation of functional disability using both the JIA-specific CHAQ and the generic CHQ-PF50 instruments. CHAQ addresses functional ability in different activities of everyday life [17]. The CHAQ was completed by children of age >9 years, and otherwise by their parents, and the corresponding Health Assessment Questionnaire (HAQ) by participants > 18 years of age. From this point on in the text, CHAQ will refer to both the CHAQ and HAQ scores. The CHQ-PF50 consists of 50 items and 12 domains assessing health-related quality of life, yielding a physical summary score (PhS) and a psychological summary score (PsS) [17]. PhS ranges from 0 to 100, with a higher score indicating better functional ability; and (4) joint damage was assessed using the Juvenile Arthritis Damage Index of articular damage (JADI-A) ranging from 0 to a maximum of 72, where 36 joints, or joint groups, are scored 0 for no damage, 1 for partial damage, or 2 for severe damage [18]. All 4 outcomes were dichotomized; remission was dichotomized into clinical remission (those achieving remission without medication), and non-achievement of remission off medication (those not achieving remission or achieving remission on medication), CHAQ and JADI-A into score = 0, indicating no functional disability or no joint damage, and positive score >0, PhS into good functional ability, defined as score ≥40, and functional disability <40. This latter cutoff level is based on a reference score of 40 being one standard deviation below the mean score of healthy children in the USA [19].

Laboratory tests

Antinuclear antibodies (ANA) and rheumatoid factor (RF) were tested at least twice with a minimum of 3 months apart. ANA was analyzed by immunofluorescence on Hep-2 cells. Tests were interpreted according to cutoff values of the local immunological laboratories. HLA-B27 was analyzed using standardized methods [20]. C-reactive protein (CRP) was measured with immunoassays, with values <10 mg/L considered normal.

Statistics

Conventional descriptive statistics (absolute numbers, median, 1st and 3rd quartile, and percentage) were used to describe demographics and clinical characteristics. Univariate logistic regression was performed to assess baseline variables as predictors for each outcome. Variables that were significant at $p < 0.05$ in the univariate analysis were considered as candidates in a prediction model.

For each outcome, multivariable logistic regression models were constructed using a combination of predefined core variables, and additional variables selected using a forward stepwise selection method. Since the predictive ability of the models is assessed using cross-validation, the conventional limitations related to the screening of a large number of covariates in multivariable models are evaded [21]. Cross-validation controlled for overfitting of the data (internal validation), and the degree of overfitting is reflected in the performance in validation sets.

Clinical characteristics included in the Wallace provisional criteria for remission were a priori included in the prediction models; the cumulative active joint count, erythrocyte sedimentation rate (ESR), CRP, physician's GA, and morning stiffness [22]. Uveitis activity applies only to a minority of the cohort and was therefore not included. The additional baseline variables were included in a stepwise fashion if they contributed to the multivariable model with $p < 0.05$ when included. Symmetric joint involvement was not considered a candidate predictor as it correlates strongly with the specific joint involvement (Fig. 1). To ensure model simplicity the total number of variables was not allowed to exceed 10. Once the set of variables were selected, the model coefficients β_i for each predictor variable x_i were estimated using multivariable logistic regression, and the probability of unfavorable outcome was given as:

$$P = 1/\left(1 + e^{-A}\right), \text{where } A = \beta_0 + \beta_1 x_1 + \ldots + \beta_n x_n.$$

For each of the four outcomes, cross-validation of the method was performed by partitioning the cohort randomly in training sets consisting of three quarters of the patients ($N = 317$) and validation sets consisting of one quarter of the patients ($N = 106$). In each realization of the random partitioning we constructed prediction models using the algorithm described above, using *only* the training set to select variables and estimate coefficients. For each of the patients in the corresponding validation set the multivariable logistic model provides a probability of the unfavorable outcome. By comparing the predicted probability of unfavorable outcome with the actual outcome at the final study visit, the receiver operating characteristic (ROC) curve was computed, and the area under the curve (AUC) was estimated. The median AUC with interquartile range (IQR) was estimated from 100 realizations of the random partitioning of the cohort. For each step in the cross-validation we omitted any patients where the outcome or the required predictor variables were not available.

Finally, in our cohort we tested the prediction model for severe disease course developed by Guzman et al. [10]. We tested Guzman's model using the 4 outcome measures described above, i.e. not the outcomes for which their model was constructed. The analysis was performed using the software packages STATA version 14, and Wolfram Mathematica version 11.1.1.0.

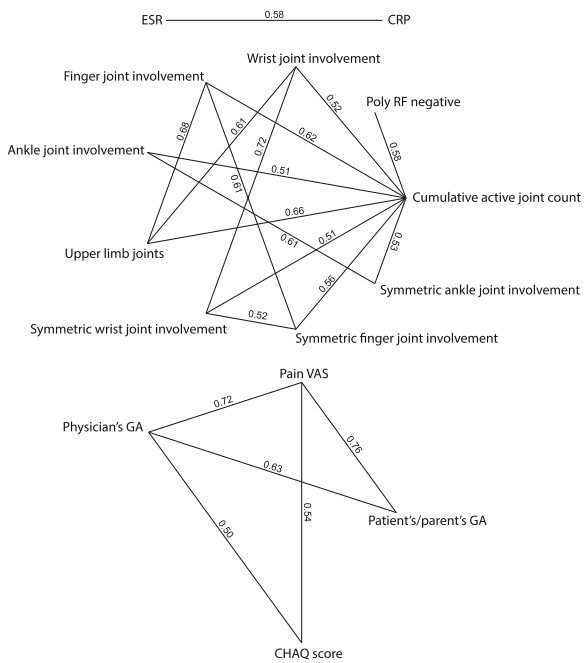

Fig. 1 Correlations between baseline variables. Lines are drawn only between pairs of baseline variables for which the sample Spearman correlation coefficient is ≥ 0.50. Baseline variables without correlation ≥0.50 are not included in the figure. RF, rheumatoid factor; VAS, visual analogue scale; GA, global assessment; CHAQ, Childhood Health Assessment Questionnaire

Ethical considerations

Approvals from medical research ethical committees and data protection authorities were granted according to the regulations of each participating country. Written informed consent was obtained from parents of children aged < 16 years, and from the children themselves if aged ≥ 16 years of age.

Results

The main finding is that in the Nordic cohort, long-term outcome in JIA can be predicted, with acceptable sensitivity and specificity, using only a handful of readily available clinical variables.

Study cohort

Characteristics of the 440 patients in the cohort have previously been published [11]. The study cohort constituted 423 children, after 17 patients with systemic JIA were excluded. The median time between disease onset and the baseline study visit was 7 (IQR 6–8) months,

Table 1 Baseline clinical characteristics as predictors of non-achievement of remission off medication in univariate logistic regression

Baseline characteristics	Total *N*	Remission off medication[a]	Not in remission[b]	OR (95% CI)	*p*
Gender female, *n* (%)	410	106 (38.8)	167 (61.2)	0.8 (0.5–1.2)	0.334
Age at disease onset, years	410	6.3 (2.5–10.0)	5.2 (2.5–9.6)	0.9 (0.9–1.0)	0.401
Time from onset to diagnosis, months	388	1.5 (0.5–2.9)	1.7 (0.5–3.6)	1.0 (1.0–1.1)	0.152
Cumulative active joint count	410	2 (1–4)	4 (2–7)	1.1 (1.1–1.2)	< 0.001
Physician's global assessment VAS	227	0.8 (0.0–1.3)	2.0 (1.0–3.8)	3.5 (1.9–6.2)	< 0.001
Polyarticular RF-positive, *n* (%)	410	1 (25.0)	3 (75.0)	2.1 (0.2–20.0)	0.535
Polyarticular RF-negative, *n* (%)	410	25 (26.9)	68 (73.1)	2.2 (1.3–3.6)	0.003
Oligoarticular, *n* (%)	410	107 (49.1)	111 (50.9)	0.5 (0.3–0.7)	< 0.001
Psoriatic arthritis, n (%)	410	3 (50.0)	3 (50.0)	0.7 (0.1–3.4)	0.635
Enthesitis-related arthritis (ERA), *n* (%)	410	11 (32.4)	23 (67.6)	1.5 (0.7–3.1)	0.315
Undifferentiated arthritis, *n* (%)	410	19 (34.5)	36 (65.5)	1.3 (0.7–2.4)	0.336
ANA-positive, ≤ 6 years, *n* (%)[c]	397	22 (31.4)	48 (68.6)	1.6 (0.9–2.7)	0.107
Specific joint involvement, *n* (%)					
Hip joint	409	18 (32.1)	38 (67.9)	1.5 (0.8–2.8)	0.168
Ankle joint	409	57 (31.0)	127 (69.0)	2.1 (1.4–3.1)	< 0.001
Tarsal joint	409	6 (16.7)	30 (83.3)	3.8 (1.5–9.2)	0.004
Subtalar joint	409	14 (26.9)	38 (73.1)	2.0 (1.1–3.8)	0.034
Wrist joint	409	33 (30.6)	75 (69.4)	1.8 (1.1–2.9)	0.014
Finger joint	409	36 (27.7)	94 (72.3)	2.3 (1.5–3.6)	< 0.001
Neck	409	9 (26.5)	25 (73.5)	2.0 (0.9–4.4)	0.085
Upper limb joints	410	67 (32.7)	138 (67.3)	1.9 (1.3–2.9)	0.001
Lower limb joints	410	144 (39.0)	225 (61.0)	1.8 (0.9–3.5)	0.073
Symmetric involvement, *n* (%)					
Hip joints	409	5 (21.7)	18 (78.3)	2.6 (0.9–7.1)	0.067
Ankle joints	409	27 (28.4)	68 (71.6)	2.0 (1.2–3.3)	0.006
Wrist joints	409	22 (34.4)	42 (65.6)	1.4 (0.8–2.4)	0.272
Finger joints	409	13 (22.0)	46 (78.0)	2.7 (1.4–5.3)	0.002
Patient-reported outcomes					
Patient's/parent's global assessment VAS	250	0.5 (0.0–2.2)	1.7 (0.5–3.5)	2.2 (1.4–3.4)	0.001
CHAQ score	257	0.1 (0.0–0.6)	0.5 (0.0–1.1)	2.0 (1.3–3.0)	0.002
Pain VAS	246	0.4 (0.0–3.0)	2.3 (0.5–4.2)	1.9 (1.3–2.8)	0.002
Morning stiffness for > 15 min, *n* (%)	314	25 (22.1)	88 (77.9)	3.6 (2.1–6.0)	< 0.001
Laboratory tests					
ESR mm/h	332	11.0 (6.0–18.0)	17.0 (9.5–34.0)	1.4 (1.2–1.7)	< 0.001
CRP >10 mg/L, *n* (%)	329	12 (16.7)	60 (83.3)	3.9 (2.0–7.5)	< 0.001
ANA-positive, *n* (%)	397	37 (33.0)	75 (67.0)	1.5 (1.0–2.4)	0.075
RF-positive, *n* (%)	221	5 (50.0)	5 (50.0)	0.6 (0.2–2.0)	0.376
HLA-B27 positive, *n* (%)	382	21 (25.9)	60 (74.1)	2.1 (1.2–3.6)	0.010

Values are the median (interquartile range, IQR), or number (percentage)

OR odds ratio, *CI* confidence interval, *VAS* visual analogue scale, *CHAQ* Childhood Health Assessment Questionnaire, *ESR* erythrocyte sedimentation rate for an increase in 10 mm/h, *CRP* C-reactive protein, *ANA* antinuclear antibody, *RF* rheumatoid factor, *HLA-B27* human leucocyte antigen

[a]Inactive disease off medication for 12 months according to the preliminary Wallace criteria

[b]Not in remission equals non-achievement of remission off medication

[c]ANA-positive patients ≤6 years at disease onset, with oligoarticular, polyarticular RF negative, psoriatic or undifferentiated arthritis

and between disease onset and the final study visit it was 98 (IQR 95–102) months. The median time from disease onset to diagnosis was 1.6 (IQR 0.5–3.3) months. A total of 280 patients (66.2%) were female, and the median age of disease onset in the cohort was 5.5 (IQR 2.5–9.7) years (Additional file 1: Table S1).

At the baseline study visit, 227/423 patients (53.7%) had oligoarthritis, 94/423 (22.2%) had rheumatoid factor (RF)-negative polyarthritis, and 4/423 (1.0%) had RF-positive polyarthritis (Additional file 1: Table S1). The median cumulative number of active joints within the first visit was 3 (IQR 1–6), and 381/423 patients (90.1%) had one or more affected lower limb joints at the baseline visit. Antinuclear antibodies (ANA) were present in 115/410 patients (28.1%), and HLA-B27 in 85/393 patients (21.6%) [23], presented in Additional file 1: Table S1. None of the children had started biologic agents before the baseline study visit, and early medications are shown in Additional file 2: Table S2. A total of 410/423 (96.9% of the total cohort) had baseline assessments and data on remission 8 years after disease onset. The corresponding numbers were 340/423 (80.4%) for CHAQ, 199/423 (47.0%) for PhS and 216/423 (51.1%) for JADI-A.

Correlation between baseline variables

The clinical predictor variables were analyzed with respect to correlation. There was significantly positive, moderate to strong correlation between several variables, especially between cumulative number of active joints, the joint-specific variables, and the polyarthritis RF-negative category. Physician's GA and the patient-reported outcomes also correlated positively with each other. The correlation structure between the predictor variables is illustrated in Fig. 1.

Prediction of non-achievement of remission off medication

Remission status at the final study visit was available for 410 patients. There were 166 (40.5%) children in remission without medication, while 38 (9.3%) were in remission on medication, and 206 (50.2%) were not in remission: 244/410 children (59.5%) did not achieve remission off medication. The baseline predictors of not achieving remission off medication were analyzed by univariate logistic regression and are presented in Table 1.

The following predictor variables were included in the multivariable prediction model for non-achievement of remission: Cumulative active joint count, ESR, CRP, morning stiffness, physician's GA, ANA, HLA-B27, and ankle joint arthritis. The first five variables were chosen a priori, and ANA, HLA-B27, and ankle joint arthritis were the variables included through the stepwise selection method (Table 2). The model has an AUC of 0.84 in the total cohort. Cross-validation yielded a median AUC = 0.78 (IQR 0.72–0.82) in the validation sets (Table 3). The corresponding ROC curves are shown in Figs. 2 and 3.

Table 2 Prediction of unfavorable outcome by multivariable modeling of baseline clinical characteristics

	Coef.	Std.Err
Not in remission[a] *N* = 156		
	β_0=-1.58	0.44
Cumulative active joint count	β_1=0.04	0.05
ESR mm/h	β_2=0.03	0.02
CRP >10 mg/L	β_3=-0.07	0.69
Morning stiffness > 15 min	β_4=1.16	0.45
Physician's global assessment VAS	β_5=0.16	0.46
ANA-positive	β_6=1.25	0.50
HLA-B27-positive	β_7=1.37	0.54
Ankle joint arthritis	β_8=1.10	0.49
Functional disability (CHAQ), *N* = 141		
	β_0=-1.68	0.35
Cumulative active joint count	β_1=-0.02	0.03
ESR mm/h	β_2=0.01	0.01
CRP > 10 mg/L	β_3=-0.20	0.63
Morning stiffness > 15 min	β_4=1.03	0.42
Physician's global assessment VAS	β_5=-0.40	0.56
Finger joint arthritis	β_6=1.21	0.54
Pain VAS	β_7 = 0.77	0.40
Functional disability (PhS), *N* = 92		
	β_0=-3.40	0.75
Cumulative active joint count	β_1=0.10	0.05
ESR mm/h	β_2=0.01	0.02
CRP > 10 mg/L	β_3=-2.06	1.28
Morning stiffness > 15 min	β_4=1.68	0.80
Physician's global assessment VAS	β_5=-0.71	0.88
Pain VAS	β_6=1.30	0.64
Joint damage (JADI-A), *N* = 141		
	β_0=-3.84	0.76
Cumulative active joint count	β_1=0.02	0.04
ESR mm/h	β_2=0.01	0.02
CRP > 10 mg/l	β_3= -0.11	0.83
Morning stiffness > 15 min	β_4=-0.59	0.61
Physician's global assessment VAS	β_5=0.28	0.52
Finger joint arthritis	β_6=1.84	0.68
Older age at disease onset (years)	β_7= 0.16	0.07

Coef. coefficients in the logistic regression, *Std.Err.* standard error in the coefficients, *VAS* visual analogue scale, *ESR* erythrocyte sedimentation rate for an increase in 10 mm/h, *CRP* C-reactive protein, *ANA* antinuclear antibody, *HLA-B27* human leucocyte antigen

[a]Not in remission equals non-achievement of remission off medication

We also developed a prediction model without the blood samples (ESR, CRP, ANA, and HLA-B27). This model yielded an AUC = 0.76 (IQR 0.72–0.80) for non-achievement of remission in the validation sets (Additional file 3: Figure S1).

Prediction of functional disability and joint damage

The CHAQ score at the final study visit was available in 340 children, and 111 (32.7%) had a CHAQ score >0. Three of the four patients with RF-positive polyarthritis reported functional disability. For univariate logistic regression results see Additional file 4: Table S3.

The prediction model for CHAQ score >0 uses cumulative active joint count, ESR, CRP, morning stiffness, physician's GA, finger joint arthritis, and pain VAS as variables (Table 2). The AUC of this model was 0.79 in the total cohort, and cross validation gave a median AUC of 0.73 (IQR 0.67–0.76) in the validation sets (Table 3). The ROC curve for the total cohort, and validation sets are shown in Figs. 2 and 3, respectively. The AUC for the model without blood samples was 0.72 (IQR 0.67–0.76) in the validation sets (Additional file 3: Figure S1).

Of the 199 patients with a physical summary score, 40 (20.1%) had a score <40. Results of the univariate analysis with PhS <40 as the outcome variable are shown in Additional file 5: Table S4. Variables included in the prediction model for PhS were cumulative active joint count, ESR, CRP, morning stiffness, Physician's GA, and pain VAS (Table 2). The AUC was 0.90 in the total cohort, and cross-validation gave a median AUC = 0.74 (IQR 0.65–0.80) in the validation sets (Table 3, Figs. 2 and 3). The AUC for the model without blood samples was 0.73 (0.66–0.79) in the validation sets (Additional file 3: Figure S1).

The JADI-A was collected for 216 patients at the final study visit, and 29 patients (13.4%) had joint damage registered 8 years after disease onset. The baseline predictors of joint damage are presented in Additional file 6: Table S5. In the prediction model, older age at disease onset and finger joint arthritis were included in addition to the five previously included variables (Table 2). The AUC was 0.84 in the cohort, and the median AUC was 0.73 (IQR 0.63–0.76) in the validation sets. The results are summarized in Table 3 and Figs. 2 and 3. Without blood tests the median AUC in the validation sets was 0.73 (IQR 0.63–0.80) (Additional file 3: Figure S1).

Other prediction models

The prediction model developed by Guzman et al. [10] was tested in our cohort by testing the ability of their model to predict the four outcomes described above. The model yielded an AUC = 0.69 for prediction of not achieving remission. For CHAQ >0, PhS <40, and JADI-A >0 the AUCs were 0.68, 0.69, and 0.71, respectively (Additional file 7: Figure S2).

Discussion

In the Nordic JIA cohort, we have developed and evaluated prediction models for long-term unfavorable outcome with acceptable sensitivity and specificity based on variables easily available at baseline, which may guide individually tailored treatment. Prediction of long-term unfavorable outcome early in the disease course may be useful in deciding when to start aggressive treatment in JIA.

To our knowledge, this is the first study on long-term prediction of well-established disease outcomes in a prospective population-based JIA cohort. Cross-validation analysis of model performance yielded AUCs of 0.78, 0.73, 0.74, and 0.73, for non-achievement of remission, CHAQ >0, PhS <40, and JADI-A >0, respectively.

An important step in developing applicable prediction models for JIA was carried out by Guzman et al. in a Canadian JIA cohort [10]. The authors recommended that their results should be tested in other JIA cohorts. We were not able to reproduce the predictive ability of their model in the Nordic JIA cohort (Additional file 7: Figure S2). One obvious reason for the discrepancy could be that Guzman's model is constructed to predict severe disease course, and not per se, any of the four pre-established, validated adverse outcomes that we assessed. Other reasons may be differences in the population-based approach, cohort composition, or ethnicity, or overfitting of models to the cohort.

The primary goal in the treatment of children with JIA is to achieve remission off medication, and the main implication of the current study is that prediction models may be useful in guiding decisions about treatment. Previous studies have indicated that the disease course may be modified by starting appropriate treatment early

Table 3 Cross-validation of the four prediction models of unfavorable long-term outcome in the Nordic JIA cohort

	Not in remission[a]	Functional disability (CHAQ)	Functional disability (PhS)	Joint damage (JADI-A)
AUC total cohort	0.84	0.79	0.90	0.84
AUC validation sets[b]	0.78 (0.72–0.82)	0.73 (0.67–0.76)	0.74 (0.65–0.80)	0.73 (0.63–0.76)

AUC area under the receiver operating characteristic curve, *CHAQ* Childhood Health Assessment Questionnaire, *PhS* Physical Summary Score, *JADI-A* Juvenile Arthritis Damage Index-Articular

[a]Not in remission equals non-achievement of remission off medication

[b]The AUCs in the validation sets are the median AUCs with the interquartile range of the 100 constructed models

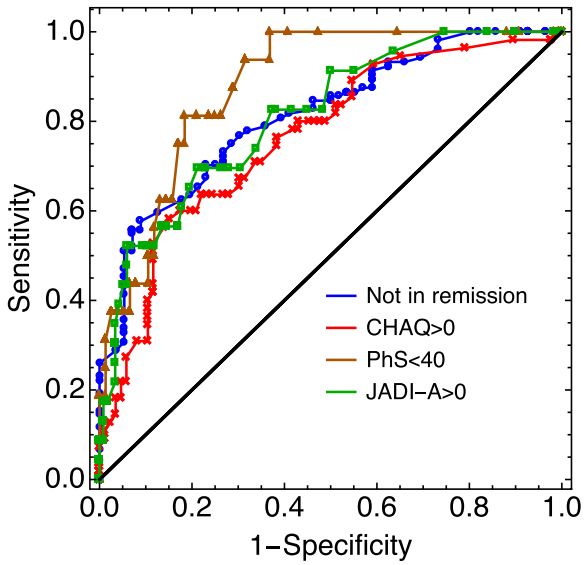

Fig. 2 Receiver operating characteristic (ROC) curves for the four unfavorable clinical outcomes in the total cohort. Non-achievement of remission off medication; CHAQ, Childhood Health Assessment Questionnaire; PhS, Physical Summary Score; JADI-A, Juvenile Arthritis Damage Index-Articular

[9, 24, 25]. To reach the goal of early inactive disease, a treat-to-target strategy including shared decision-making with well-informed children and parents is currently recommended [6, 9]. Even with promising advances in using gene expression profiles and biomarkers as predictors of treatment response and flare risk [26–29], the practical value of prediction based on a handful of readily available clinical variables cannot be understated.

The main strengths of our study are the use of validated outcome measures, the simplicity of the models, and the strict cross-validations. The use of validated outcomes is called for in reports on prognosis in JIA [3, 30, 31]. Model simplicity is ensured through the model construction method, where the main variables in the preliminary Wallace criteria of remission are included in the models a priori [15, 22]. The additional variables that were included in our models have independently been associated with adverse outcomes in previous studies [4, 23, 32–36].

The model performance was assessed using cross-validations, where predictions were performed on validation sets that were completely separate from the data used to construct the models. The 100 repeated model constructions and evaluations prevent overfitting the data. Despite

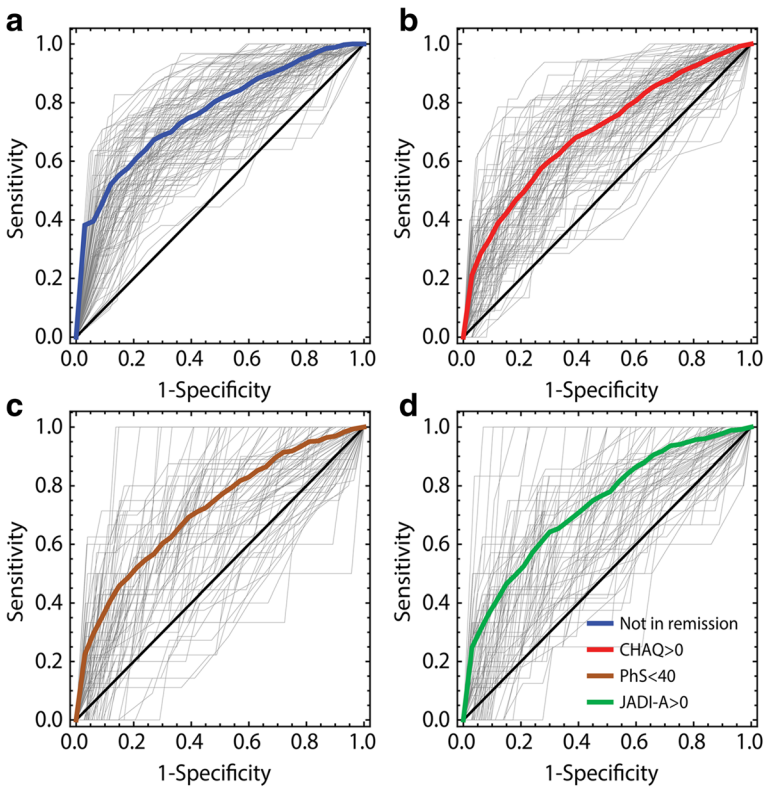

Fig. 3 Receiver operating characteristic (ROC) curves for the four unfavorable clinical outcomes in the validation sets. The colored lines are the mean ROC curves for the 100 different realizations of the partitioning of the cohort into training sets and validation sets (thin gray curves). **a** Not in remission. **b** Childhood Health Assessment Questionnaire (CHAQ) >0. **c** Physical Summary Score (PhS) <40. **d** Juvenile Arthritis Damage Index-Articular (JADI-A) >0

the strictness of the model-developing procedure, we still obtained acceptable predictive ability. The robustness and applicability of the prediction rules are emphasized by the fact that when the analyses were repeated without any blood tests, the performance was similar. An online calculator based on our models is available at the web-page http://predictions.no. An iOS app is also designed, and the test versions are available on request.

One of the limitations of our study is that for some of the patients, the baseline study visit scheduled 6 months after disease onset was not the first clinical visit. Some children had therefore already started treatment, mostly with nonsteroidal anti-inflammatory drugs (NSAIDs) or intraarticular corticosteroids, and were not treatment naïve when the predictor variables were assessed. This baseline time point, however, allowed use of the cumulative active joint count during the first 6 months of the disease, which is an important measure of early disease severity in line with the International League of Associations for Rheumatology (ILAR) criteria. A limitation is also that the primary outcome, non-achievement of remission off medication, is defined as inactive disease for more than 1 year, and this outcome does not necessarily reflect the disease course during the whole 8-year period. In addition, JADI-A is a rather crude measure of joint damage, and future predictive studies should therefore include imaging in joint damage assessment. Finally, the treatment given during the disease course may have altered the disease outcome, even though biologic medications were not generally available in the beginning of the study period in 1997. The natural history of JIA disease course without treatment is clearly impossible and unethical to study.

Conclusion

We have developed statistical models for predicting non-achievement of remission off medication, functional disability, and joint damage in children with JIA. The models are easy to use, and may provide a valuable tool to aid early treatment decisions on the need for DMARDs including biologic agents if validation in other JIA cohorts and across ethnicities can confirm our results [37]. We encourage further testing of our models before the applicability can be generalized and recommended.

Additional files

Additional file 1: Table S1. Characteristics of the 423 children in the Nordic juvenile idiopathic arthritis cohort at baseline. (PDF 134 kb)

Additional file 2: Table S2. Medications given before the baseline study visit. (PDF 108 kb)

Additional file 3: Figure S1. Receiver operating characteristic (ROC) curves for the four unfavorable clinical outcomes in the validation sets, but for models constructed without using blood samples as predictors. The colored lines are the mean ROC curves for the 100 different realizations of the partitioning of the cohort into training sets and validation sets (thin gray curves). (**a**) Not in remission. (**b**) Childhood Health Assessment Questionnaire (CHAQ) >0. (**c**) Physical Summary Score (PhS) <40. (**d**) Juvenile Arthritis Damage Index-Articular (JADI-A) >0. (PDF 435 kb)

Additional file 4: Table S3. Baseline clinical characteristics as predictors of functional disability (CHAQ) in univariate logistic regression. (PDF 125 kb)

Additional file 5: Table S4. Baseline clinical characteristics as predictors of functional disability (PhS) in univariate logistic regression. (PDF 163 kb)

Additional file 6: Table S5. Baseline clinical characteristics as predictors of joint damage (JADI-A) in univariate logistic regression. (PDF 161 kb)

Additional file 7: Figure S2. Receiver operating characteristic (ROC) curves for a test in the Nordic JIA cohort of the prediction model for severe disease course by Guzman et al. The area under the curve (AUC) values were 0.69 for non-achievement of remission off medication, 0.68 for Childhood Health Assessment Questionnaire (CHAQ) >0, 0.69 for Physical Summary Score (PhS) <40, and 0.71 for joint damage (JADI-A) >0. (PDF 287 kb)

Abbreviations

ANA: Antinuclear antibodies; AUC: Area under the receiver operating characteristic curve; CHAQ: Childhood Health Assessment Questionnaire; CRP: C-reactive protein; DMARD: Disease-modifying anti-rheumatic drug; ESR: Erythrocyte sedimentation rate; GA: Global assessment; ILAR: International League of Associations for Rheumatology; IQR: Interquartile range; JADI-A: Juvenile Arthritis Damage Index-Articular; JIA: Juvenile idiopathic arthritis; NSAIDs: Nonsteroidal anti-inflammatory drugs; PhS: Physical Summary Score; RF: Rheumatoid factor; ROC: Receiver operating characteristics; VAS: Visual analogue scale

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available for ethical and privacy reasons, but are available from the Nordic Study group of Pediatric Rheumatology (NoSPeR) on reasonable request.

Authors' contributions

VR, EN, AF, TH, LB, SN, and MR were involved in the conception and design of the study, and/or basic analysis and interpretation of data, drafting of the manuscript, and revising it critically for important intellectual content. VR and MR performed the statistical analysis. VR, KA, MZ, EA, MG, SP, and ME were involved in the acquisition of data, and/or drafting of the manuscript and revising it critically for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Approval from medical research ethical committees and data protection authorities was granted according to the regulations of each participating country; in Norway this was from the Regional Committee for Medical and Health Research Ethics NORD, number 53/96. Oral informed assent was obtained from all children. Written informed consent was obtained from parents of children aged < 16 years and from the children if aged ≥ 16 years of age.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Publisher's Note

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PAPER II

Validation of prediction models of severe disease course and non-achievement of remission in juvenile idiopathic arthritis: part 1 – results of the Canadian model in the Nordic cohort

Rypdal V, Guzman J, Henrey A, Loughin T, Glerup M, Arnstad E. D, Aalto K, Rygg M, Nielsen S, Herlin T, Fasth A, Berntson L, Rypdal M, Nordal E and for the ReACCh-Out and NoSPeR Investigators

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Validation of prediction models of severe disease course and non-achievement of remission in juvenile idiopathic arthritis: part 1—results of the Canadian model in the Nordic cohort

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Abstract

Background: Models to predict disease course and long-term outcome based on clinical characteristics at disease onset may guide early treatment strategies in juvenile idiopathic arthritis (JIA). Before a prediction model can be recommended for use in clinical practice, it needs to be validated in a different cohort than the one used for building the model. The aim of the current study was to validate the predictive performance of the Canadian prediction model developed by Guzman et al. and the Nordic model derived from Rypdal et al. to predict severe disease course and non-achievement of remission in Nordic patients with JIA.

Methods: The Canadian and Nordic multivariable logistic regression models were evaluated in the Nordic JIA cohort for prediction of non-achievement of remission, and the data-driven outcome denoted severe disease course. A total of 440 patients in the Nordic cohort with a baseline visit and an 8-year visit were included. The Canadian prediction model was first externally validated exactly as published. Both the Nordic and Canadian models were subsequently evaluated with repeated fine-tuning of model coefficients in training sets and testing in disjoint validation sets. The predictive performances of the models were assessed with receiver operating characteristic curves and C-indices. A model with a C-index above 0.7 was considered useful for clinical prediction.

Results: The Canadian prediction model had excellent predictive ability and was comparable in performance to the Nordic model in predicting severe disease course in the Nordic JIA cohort. The Canadian model yielded a C-index of 0.85 (IQR 0.83–0.87) for prediction of severe disease course and a C-index of 0.66 (0.63–0.68) for prediction of non-achievement of remission when applied directly. The median C-indices after fine-tuning were 0.85 (0.80–0.89) and 0.69 (0.65–0.73), respectively. Internal validation of the Nordic model for prediction of severe disease course resulted in a median C-index of 0.90 (0.86–0.92).

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Conclusions: External validation of the Canadian model and internal validation of the Nordic model with severe disease course as outcome confirm their predictive abilities. Our findings suggest that predicting long-term remission is more challenging than predicting severe disease course.

Keywords: Juvenile idiopathic arthritis, Prediction, Validation, Outcome research, Remission

Background

Population-based studies show that juvenile idiopathic arthritis (JIA) is a chronic childhood rheumatic disease with diverse disease manifestations, courses, and prognoses [1–4]. Prognostic prediction models are increasingly important tools for informed decision-making in medicine [5, 6]. In a newly diagnosed patient with JIA, it can be challenging to decide if a potent treatment with possible serious side effects should be started early in the disease course. A well-performing prediction model can help assess the risk of severe disease and hence guide decisions on starting or stepping up disease-modifying antirheumatic drugs, including biologic treatments. This may facilitate individually tailored treatment strategies within the so-called window of opportunity [7–10]. Before such prediction models can be recommended for general use in clinical practice, we need to ensure they have good predictive performance across different JIA populations. Unfortunately, studies on development of prediction models in pediatrics [11] and in JIA are scarce [12–18]. As far as we know, no study has previously reported a quantitative external validation of prediction models in JIA in a different population.

To address this knowledge gap, a collaboration has been initiated between two prospective and well-defined longitudinal cohort studies: the Research in Arthritis in Canadian Children Emphasizing Outcomes (ReACCh-Out) Cohort and the Nordic JIA cohort. The first results of the collaboration are presented here and in the twin study by Henrey et al. (part 2). These studies analyze prediction models recently proposed by Guzman et al. [17] and Rypdal et al. [19]. Guzman et al. constructed a model for predicting *severe disease course* derived from the ReACCh-Out study (the Canadian model). The model had a C-index of 0.85 in internal validation in the Canadian cohort. Rypdal et al. constructed a model for prediction of *non-achievement of remission* (the Nordic model), and this model had a C-index of 0.78 in internal validation in the Nordic cohort.

In the present study, our aims were to validate the predictive ability of the Canadian model in the Nordic JIA cohort and to internally validate the performance of the Nordic model to predict *severe disease course*, an outcome originally constructed from data in the Canadian cohort [17, 20]. Conversely, the Nordic prediction model was tested for these outcomes in the Canadian cohort, with results presented in the twin paper by Henrey et al. (part 2). The validated prediction models may in the future be updated, harmonized, and eventually used as clinical tools in decision-making regarding early individualized treatment in JIA.

Patients and methods

The Nordic JIA study is a prospective, longitudinal, multicenter cohort [2, 21]. Measures were taken to ensure a population-based approach; all consecutive newly diagnosed JIA patients from 12 pediatric rheumatology centers in defined geographical areas of Denmark, Finland, Norway, and Sweden were included if disease onset was between January 1, 1997, and June 30, 2000, and the International League of Associations for Rheumatology criteria for JIA [2] were fulfilled. The aim was to have a baseline visit 6 months after disease onset, and the patients were followed at regular visits with 1-to-3-year intervals up to 8-years after disease onset.

The ReACCh-Out study is also a multicenter prospective study. A total of 16 pediatric rheumatology centers across Canada participated, and consecutive patients with newly diagnosed JIA were recruited between January 2005 and December 2010. The first visit occurred as soon as possible after diagnosis, but the time from diagnosis to the first visit could be up to 1 year. The inclusion criterion in the Canadian prediction study was attendance in at least 6 of 8 study visits, which were scheduled every 6 months for 2 years, and then yearly up to 5 years. It was also required that information was available at least at one visit, for each of the 5 clinical variables used to construct the *severe disease course* outcome [17].

Both studies collected extensive clinical and laboratory data at the study visits as previously reported [17, 19]. Characteristics of the two study populations are presented in Table 1.

The current study is reported according to the TRIPOD guideline (Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) [4, 22].

Patients

The present study includes all patients from the Nordic cohort with data available from at least a baseline and an 8-year visit. This includes 440 (88%) of the 500 patients originally included at baseline. In contrast to the previous work on prediction models in the Nordic cohort

Table 1 JIA-study population in the Canadian ReACCh-Out and the Nordic JIA cohort

Characteristics	Canadian development cohort	Nordic validation cohort
Study design	Prospective multicenter	Prospective multicenter
Patient recruitment period[a]	January 2005–December 2010	January 1997–June 2000
Total participants, *n*	1497	500
Time from onset to baseline study visit, months[b]	5.8 (3.0–11.0)	7.0 (6.0–8.0)
Time from onset to outcome assessment, months[b]	49 (38–59)[c]	98 (95–102)
Participants in the current study, *n*	609	440
Inclusion criteria	6 of 8 study visits[d]	Baseline and 8-year study visit
Main outcome	Severe disease course	Non-achievement of remission

[a]Newly diagnosed JIA patients
[b]Median interquartile range (IQR)
[c]Severe disease course outcome was assessed over time, not at a single point
[d]Additionally, at least one value available for each of the five patient-relevant variables

[19], patients with systemic JIA are included in the current study.

Outcomes

The main outcome predicted in the previous Nordic study was *non-achievement of remission* at the 8-year visit, which included patients with active disease, inactive disease on medications, or inactive disease off medications for less than 12 months. Inactive disease was defined by the Wallace 2004 criteria, the current criteria at the time the 8-year study was conducted [23, 24].

The main outcome in the Canadian study was *severe disease course*. The method used to develop and define this outcome was previously reported [17]. In summary, the clinical JIA course was described according to five variables: participant-defined quality of life and pain reports, both assessed on 10-cm visual analogue scales (VAS); active joint count; medication requirements; and medication side effects. Based on this information, four different clinical courses were identified by a clustering algorithm. The main outcome, *severe disease course*, was the union of the two worst groups, severe controlled course and severe persistent course, as defined by Guzman et al. [17].

In the present study, a version of the Canadian outcome was constructed in the Nordic cohort using information on four variables collected at the 8-year study visit. This outcome is also denoted *severe disease course*, but the construct variables in the Nordic cohort were the cumulative active joint count, the remission status, the Childhood Health Assessment Questionnaire disability index (CHAQ), and the Physical Summary Score (PhS) derived from the Child Health Questionnaire Parent form (CHQ-PF50) [25]. The aim was to construct a *severe disease course* group corresponding as closely as possible to the outcome used in the ReACCh-Out prediction study. Accordingly, we used these four variables and a clustering algorithm to divide the Nordic cohort in four disease course groups. The two most severe courses were defined to have a *severe disease course*. Characteristics of the four disease course clusters in the Nordic JIA cohort are presented in Additional file 1: Table S1.

We also constructed an alternative definition of the outcome using five variables, the four described above in addition to the pain-VAS report at the 8-year follow-up. Both constructions corresponded reasonably well with the construction in the ReACCh-Out study, and the results of the external validation of the Canadian model were similar in the two cases. In both cases, we made a series of choices and essentially tuned the construction to obtain clusters that corresponded in relative size to those found in the Canadian study. We used linear dimensionality reduction and then the *K*-means or the *K*-medoids clustering algorithm [26] to construct clusters.

Predictors in the Nordic and the Canadian model

The baseline predictors that we considered as candidates for the Nordic multivariable logistic regression model are previously published [19]. The following eight predictors constituted the final multivariable model: cumulative active joint count; erythrocyte sedimentation rate (ESR) mm/hour, measured as a continuous variable; C-reactive protein (CRP) mg/l, with values < 10 mg/l considered to be normal; morning stiffness > 15 min; physician's global assessment of disease activity on a 10-cm VAS; presence of antinuclear antibodies (ANA) analyzed by immunofluorescence on Hep-2cells and tested at least twice with a minimum of 3 months apart; presence of human leucocyte antigen (HLA)-B27; and ankle joint arthritis. The first five variables were included a priori based on a clinical judgment and justified on the basis that these variables are central in the American College of Rheumatology (ACR) for clinical active disease [27].

The Canadian multivariable logistic regression model used 16 variables: active joint count, psoriatic arthritis, oligoarthritis, RF-negative polyarthritis, upper limb joint involvement, symmetric joint involvement, RF positivity,

subtalar joint involvement, finger joint involvement, cervical spine involvement, ankle joint involvement, presence of morning stiffness, hip joint involvement, temporomandibular joint involvement, mid-foot involvement, and the presence of enthesitis. Details regarding measurement and assessment of these variables were previously reported [17].

Model validation

This study presents external validation of the Canadian model and internal validation of the Nordic model. The Canadian model was tested for its ability to predict *severe disease course* and *non-achievement of remission* in a separate cohort from the one used to build the model. The Canadian model was first tested exactly as published by Guzman et al., and also after fine-tuning, i.e., with re-estimated coefficients. The Nordic model was tested for its ability to predict *severe disease course* by internal validation, involving repeated partitioning of the cohort in multiple training sets for model building and validation sets for model testing.

Statistical analyses

Rypdal et al. constructed multivariable logistic regression models using a set of 5 pre-defined variables and a stepwise forward selection method to obtain additional variables from a set of 29 candidate variables. Variables with a P value > 0.05 were removed. Selections of variables were performed in training sets, and no more than 10 predictor variables were allowed in each of the models. The final model included 8 predictors, as previously described [19].

Guzman et al. constructed their model through a version of backwards elimination starting with a full model of 52 predictors and retaining 16 predictor variables in their multivariable logistic regression model. Both the Nordic and the Canadian models underwent internal validation with the repeated random split-sample technique and cross-validation in their respective cohorts.

External validation of the Canadian model

The model [17] is tested by computing the probability of *severe disease course* and *non-achievement of remission* according to the formula:

$$p = \frac{1}{1 + e^{-A}}$$

where $A = \beta_0 + \beta_1 x_1 + \ldots + \beta_{16} x_{16}$ is a linear combination of predictors. Apart from the active joint count, all variables are dichotomous. In external validation, we used the coefficients β_i from the ReACCh-Out cohort exactly as published [17]. A probability of *severe disease course* and *non-achievement of remission* was computed for each patient in the Nordic cohort, and these probabilities were compared to the outcomes described above. By varying the probability threshold, pairs of corresponding sensitivity and specificity values were obtained, and consequently a receiver operating characteristic (ROC) curve. The area under the curve (AUC), or C-statistic, was computed from the ROC curve for each outcome. This is reported as the C-index. For each outcome, the uncertainty in the C-statistic was quantified by a standard bootstrapping (resampling) method and reported as interquartile range (IQR).

Testing of the Canadian model after fine-tuning

This involved re-estimating the coefficients β_i in subsets (training sets) of the Nordic cohort and evaluating the corresponding models (using the same method) as described above on disjoint validation sets. We used 500 repeated random splits into training and validation sets, and the median C-statistics with IQRs were computed. For each random split, we used 75% of available patients for training, and 25% for testing.

Internal validation of the Nordic model

The Nordic model was validated by constructing and training models on training sets and tested on disjoint validation sets as described above. For the Nordic model, the training involved not only the estimation of coefficients β_i, but also the variable selection as reported [19]. The results for prediction of *non-achievement of remission* have been previously reported, but in the present study, we extended this analysis to prediction of *severe disease course*. For comparison, we also carried out this analysis for a univariate logistic regression model with cumulative active joint count at baseline as the only predictor. The sample size was determined by the number of patients with available data for analyses in the Nordic JIA cohort.

For the construction of the *severe disease course* outcome, there were 1 or more missing values for 248 of the 440 patients. Since *severe disease course* is a data-driven outcome, it was necessary to impute these missing values. For this purpose, we used the linear dimension-reduction algorithm in the Wolfram Mathematica software. The results presented in this study are without imputation of missing data for the predictor variables; thus, patients with 1 or more missing predictor variables were omitted from the testing of that particular model. For the external validation of the Canadian model, we lost 222 of 440 patients due to missing data in 1 or more of the 16 predictors. Most of these were missing tests of RF positivity (repeated twice at least 3 months apart). To test the effect of the missing predictor data on the main result, we performed a sensitivity analysis where we imputed missing data in predictor variables and re-tested the Canadian model. Results did not change significantly.

The statistical analyses in the current study were performed using Stata/MP version 15 and Wolfram Mathematica version 11.3.0.0.

Table 2 Baseline clinical characteristics for patients in the ReACCh-Out and the Nordic JIA cohort according to severe disease course or non-severe disease course

Characteristics	ReACCh-Out development cohort		Nordic validation cohort	
	Severe disease ($n = 125$)	Non-severe ($n = 484$)	Severe disease ($n = 98$)	Non-severe ($n = 342$)
Age at onset, years	9.9 (5.4–12.0), $n = 123$	6.9 (2.5–10.7), $n = 474$	8.1 (2.9–11.0)	5.2 (2.3–9.0)
Female, *n* (%)	88 (70.4)	325 (67.1)	78 (79.6)	213 (62.3)
Disease onset to diagnosis, months	5.6 (2.4–13.9)	3.3 (1.6–6.4)	2.4 (1.4–5.1), $n = 94$	1.4 (1.4–2.8), $n = 321$
Disease onset to enrollment, months	8.8 (4.9–17.0)	5.5 (2.8–9.9)	6.0 (6.0–9.0)	7.0 (6.0–8.0)
JIA category, *n* (%)				
Oligoarthritis	9 (7.2)	214 (44.2)	27 (27.6)	200 (58.5)
RF-neg. polyarthritis	44 (35.2)	85 (17.6)	37 (37.8)	57 (16.7)
RF-pos. polyarthritis	20 (16.0)	6 (1.2)	3 (3.1)	1 (0.3)
Systemic	10 (8.0)	37 (7.6)	2 (2.0)	15 (4.4)
Enthesitis-related	24 (19.2)	57 (11.8)	9 (9.2)	25 (7.3)
Psoriatic	4 (3.2)	32 (6.6)	1 (1.0)	5 (1.5)
Undifferentiated	14 (11.2)	53 (11.0)	19 (19.4)	39 (11.4)
Active joints, *n* (%)				
Cervical arthritis	21 (16.8)	8 (1.7)	22 (22.7)	16 (4.7)
Finger arthritis	86 (68.8)	122 (25.2)	63 (65.0)	72 (21.1)
Ankle arthritis	78 (62.4)	140 (28.9)	61 (62.9)	137 (40.1)
Hip arthritis	35 (28.0)	34 (7.0)	19 (19.6)	45 (13.2)
Cumulative active joint count[a]	13 (4–26)	2 (1–4)	9 (5–14)	2 (1–5)
Physician global assessment VAS	5.3 (3.2–7.2)	2.3 (1.0–4.6)	2.4 (1.0–4.7), $n = 75$	1.0 (0.3–2.1), $n = 173$
Parents' global assessment VAS	3.6 (1.8–5.7), $n = 114$	1.3 (0.3–3.5), $n = 440$	2.3 (1.0–5.0), $n = 76$	0.9 (0.0–2.5), $n = 195$
Pain VAS	5.0 (2.7–6.8), $n = 114$	2.0 (0.5–5.0), $n = 440$	3.4 (1.1–5.0), $n = 75$	0.8 (0.0–2.8), $n = 192$
CHAQ	0.9 (0.3–1.4), $n = 109$	0.3 (0.0–0.8), $n = 408$	0.9 (0.3–1.4), $n = 78$	0.1 (0.0–0.7), $n = 200$
Morning stiffness, *n* (%)	102/124 (82.3)[b]	334/447 (74.7)[b]	60/86 (69.8)[c]	60/254 (23.6)[c]
ESR mm/hour	20 (9–45), $n = 119$	20 (9–36), $n = 433$	16 (8–39), $n = 77$	14 (8–25), $n = 281$
CRP mg/l	5.8 (0.4–34.0), $n = 98$	2.0 (0.1–10.0), $n = 371$	0.0 (0.0–22.5), $n = 80$	0.0 (0.0–10.0), $n = 274$
ANA positive, *n* (%)	54 (43.0)[d]	233 (48.0)[d]	22/95 (23.2)	93/332 (28.3)
RF positive, *n* (%)	24 (19.2)[d]	21 (4.3)[d]	4/70 (5.7)	6/171 (3.5)
HLA B27 positive, *n* (%)	18 (14.4)[d]	46 (9.5)[d]	23/96 (24.0)	63/314 (20.1)
Treatment by first study visit, *n* (%)				
NSAIDs	115/125 (92.0)	451/484 (93.2)	83/97 (85.6)	290/337 (86.1)
Joint injections	9/125 (7.2)	92/484 (19.0)	46/95 (48.4)	195/334 (58.4)
DMARDs	89/125 (71.2)	114/484 (23.6)	39/94 (41.5)	53/320 (16.6)
Biologics	2/125 (1.6)	0	0	0

Numbers are median interquartile range (IQR) unless otherwise specified

VAS visual analogue scale, *CHAQ* Childhood Health Assessment Questionnaire, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *ANA* antinuclear antibodies, *RF* rheumatoid factor, *HLA B27* Human Leucocyte Antigen B27, *NSAID* non-steroidal anti-inflammatory drug, *DMARD* disease modifying antirheumatic drug

[a]The Nordic cohort used the cumulative joint count within 6 months of disease onset, and the ReACCh-Out cohort used the active joint count at baseline

[b]Morning stiffness > 30 min

[c]Morning stiffness > 15 min

[d]Values on ANA, RF, and HLA B7 for the Canadian cohort are after imputation

Results

Among the 440 patients in the Nordic cohort, 98/440 (22%) were identified with a severe disease course. This ratio is similar to the 125 (21%) of 609 patients identified with a severe disease course in the ReACCh-Out study. Altogether, 246/427 (58%) were not in remission off medication at the 8-year visit. The general characteristics of the 2 study populations are presented in Table 1, and

Table 3 C-indices for testing of Canadian and Nordic prediction models

Prediction model	Severe disease course outcome	Non-achievement of remission outcome	Validation method
Original Canadian model	0.85 (0.83–0.87)	0.66 (0.63–0.68)	External validation (bootstrapping)
Canadian model fine-tuned for Nordic population	0.85 (0.81–0.89)	0.69 (0.65–0.73)	Fine-tuning (repeated random splits)
Nordic model	0.90 (0.86–0.92)	0.78 (0.72–0.82)[a]	Internal validation (repeated random splits)

C-indices with median interquartile range (IQR)
C-index presented includes patients with systemic JIA, except for [a]the C-index for the Nordic model and the outcome non-achievement of remission previously published by Rypdal et al. [19]

detailed clinical characteristics of the groups of patients with severe disease course in the two cohorts are presented in Table 2.

In the Nordic validation cohort, 66.2% were female. The baseline visit took place at a median of 7 (IQR 6–8) months after the first symptom of JIA, and the median time for assessment of the outcome was 98 (IQR 95–102) months after disease onset. Time from disease onset to JIA diagnosis was 1.6 (IQR 1.4–3.3) months. The median age at disease onset was 5.5 (IQR 2.5–9.7) years.

In the Canadian development cohort, 67.9% were female. The median time from disease onset to the baseline visit was 5.8 (IQR 3–11) months. The outcome was assessed on patients that attended at least six of eight planned visits, which correspond to a follow-up of 3 to 5 years. Time from first symptom to diagnosis was 3.7 (IQR 1.8–7.3) months, and the median age at disease onset was 8.4 (IQR 3.4–11.9) years.

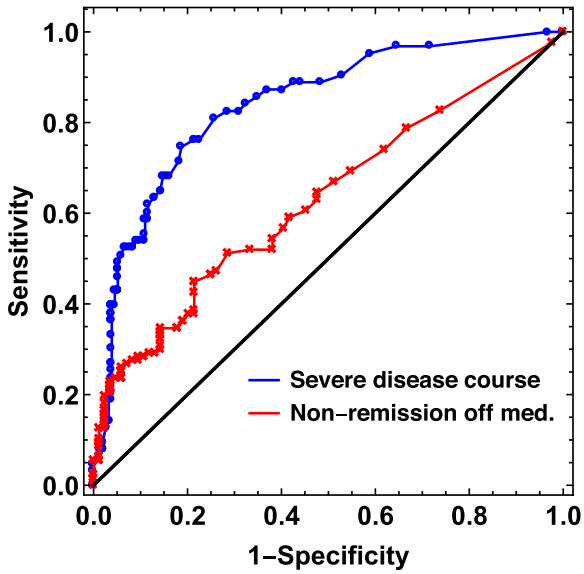

Fig. 1 Receiver operating characteristic (ROC) curves showing external validation of the Canadian prediction model in the Nordic JIA cohort. Blue curve: using severe disease course as outcome. C-index with IQR = 0.85 (0.83–0.87). Red curve: using non-achievement of remission as outcome. C-index with IQR = 0.66 (0.63–0.68)

Model validation

The external validation with *severe disease course* as outcome resulted in a C-index of 0.85, and bootstrapping gave an estimated IQR of 0.83–0.87. For *non-achievement of remission*, the C-index was 0.66 (IQR 0.63–0.68) (Table 3). The corresponding ROC curves for the external validation are shown in Fig. 1, and the calibration plots are shown in the Additional file 2: Figure S1. The alternative construction of *severe disease course*, based on five rather than four variables at the 8-year follow-up, gave a C-index of 0.84 with an IQR of 0.82–0.87. After imputation of missing data in predictor variables the C-index was 0.83.

After fine-tuning in training sets, the Canadian model had a median C-index of 0.85 (IQR 0.80–0.89) with *severe disease course* as outcome (Table 3 and Fig. 2a). The same analysis with *non-achievement of remission* as outcome gave a C-index of 0.69 (IQR 0.65–0.73) (Table 3, Fig. 2b). The model variables and their corresponding β_i-coefficients for the original ReACCh-Out model and the model fine-tuned to the Nordic population are presented in Table 4.

We also performed *internal validation* of our Nordic model using *severe disease course* as outcome. This gave a median C-index of 0.90 (IQR 0.86–0.92) (Table 3, Fig. 2c). Ultimately, we tested a very simple prediction model with cumulative active joint count at baseline as the only predictor. For this model, a C-index of 0.85 (IQR 0.82–0.88) was estimated. The corresponding ROC curve is presented in Additional file 3: Figure S2.

Discussion

A clinically useful prediction model for long-term outcome in JIA should be tested for reliability and accuracy across cohorts, countries, and ethnicities to avoid overestimating the predictive performance of the model. To our knowledge, the two studies presented in this issue are the first where prediction models for unfavorable outcomes in JIA are tested on cohorts completely different to those used to construct the models.

The main result of this study is that the external validation of the Canadian prediction model yielded excellent predictive performance with a C-index of 0.85 (IQR

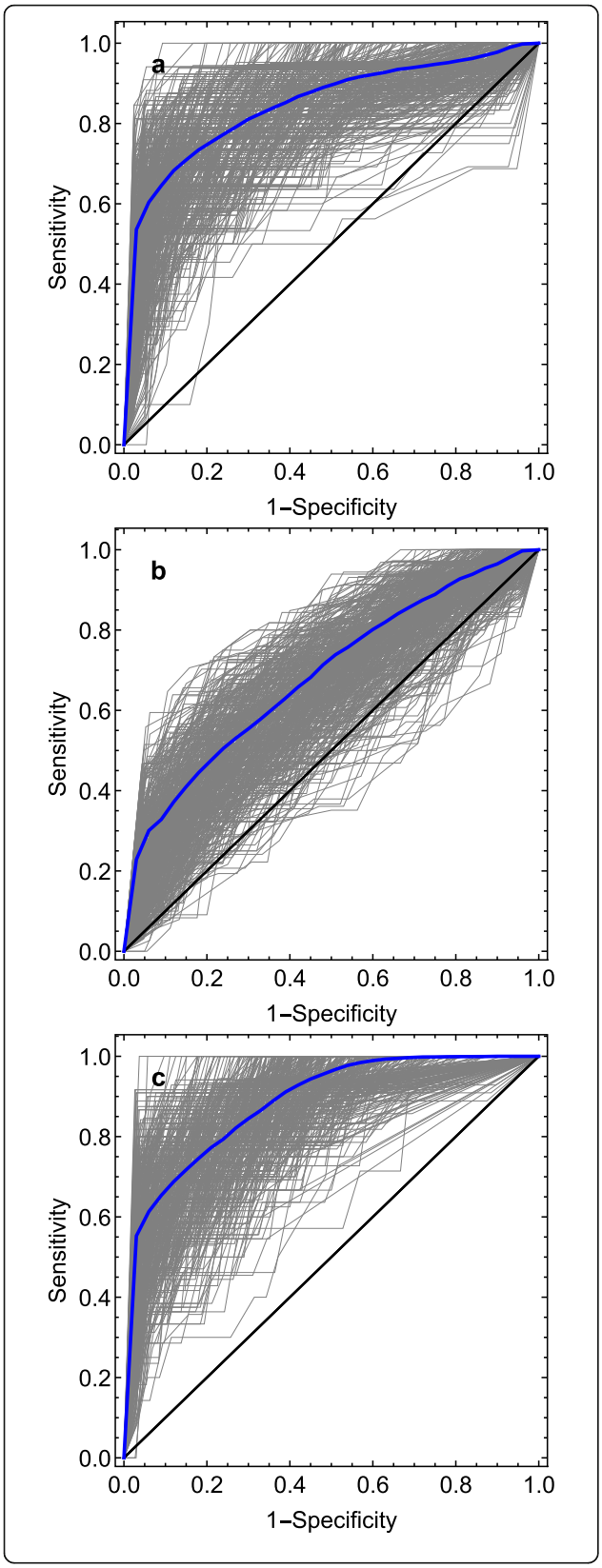

Fig. 2 Receiver operating characteristic (ROC) curves showing results of fine-tuned models in the Nordic JIA cohort for different outcomes. **a** Fine-tuned Canadian prediction model using severe disease course as outcome. **b** Fine-tuned Canadian prediction model using non-achievement of remission as outcome. **c** Internal validation of Nordic prediction model using severe disease course as outcome

0.83–0.87) for *severe disease course* in the Nordic cohort. The result is consistent with the internal validation in the Canadian cohort, where a C-index of 0.85 was obtained [17]. The Canadian model was also tested after fine-tuning on repeated random splits, giving a similar result to the ones in external validation. Internal validation of the Nordic model also indicated excellent performance (C-index of 0.90) for predicting a *severe disease course.*

In all comparisons, C-indices for prediction of *severe disease course* were higher than for prediction of *non-achievement of remission*.

Recently, several prediction models in JIA have been published, but predictive abilities are suboptimal, and none of them have been externally validated in an entirely different population [14–16, 18, 19]. The current study highlights two key points: (1) The choice of outcome to be predicted is essential for predictive performance and perhaps more important than model design. (2) Prediction models based on a few key variables may have similar predictive ability to more complex models, at least for the outcomes examined in this study.

The first point is supported by the comparison of *non-achievement of remission* and *severe disease course.* It seems the latter defines a narrower and more homogeneous group of patients that is easier to identify and predict. In our opinion, severe disease course is clinically relevant because it captures a group of JIA patients most severely affected by the disease. This adverse outcome may correspond better with the threshold in many countries for initiating biologic treatment and therefore be a better prediction target to guide early aggressive treatment [8–10, 28].

The second point is supported by observing that in this study, the predictive abilities of the most complex models are not much better than those of simpler models. The Nordic model for prediction of *non-achievement of remission* was designed with specific conditions in place to ensure model simplicity. It is comparable to the Canadian model in performance. However, the Canadian model is based on 16 variables and may be more difficult to use in clinical practice, even though an available online calculator is easy to use. Besides its predictive performance, one of the key features of a good clinical prediction rule is simplicity [29].

To further investigate the potential of very simple prediction models, we also assessed a univariate logistic

Table 4 Canadian prediction model with respective β_i coefficients before and after fine-tuning in the Nordic JIA cohort

Predictor variables in the Canadian model	Original ReACCh-Out cohort[a]	Fine-tuned in the Nordic cohort[b]
Constant	Intercept = − 2.92	Intercept = 2.76
Active joint count, *n* = 440	0.18	0.21
Psoriatic arthritis, *n* = 440	− 1.23	− 1.40
Oligoarthritis, *n* = 440	− 1.14	− 0.72
RF-negative polyarthritis, *n* = 440	− 0.49	− 0.68
Upper limb joint involvement, *n* = 440	0.75	− 1.11
Symmetric joint involvement, *n* = 439	− 0.88	0.68
RF positivity, *n* = 241	1.31	− 1.06
Subtalar joint involvement, *n* = 439	− 1.42	− 2.81
Finger joint involvement, *n* = 439	− 0.31	1.31
Cervical spine involvement, *n* = 439	0.84	0.38
Ankle joint involvement, *n* = 439	0.48	− 0.25
Presence of morning stiffness, *n* = 340	0.56	1.64
Hip involvement, *n* = 439	0.06	− 0.50
TMJ-involvement, *n* = 439	1.50	0.09
Mid foot involvement, *n* = 439	0.54	0.39
Presence of enthesitis, *n* = 437	0.86	1.26

[a]Coefficients found by logistic regression in the Canadian cohort, previously reported [17]
[b]The changes in coefficients after fine-tuning in the Nordic JIA cohort

regression model using cumulative active joint count during the first 6 months after disease onset as the only predictor. The model achieved high predictive performance for *severe disease course*, and we take this as an indication that model simplification is feasible. However, the high predictive ability of this very simple model may be explained by the dependence between cumulative active joint count at baseline and the cumulative active joint count later in the disease.

Simple prediction models may perform well for a large group of JIA patients, where the total number of joints affected explains much of the disease burden, but they may be of little use for patients with, for example, systemic JIA or enthesitis-related arthritis, where the severity of the disease may be strongly associated with other clinical features [30]. The heterogeneity of JIA is therefore an argument against oversimplified prediction models, and multivariable models may have greater applicability across the whole spectrum of JIA. While separate models for different JIA categories may be more accurate [15], they may add complexity to prediction.

Study strengths and limitations

The main strength of this work is that we validate a model constructed in the Canadian cohort in the completely separate Nordic cohort. Both studies were multicenter, prospective, longitudinal studies and collected extensive clinical information. However, both the Canadian and Nordic models were constructed starting from a large number of clinical variables, which may have increased the risk of retaining uninformative predictors in the models and overfitting. A weakness of our study is missing data in predictor and outcome variables, which is a common problem in prediction studies [31]. We have tried to address this issue by imputing the values for the variables used in the data-driven outcome and by not omitting patients who lack information on predictor variables. Selecting only patients with complete data may lead to biased results.

In conclusion, we found excellent predictive performance of both the Canadian and Nordic prediction models for predicting a *severe disease course* in children with JIA. Severe disease course was identified using an implicit, data-driven clustering method. Identifying an objective definition of a severe disease course was beyond the scope of this paper, but a clinical definition of severe disease course in JIA is clearly needed. Future studies on prediction models in JIA are necessary, focusing not only on constructing simplified prediction models, but also on determining improved disease-outcome definitions in JIA. Once objective outcome definitions are in place, we can use the knowledge gained from the Nordic-Canadian collaboration to develop new models that can be tested in a third and independent cohort. The ultimate step will be testing the model in a randomized controlled trial to verify if it can significantly improve patient outcomes. The aim is to develop models that can be used in every day clinical practice. We have

developed a smartphone application for the Nordic model, and online web-based calculators exist for both the Nordic (http://predictions.no) and the Canadian (https://shiny.rcg.sfu.ca/jia-sdcc/) models [17, 19]. These tools can easily be extended to new models. As we better understand the accuracies and limitations of the models, physicians may incorporate them in their overall assessments to improve outcome in JIA.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13075-019-2060-2.

Additional file 1: Table S1. Characteristics of the four clusters identified in the Nordic JIA cohort. Cluster 3 and 4 correspond to the severe disease course outcome defined in the ReACCh-Out cohort.

Additional file 2: Figure S1. Calibration curves for the Canadian model in the Nordic JIA cohort. Each point represents one tenth of the patient sample, arranged from lowest to highest probability of the outcome. A: For predicting severe disease course. B: For predicting non-achievement of remission.

Additional file 3: Figure S2. Receiver operating characteristic (ROC) curve showing the result of the univariate logistic regression model with cumulative active joint count as the predictor variable and severe disease course as the outcome. C-index of 0.85 (IQR 0.82–0.88).

Abbreviations

JIA: Juvenile idiopathic arthritis; IQR: Interquartile range, 25th, 75th centiles; ReACCh-Out: Research in Arthritis in Canadian Children Emphasizing Outcomes; TRIPOD: Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis; VAS: Visual analogue scale; CHAQ: Childhood Health Assessment Questionnaire; PhS: Physical Summary Score; CHQ-PF50: Child Health Questionnaire Parent form; ANA: Antinuclear antibodies; RF: Rheumatoid factor; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; ACR: American College of Rheumatology; HLA-B27: Human leucocyte antigen B27; ROC: Receiver operating characteristic; AUC: Area under the (ROC) curve; NSAIDs: Non-steroidal anti-inflammatory drugs; DMARDs: Disease modifying antirheumatic drugs

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Authors' contributions

VR, JG, AH, TL, MRyp, and EN were involved in the conception and design of the study, and/or basic analysis and interpretation of data, drafting of the manuscript, and critical revision for important intellectual content. VR and MRyp performed the statistical analysis. All authors were involved in the acquisition of data, and/or drafting of the manuscript and critical revision for important intellectual content. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available for ethical and privacy reasons but are available from the Nordic Study group of Pediatric Rheumatology (NoSPeR) on reasonable request.

Ethics approval and consent to participate

Approval from medical research ethical committees and data protection authorities was granted according to the regulations of each participating country; in Norway, this was from the Regional Committee for Medical and Health Research Ethics NORD, number 53/96. Oral informed assent was obtained from all children. Written informed consent was obtained from parents of children aged < 16 years and from the children if aged ≥ 16 years of age.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

PAPER III

Validation of prediction models of severe disease course and non-achievement of remission in juvenile idiopathic arthritis part 2: results of the Nordic model in the Canadian cohort

Rypdal V, Glerup M, Songstad N. T, Bertelsen G, Christoffersen T, Arnstad E. D, Aalto K, Berntson L, Fasth A, Herlin T, Ekelund M, Peltoniemi S, Toftedal P, Nielsen S, Leinonen S, Bangsgaard R, Nielsen R, Rygg M, Nordal E and for the Nordic Study Group of Pediatric Rheumatology (NoSPeR)

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Validation of prediction models of severe disease course and non-achievement of remission in juvenile idiopathic arthritis part 2: results of the Nordic model in the Canadian cohort

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Abstract

Background: Validated clinical prediction models to identify children with poor prognosis at the time of juvenile idiopathic arthritis (JIA) diagnosis would be very helpful for tailoring treatments, and avoiding under- or over-treatment. Our objective was to externally validate Nordic clinical prediction models in Canadian patients with JIA.

Methods: We used data from 513 subjects at the 3-year follow-up from the Research in Arthritis in Canadian Children emphasizing Outcomes (ReACCh-Out) cohort. The predicted outcomes were non-achievement of remission, severe disease course, and functional disability. The Nordic models were evaluated exactly as published and after fine-tuning the logistic regression coefficients using multiple data splits of the Canadian cohort. Missing data was handled with multiple imputation, and prediction ability was assessed with C-indices. C-index values > 0.7 were deemed to reflect helpful prediction.

Results: Overall, 81% of evaluable patients did not achieve remission off medications, 15% experienced a severe disease course, and 38% reported disability (CHAQ score > 0). The Nordic model for predicting non-achievement of remission had a C-index of 0.68 (95% CI 0.62–0.74), and 0.74 (0.67–0.80) after fine-tuning. For prediction of severe disease course, it had a C-index of 0.69 (0.61–0.78), and 0.79 (0.68–0.91) after fine-tuning. The fine-tuned Nordic model identified 85% of the cohort as low risk for a severe disease course (< 20% chance) and 7% as high risk (> 60% chance). The Nordic model to predict functional disability had a C-index of 0.57 (0.50–0.63), and 0.51 (0.39–0.63) after fine-tuning.

Conclusions: Fine-tuned Nordic models, combining active joint count, physician global assessment of disease activity, morning stiffness, and ankle involvement, predicted well non-achievement of remission and severe disease course in Canadian patients with JIA. The Nordic model for predicting disability could not predict functional disability in Canadian patients.

Keywords: Juvenile idiopathic arthritis, Prediction model, Validation, Prognosis

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Background

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of conditions characterized by chronic arthritis of unknown cause with onset before the age of 16 years [1]. Validated clinical prediction models to identify children with poor prognosis at diagnosis would be very helpful for tailoring aggressive treatments, such as synthetic and/or biologic DMARDS prescribed shortly after diagnosis, to patients with poor prognosis and prevent under- or over-treatment.

Clinical prediction models are relatively recent developments in JIA, but they are widely used to tailor treatments in practice guidelines, e.g., in cardiovascular disease [2] or osteoporosis [3]. Good practices for development of clinical prediction models and consensus statements for reporting these studies are available [4, 5]. Their discrimination accuracy is often assessed with the C-index, equivalent to the area under the Receiver Operating Characteristic curve (AUC), where 1.0 reflects perfect prediction and 0.5 reflects chance alone. In the cardiovascular literature, prediction models with C-index values > 0.7 are considered helpful and those with values > 0.8 are considered excellent [6].

Using data from the Research in Arthritis in Canadian Children Emphasizing Outcomes (ReACCh-Out) Cohort, Guzman et al. developed a clinical prediction model to predict a severe disease course that had a C-index of 0.85 in internal validation in that cohort [7]. Using data from the Nordic Study Group of Pediatric Rheumatology (NoSPeR) cohort, Rypdal et al. developed models to predict non-achievement of remission, functional disability, and articular damage 8 years after disease onset. For prediction of non-achievement of remission and functional disability, the C-indices in split validation sets were 0.78 and 0.73, respectively [8]. The mathematical models for Canadian and Nordic prediction tools are shown in Table 1, and user-friendly online calculators are available at https://shiny.rcg.sfu.ca/jia-sdcc/ and http://predictions.no.

Although they aimed to predict different outcomes, there are similarities between the Canadian model to predict a severe disease course and the Nordic model to predict non-achievement of remission. Both are multivariable logistic regression models that combine routine clinical and laboratory variables available early in the disease and both include the active joint count, ankle involvement, and presence of morning stiffness. The main differences are that the Canadian model uses twice as many variables (16 vs 8), including JIA category, presence of enthesitis, and involvement of joints other than

Table 1 The original Canadian and Nordic prediction models for juvenile idiopathic arthritis

Source	Outcome predicted	Calculate *A*	Use *A* to calculate chance of outcome (%)
Guzman et al., Canada 2017 [7]	Severe disease course, defined by trajectory of quality of life, pain, active joint count, medication requirements, and medication side effects over the 5 years after diagnosis	$A = -2.92 + 0.18 \times$ (active joint count at baseline) $- 1.23 \times$ (psoriatic arthritis) $- 1.14 \times$ (oligoarthritis) $- 0.49 \times$ (RF-negative polyarthritis) $+ 0.75 \times$ (upper limb joint involvement) $- 0.88 \times$ (symmetric joint involvement) $+ 1.31 \times$ (RF positivity) $- 1.42 \times$ (subtalar joint involvement) $- 0.31 \times$ (finger joint involvement) $+ 0.84 \times$ (cervical spine involvement) $+ 0.48 \times$ (ankle joint involvement) $+ 0.56 \times$ (presence of morning stiffness) $+ 0.06 \times$ (hip involvement) $+ 1.50 \times$ (temporal mandibular joint involvement) $+ 0.54 \times$ (mid-foot involvement) $+ 0.86 \times$ (presence of enthesitis)	$[e^A/(1 + e^A)] \times 100$ where e^A is the natural antilogarithm of *A*
Rypdal et al., Norway 2018 [8]	Non-achievement of remission 8 years after onset	$A = -1.58 + 0.04 \times$ (cumulative joint count within 6 months of onset) $+ 0.03 \times$ (ESR in mm/h) $- 0.07 \times$ (CRP > 10 mg/L) $+ 1.16 \times$ (morning stiffness > 15 min) $+ 0.16 \times$ (physician global assessment) $+ 1.25 \times$ (ANA positive) $+ 1.37 \times$ (B27 positive) $+ 1.10 \times$ (ankle joint arthritis)	$[e^A/(1 + e^A)] \times 100$ where e^A is the natural antilogarithm of *A*
Rypdal et al., Norway 2018 [8]	Functional disability (CHAQ > 0) 8 years after onset	$A = -1.68 - 0.02 \times$ (cumulative joint count within 6 months of onset) $+ 0.01 \times$ (ESR in mm/h) $- 0.20 \times$ (CRP > 10 mg/L) $+ 1.03 \times$ (morning stiffness > 15 min) $- 0.40 \times$ (physician global assessment VAS) $+ 1.21 \times$ (finger joint arthritis) $+ 0.77 \times$ (pain VAS)	$[e^A/(1 + e^A)] \times 100$ where e^A is the natural antilogarithm of *A*

RF rheumatoid factor, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *ANA* antinuclear antibody test, *B27* human leucocyte antigen B27, *VAS* visual analogue scale from 0 to 10 with 10 indicating worse values

the ankles, and that the Canadian model uses active joint count at presentation, while the Nordic model uses cumulative joint count 6 months after onset.

External validation of clinical prediction models in populations different than those in which they were developed is essential before general adoption can be recommended [5]. The goal of this collaboration between ReACCh-Out and NoSPeR researchers was to determine if clinical prediction models developed in one cohort could be externally validated in the other cohort. The aim of the present study was to externally validate the Nordic models in Canadian patients. A twin study by Rypdal et al. externally validated the Canadian model in Nordic patients [9].

Patients and methods

The ReACCh-Out cohort has been previously described in detail [10, 11]. In brief, 1497 patients newly diagnosed with JIA were recruited at 16 pediatric rheumatology centers across Canada from January 2005 to December 2010. The first visit occurred as soon as possible after diagnosis, but the time from diagnosis to the first visit could be as long as 1 year. Follow-up visits were scheduled every 6 months for 2 years and then yearly up to 5 years, or until May 2012. At each official study visit, full clinical information was collected, including the American College of Rheumatology (ACR) core variables [12], treatment information, and patient-reported outcomes. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were only measured if clinically indicated. At interim clinic visits between study visits, a reduced dataset was collected, including the number of active joints, limited joints or enthesitis sites, treatment information, and ESR and CRP levels if measured. ReACCh-Out was approved by Research Ethics Boards at all participating institutions and performed in accordance with the Declaration of Helsinki, including informed written consent.

The Nordic Cohort recruited 500 patients newly diagnosed with JIA in defined geographical locations of Norway, Sweden, Finland, and Denmark in 1997–2000. First visit occurred approximately 6 months after disease onset, then at 12 months, and then every 1–3 years with an obligatory visit at approximately 8 years after disease onset (available for 440 subjects) [13].

Patients

For the current study, the goal was to select patients recruited in ReACCh-Out who were as similar as possible to the population used for development of the original Nordic prediction models. We considered including only patients with information at the 5-year follow-up, but this would have reduced our sample size considerably. Moreover, since ReACCh-Out did not follow patients into adulthood, many children who entered the cohort as teenagers would have been excluded, resulting in under-representation of JIA categories commonly seen in teenagers. We chose instead to include data of patients recruited within 3 months of diagnosis who had enough information at the 3-year visit to ascertain the outcomes of interest.

Outcomes

Our primary outcome was non-achievement of remission at the 3-year visit. We were not able to use the exact same outcome definition as in the original Nordic study, since the schedule of visits and other features differed between the two cohorts. We designated a primary definition and examined several alternative definitions. The primary definition of remission was clinical inactive disease for at least 12 months while off treatment [14]. We also examined the model's ability to predict a severe disease course as defined by Guzman et al. [7], based on cluster analysis of changes in pain, health related quality of life, number of active joints, medication requirements, and medication side effects over 5 years.

Clinical inactive disease was defined as no active joints, no active extra-articular manifestations (no enthesitis, uveitis, or systemic manifestations), and a physician global assessment of disease activity (PGA) of < 1 cm in a 10-cm visual analogue scale (VAS). This definition was based on the 2004 Wallace criteria [14] and has been previously used by our group [11, 15]. The main differences relative to the current American College of Rheumatology (ACR) provisional criteria [16] are that a morning stiffness of 15 min or less and normal acute phase reactants were not required.

We defined functional disability as a Childhood Health Assessment Questionnaire (CHAQ) disability index [17] greater than 0 at the 3-year visit. This is the same instrument and cutoff used in the Nordic study, but at a different follow-up time. The Nordic study also developed a model to predict functional disability defined by the Child Health Questionnaire physical summary score [18], but the Canadian cohort did not use that instrument.

Model validation

For each subject in the Canadian cohort, we first computed the probabilities of non-achievement of remission and functional disability, using the Nordic models exactly as published (i.e., with the same intercept and coefficients). We compared this prediction to the observed outcome to assess prediction accuracy (C-index and confidence intervals, details below). If the resulting value was substantially lower than the value originally published in the Nordic cohort, we proceeded to fine-tune the models. Fine-tuning means re-estimation of the

model's intercept and coefficients to better fit a new population, while keeping the same predictors and same logistic regression methods to combine predictors. Intercept and coefficients were re-estimated using multiple splits of the Canadian cohort.

In pre-specified sensitivity analyses, we assessed the ability of the Nordic model to predict alternative definitions of remission, including inactive disease while off treatment (i.e., without requiring 12 months) and inactive disease for > 6 months irrespective of treatment. We also looked at the model's ability to predict a severe disease course, as defined by Guzman et al [7]. This analysis was not pre-specified. Similar to what was reported in the Nordic cohort [8], we looked at the performance of prediction models that excluded the laboratory variables from the prediction model. Additional post hoc analyses assessed the models' performance after excluding patients with systemic JIA and in a subsample of patients who attended the 5-year follow-up. Lastly, we examined the prediction ability of a model that included only the active joint count at baseline.

Statistical analysis

All analyses were conducted using R software. The Canadian cohort had an overall 10% missing rate of baseline data. Missing data were imputed in 20 datasets using the method of multiple imputation by chained equations (MICE) [19]. Outcome data was not imputed. Our reported average C-indices and average coefficient estimates are unweighted means across all 20 imputed datasets. We followed Rubin's rules [20] to compute standard errors (SEs) for all quantities across the 20 imputed datasets.

To validate the original un-tuned Nordic models in Canadian children, we fit each model to 100% of the data within each of 20 imputed datasets. From each dataset, we computed the C-index and the SE of the C-index. We then combined these individual SEs to produce the overall C-index SE.

For the fine-tuned models, we needed to ensure that the model-evaluation statistics were computed on data not used to estimate the coefficients. We followed the procedure published by Jiang et al. [21] and modified it to compute the C-index. For a given imputed dataset, we estimated the average C-index using their recommendation of the Leave-One-Out Cross-Validation (LOOCV) error. To estimate the within-dataset standard error, we used their recommendation of a nested cross-validation within a bootstrap (the BCCV algorithm). We created $B = 25$ bootstrap samples on an imputed dataset. Within each bootstrap sample, we removed one original observation (if it occurred multiple times in the imputed data, we removed all cases) and predicted this observation using the fitted model. We repeated this process for each observation in turn to obtain predictions on each case. We then computed a C-index on all predicted values of that bootstrap sample. We then computed the standard deviation (SD) of the $B = 25$ bootstrap sample C-indices as an estimate of the within-dataset SD of the C-index. The between-dataset and within-dataset SDs were combined to produce the overall multiple imputation SE using Rubin's rules [20].

To obtain SE of coefficients, we fitted the model on each of $B = 25$ bootstrap samples from each imputed dataset (a total of 500 fits). For each imputed dataset, we estimated the within-dataset SE of the coefficients using the SD of the coefficient estimates from the glm package in R across the 25 bootstrap samples. Again, we combined this with the between-dataset SD to get the overall SE.

Results

A total of 513 subjects fulfilled our inclusion criteria at the 3-year visit, which occurred on average 3.75 years after JIA onset. The patient flow chart is shown in Fig. 1. The figure also shows the corresponding patient flow chart used to select subjects for the original Nordic study.

Baseline patient characteristics in the validation cohort are compared with the reported characteristics in the original development cohort in Table 2. Overall, the cohorts are similar to each other and to other inception cohorts of JIA reported in western populations. The original Nordic study excluded patients with systemic JIA from model development and had only four patients with RF-positive polyarthritis [8].

In total, 408 of 506 evaluable Canadian patients (81%) were not in remission at the 3-year visit. Applying the Nordic model for prediction of non-achievement of remission exactly as published resulted on a C-index of 0.68 (95% CI 0.62–0.74). As this was lower than the published value (median AUC 0.78, IQR 0.72, 0.82), we proceeded with fine-tuning of coefficients. After fine-tuning, the C-index tested in multiple splits of the Canadian cohort was 0.74 (0.67–0.80). Figure 2 shows the corresponding Receiver Operating Characteristic (ROC) curves (panels a and b). The coefficients for original and fine-tuned models are shown in Table 3. Excluding patients with systemic JIA had a small impact on model performance, with a C-index of 0.73 (0.66–0.80) for the original model and 0.76 (0.69–0.83) for the fine-tuned model.

In secondary analyses, the C-index values calculated when using alternative definitions of remission were nominally lower than when using our primary definition of remission. For inactive disease while off treatment, it was 0.66 (0.60–0.71), and after fine-tuning, it was 0.69 (0.63–0.75). For inactive disease > 6 months irrespective

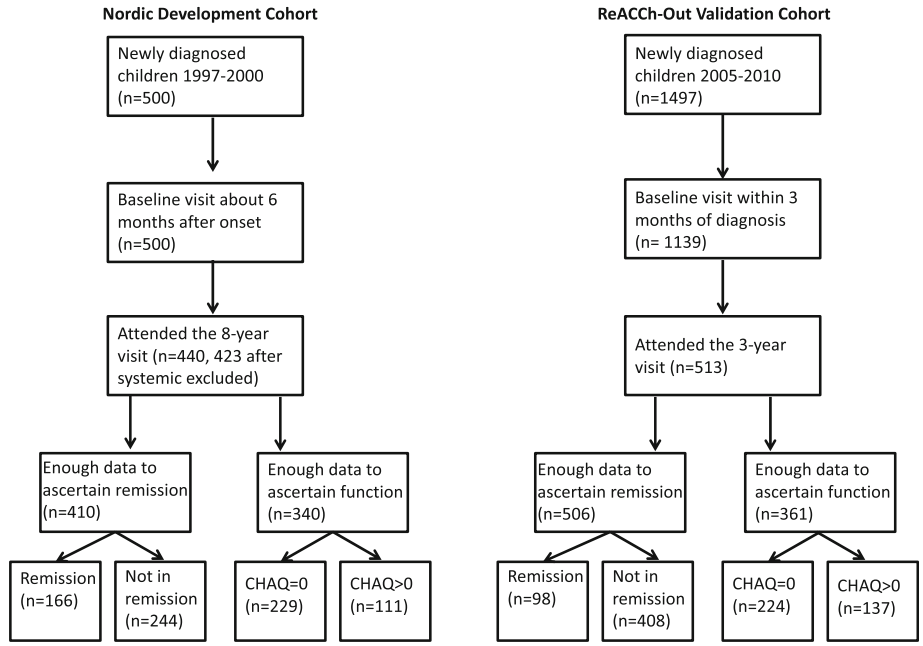

Fig. 1 Patient flow charts for the development and validation cohorts

of treatment, it was 0.62 (0.53–0.71), and after fine-tuning, it was 0.63 (0.50–0.75). We also calculated the C-index for a subsample of patients assessed at the 5-year follow-up in the ReACCh-Out cohort; the C-index was 0.57 (0.35–0.79), but this subsample was no longer representative of all patients with JIA since patients diagnosed as teenagers were not followed into adulthood, and the subsample was small, resulting in wide confidence intervals.

A severe disease course was observed in 53 of 354 (15%) evaluable patients. Prediction with the Nordic model had a C-index of 0.69 (CI 0.61–0.78), and after fine-tuning, it was 0.79 (0.68–0.91). The corresponding ROC curves are shown in Fig. 2c, d. The calibration curves for the fine-tuned Nordic models are shown in Fig. 3. The Nordic model fine-tuned for severe disease course identified 85% of the cohort as low risk for severe disease (< 20% chance) and 7% of the cohort as high risk (> 60% chance).

We also examined the predictive ability of the model after exclusion of laboratory variables as it was done in the original publication. Fine-tuned versions with no laboratory values had a C-index of 0.74 (CI 0.67–0.81) when predicting non-achievement of remission and 0.79 (CI 0.69–0.89) when predicting a severe disease course, virtually the same values as models including laboratory variables. Lastly, a model using the baseline active joint count alone had a C-index of 0.66 (0.61–0.71) to predict non-achievement of remission and 0.76 (0.66–0.86) to predict a severe disease course.

Functional disability defined as a CHAQ > 0 was reported by 137 of 361 (38%) evaluable patients. Prediction with the Nordic model for functional disability had a C-index of 0.57 (0.50–0.63), and fine-tuning of coefficients was not able to improve accuracy, with a C-index of 0.51 (0.39–0.63). The corresponding ROC curves are shown in Additional file 1: Figure S1.

We note that the Nordic model for functional disability differed from the model for non-achievement of remission not only by the value of its coefficients, but also by the set of predictor variables. In the study of Rypdal et al., there was no model for prediction of severe disease course [8], and we used the model for non-achievement of remission when we tested for ability to predict severe disease course.

Discussion

The aim of this study was to externally validate prediction models for poor prognosis in JIA developed in the Nordic cohort by assessing their performance in Canadian patients enrolled in the ReACCh-Out cohort. We found that after fine-tuning of coefficients, the Nordic model for predicting non-achievement of remission 8 years after disease onset had good accuracy to predict non-achievement of remission 3.75 years after onset (C-index 0.74) and a severe disease course over 5 years (C-index 0.79) in Canadian patients, even after laboratory variables were excluded. As shown in Table 3, fine-tuning of the model to predict non-achievement of remission increased the relative contribution of active joint count (beta coefficient changed from 0.04 to 0.16) and decreased the relative contribution of morning stiffness, ankle joint arthritis, and laboratory test results. The

Table 2 Baseline characteristics for patients in the development and validation cohorts according to non-achievement of remission

q	Nordic development cohort (*N* = 427)		ReACCh-Out validation cohort (*N* = 506)	
	Remission (*n* = 181)	Non-remission (*n* = 246)	Remission (*n* = 98)	Non-remission (*n* = 408)
Characteristics				
Age at onset, years	5.9 (2.5, 10.0)*	5.2 (2.5, 9.5)	8.0 (3.6, 11.5)	7.2 (2.6, 11.1)
Female, *n* (%)	115 (63.5)	169 (68.7)	62 (63.3)	285 (70.4)
Onset to enrolment, months	7 (6, 8)	6.5 (6, 8)	3.9 (2.4, 6.0)	5.1 (2.7, 9.7)
JIA category, *n* (%)**				
Oligoarthritis	107 (59.1)	111 (45.1)	55 (56.1)	137 (33.6)
RF-neg. polyarthritis	25 (13.8)	68 (27.6)	4 (4.1)	113 (27.7)
RF-pos. polyarthritis	1 (0.6)	3 (1.2)	0 (0.0)	17 (4.2)
Systemic	15 (8.3)	2 (0.8)	13 (13.3)	28 (6.9)
Enthesitis-related	11 (6.1)	23 (9.3)	8 (8.2)	50 (12.3)
Psoriatic	3 (1.7)	3 (1.2)	8 (8.2)	20 (4.9)
Undifferentiated	19 (10.5)	36 (14.6)	10 (10.2)	43 (10.5)
Assessments and laboratory tests				
Active joints, *n* (%)				
Cervical arthritis	13 (7.2)	25 (10.2)	0 (0.0)	26 (7.0)
Finger arthritis	40 (22.1)	94 (38.2)	16 (19.3)	167 (44.7)
Ankle arthritis	65 (35.9)	129 (52.4)	17 (20.5)	186 (49.7)
Hip arthritis	24 (13.3)	38 (15.4)	7 (8.4)	50 (13.4)
Active joint count***	2 (1, 4)	4 (2, 7)	1 (1, 2)	3 (1, 9)
Physician global assessment	0.8 (0.0, 1.3)	2.0 (1.0, 3.8)	1.9 (1.0, 3.2)	3.8 (2.0, 6.0)
Parent global assessment	0.6 (0.0, 2.0)	1.7 (0.5, 3.5)	0.7 (0.2, 2.4)	2.3 (0.7, 4.9)
Pain	0.4 (0.0, 3.0)	2.3 (0.5, 4.2)	1.0 (0.2, 3.0)	3.9 (1.0, 6.1)
CHAQ DI	0.1 (0.0, 0.6)	0.5 (0.0, 1.1)	0.1 (0.0, 0.5)	0.5 (0.1, 1.1)
Stiffness > 15 min (%)	30 (16.6)	90 (36.6)	45 (55.6)	184 (65.0)
ESR****	11.5 (6, 20)	17.5 (10, 31)	20 (9, 34)	21 (9, 40)
CRP****	0.0 (0, 0)	0.0 (0, 15)	2.0 (0.2, 10)	3.0 (0.3, 17)
ANA	37 (20.4)	76 (30.9)	49 (50.0)	182 (50.7)
RF	5 (2.8)	5 (2.0)	5 (5.1)	23 (6.4)
HLA B27	22 (12.2)	60 (24.4)	5 (5.1)	36 (10.0)
Treatment by first study visit (%)				
NSAIDs	152 (84.0)	215 (87.4)	88 (89.8)	390 (95.6)
Joint injections	84 (46.4)	152 (61.8)	24 (24.5)	88 (21.6)
DMARDs	20 (11.0)	71 (28.9)	9 (9.2)	137 (33.6)
Biologics	0	0	1 (1)	1 (0.2)

*Numbers are median (25th centile, 75th centile) or number of patients (%)
**Patients with systemic JIA were excluded from the Nordic prediction model development study. They are included in the validation cohort and in this table
***The Nordic development cohort used the cumulative active joint count within 6 months of disease onset, and the ReACCh-Out validation cohort used the active joint count at baseline
****Erythrocyte sedimentation rate measurements were available for 322 of 427 patients (75.4%) in the Nordic cohort and for 458 of 506 patients (90.5%) in the ReACCh-Out cohort. C-reactive protein measurements were available for 345 of 427 patients (80.8%) in the Nordic cohort and 404 of 506 patients (79.8%) in the ReACCh-Out cohort

contribution of the physician global assessment was virtually the same (from 0.16 to 0.15). In contrast, the model to predict functional disability had a low C-index of 0.57 and fine-tuning did not improve accuracy (C-index 0.51).

For decades, prognostic research in JIA has concentrated on identifying features of poor prognosis [22], but the last decade has seen publication of several models that combine prognostic features to estimate the likelihood of an outcome for each patient. In 2012, Bulatovic

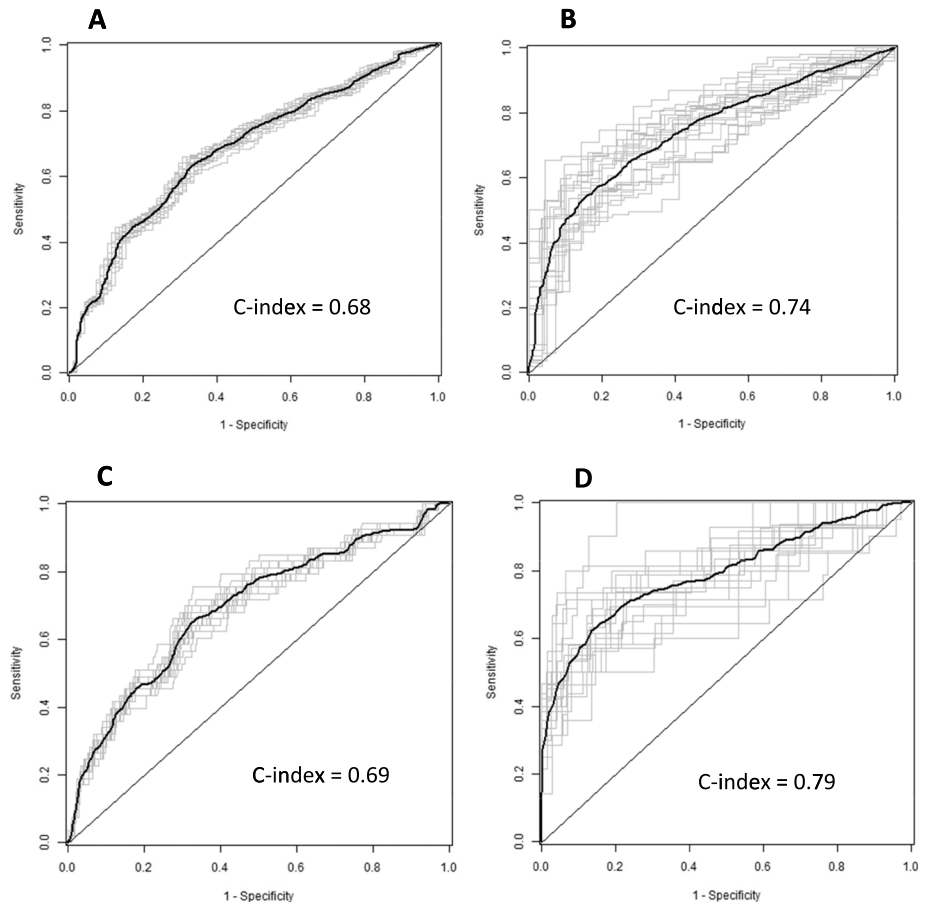

Fig. 2 Receiver Operating Characteristic (ROC) curves for the Nordic model to predict non-achievement of remission when applied to Canadian data. **a** Original model predicting non-remission. **b** Fine-tuned model predicting non-remission. **c** Original model predicting a severe disease course. **d** Fine-tuned model predicting a severe disease course

Table 3 Changes to model coefficients for the Nordic model to predict non-achievement of remission made during the fine-tuning process

Variable	Original Nordic	Fine-tuned Canada to predict non-achievement of remission		Fine-tuned Canada to predict severe disease course	
		With lab tests	No lab tests	With lab tests	No lab tests
Constant (intercept)	- 1.58 (- 0.70, -2.46)*	0.24	0.17	− 2.9	− 2.8
Active joint count**	0.04 (- 0.06, 0.14)	0.16	0.15	0.22	0.21
ESR in mm/h	0.03 (- 0.01, 0.07)	- 0.01	–	− 0.01	–
CRP > 10 mg/L	- 0.07 (- 1.45, 1.31)	0.12	–	0.08	–
Morning stiffness > 15 min	1.16 (0.26, 2.06)	0.42	0.38	0.23	− 0.03
Physician global assessment	0.16 (- 0.76, 1.08)	0.15	0.14	− 0.05	− 0.06
ANA positive	1.25 (0.25, 2.25)	0.03	–	− 0.56	–
HLA-B27 positive	1.37 (0.29, 2.45)	1.07	–	0.85	–
Ankle joint arthritis	1.10 (0.12, 2.08)	0.52	0.53	− 0.70	− 0.70
C-index (95% CI)	0.68 (0.62, 0.74)	0.74 (0.67, 0.80)	0.74 (0.67, 0.81)	0.79 (0.68, 0.91)	0.79 (0.69, 0.89)

*Numbers in parentheses are the 95% confidence interval
**The Nordic cohort used the cumulative active joint count within 6 months of disease onset, while the ReACCh-Out cohort used the active joint count at baseline

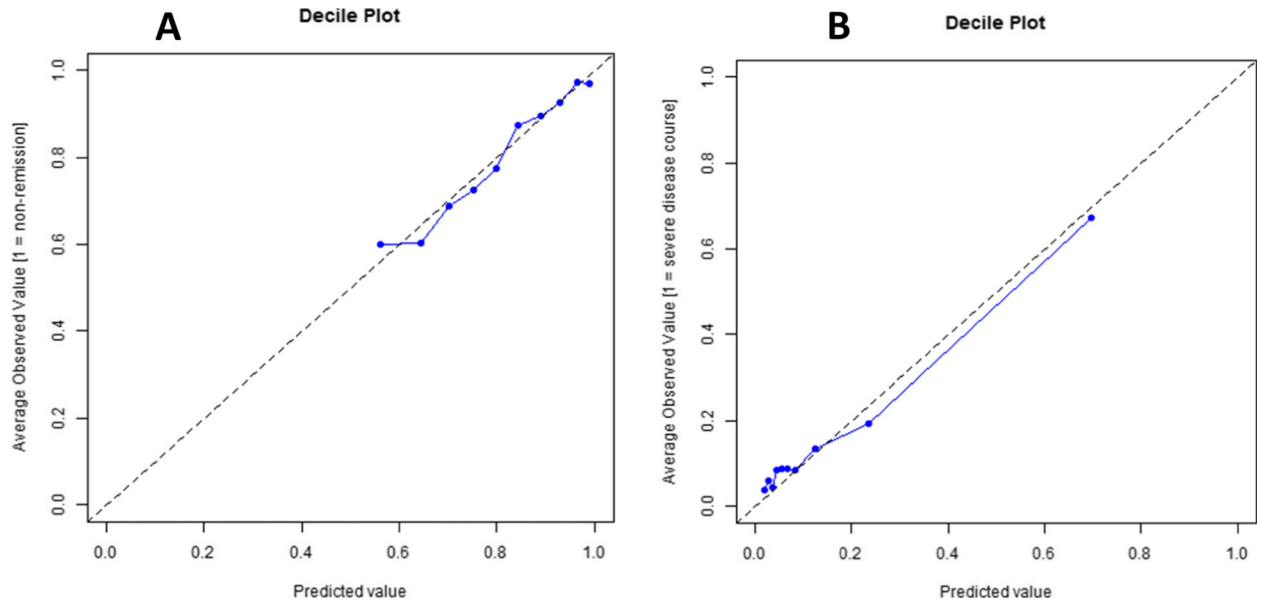

Fig. 3 Calibration curves for the Nordic model to predict non-achievement of remission fine-tuned to Canadian data. **a** When predicting non-achievement of remission. **b** When predicting a severe disease course. Each point represents one tenth of the testing patient sample, arranged from lowest to highest probability of the outcome

et al. reported a model to predict non-response to methotrexate with an AUC of 0.65 [23], and in 2015, van Dijkhuizen et al. reported a model to predict methotrexate intolerance with C-index of 0.77 in internal validation [24]. More recently, van Dijkhuizen et al. combined clinical characteristics, Luminex biomarkers, and microbiota information to predict attainment of inactive disease within 2 years of diagnosis, but the resulting overall model was deemed not satisfactory with a AUC-like statistic of 0.65 [25]. Also recently, Guzman et al. used routine clinical and laboratory data at the time of diagnosis to predict early remission on medication (within 1 year of diagnosis) and the resulting model had a C-index of 0.69 in internal validation, just short of the conventional threshold of > 0.7 to consider a prediction model helpful [26].

In the context of these studies, our current findings raise four important questions: (1) Does the timing of outcome measurement influence our ability to predict inactive disease or remission? (2) Is the overall course of JIA a better prediction target than remission at a single point in time? (3) Should we eliminate laboratory values from the Nordic model altogether? (4) Is the fine-tuned Nordic model a better model to predict JIA disease course than the Canadian model?

In our opinion, the timing of assessment of inactive disease and remission will indeed influence the accuracy of a prediction model, particularly since it is well known that early in the course of JIA patients often transition in and out of inactive disease with subsequent visits [27, 28]. Later in the disease course, remission off medications may be a relatively stable target. This may be one reason why the Nordic model performed slightly better when predicting remission at 8 years in the original cohort than when predicting remission at 3.75 years in the current study. In addition to shorter follow-up, there were some differences in cohort composition, in ascertainment of predictors, and in the definition of inactive disease.

Whether the overall disease course is a better prediction target than remission is open to discussion. It is somewhat surprising that the Nordic model developed for predicting non-achievement of remission performed better at predicting a severe disease course than non-achievement of remission, since the severe-disease-course outcome is constructed very differently from non-achievement of remission. The results suggest that there are strong dependencies between outcome variables that are not fully understood, and that data-driven outcome measures, such as severe disease course, may be more valuable than previously assumed. The definition of a severe disease course is based on the overall trajectory of variables that are meaningful for families and clinicians, instead of accepted JIA core variables measured at a single point in time [7]. That said, remission is a well-accepted and easy to comprehend concept, although using ACR criteria for inactive disease [16] identifies a different patient population than using JADAS criteria [29, 30]. In the context of prediction studies, a targeted outcome needs to be useful for

clinical decision-making but also well-suited for prediction. Future work should focus on rigorous clinical definitions of predicted outcomes. Such definitions will facilitate more accurate validation studies across cohorts.

It is remarkable that the exclusion of laboratory values (ESR, CRP, ANA, B27) had negligible impact on model accuracy, replicating the original findings in the Nordic cohort [8]. This means that a simple combination of active joint count, physician global assessment of disease activity, morning stiffness > 15 min, and presence of ankle involvement at baseline predicts well non-achievement of remission 3 or 8 years later, as well as a severe disease course during the first 5 years after diagnosis. Now that this has been demonstrated in both cohorts, it is hard to think of a good reason to keep laboratory values in the Nordic model.

The final question, which model is preferable, is also open to discussion. Although the Nordic model is simple and a simpler model is generally preferable, our results suggest that the accuracy of the fine-tuned Nordic model is somewhat lower than that of the Canadian model (C-index of 0.79 vs 0.85), but this could be simply due to the fact that the latter model was developed in the same Canadian cohort used in this study. A definitive answer to this question may require testing both models side by side in a third separate independent cohort.

Study strengths and limitations

The main strength of our study is that it provides external validation of the Nordic prediction model in an entirely independent inception cohort with prospectively determined outcome measures. Study limitations include that our definition of remission is not exactly the same and the timeline for assessment is shorter than in the original study. A second limitation is the 10% rate of missing data on predictors, but we used multiple imputation by chained equations, which is a well-established method. A third limitation is that we used the baseline active joint count, instead of the cumulative active joint count within 6 months of disease onset used in the original Nordic model, yet we suspect they would be very similar, given that the baseline active joint count was obtained around the time of diagnosis and the start of treatment. Lastly, the observed improvements in accuracy with fine-tuning of coefficients suggest that for optimal accuracy, the Nordic model should be fine-tuned to the population in which it will be used. This may be problematic as the necessary cohorts for fine-tuning are only available in a few countries. Alternatively, this could indicate slight overfitting during model development in the Nordic cohort.

Conclusions

The Nordic model developed to predict non-achievement of remission 8 years after JIA onset accurately predicted non-achievement of remission 3.75 years after onset and the overall disease course over 5 years after diagnosis in a Canadian cohort after the model coefficients were fine-tuned. The model is simple (active joint count, physician global assessment, morning stiffness, and ankle involvement with or without routine laboratory results), and it should be tested in clinical care to assess whether it improves the tailoring of treatment, i.e., more aggressive treatments for patients at high risk of non-achievement of remission, and whether this actually changes the subsequent disease course and prognosis. This should in turn lead to increased cost-effectiveness of care and, most importantly, improved patient outcomes.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13075-019-2091-8.

Additional file 1 : Figure S1. Receiver Operating Characteristics (ROC) curves for the Nordic prediction model to predict disability

Abbreviations

ACR: American College of Rheumatology; ANA: Antinuclear antibody test; AUC: Area under the Receiver Operating Characteristic curve; CHAQ: Childhood Health Assessment Questionnaire disability index; CI: Confidence interval; CRP: C-reactive protein; DMARDs: Disease modifying anti-rheumatic drugs; ESR: Erythrocyte sedimentation rate; HLA-B27: Human leucocyte antigen B27; IQR: Interquartile range, 25th, 75th centiles; JIA: Juvenile idiopathic arthritis; PGA: Physician global assessment of disease activity; NoSPeR: Nordic Study Group of Pediatric Rheumatology; NSAIDs: Non-steroidal anti-inflammatory drugs; ROC: Receiver Operating Characteristic curve; ReACCh-Out: Research in arthritis in Canadian children emphasizing outcomes; RF: Rheumatoid factor; SD: Standard deviation; SE: Standard error; VAS: Visual analogue scale

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Accession number to microarray data
Not applicable.

Clinical trial registration number
Not applicable.

Authors' contributions
AH, VR, MR, TL, EN, and JG contributed to the study idea and design. AH and TL contributed to the statistical analysis. JG contributed to the collection of data. AH, VR, MR, TL, EN, and JG contributed to the drafting and approval of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
Data is available to research teams that include at least one ReACCh-Out investigator and have a research protocol approved by the Scientific Protocol Evaluation Committee of the Canadian Alliance of Pediatric Rheumatology Investigators.

Ethics approval and consent to participate
ReACCh-Out was approved by Research Ethics Boards at all participating institutions and performed in accordance with the Declaration of Helsinki, including informed written consent.

Consent for publication
Not applicable.

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The authors declare that they have no competing interests.

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Publisher's Note

PAPER IV

Uveitis in Juvenile Idiopathic Arthritis 18-year Outcome in the Population-based Nordic Cohort Study

Rypdal V, Glerup M, Songstad N. T, Bertelsen G, Christoffersen T, Arnstad E. D, Aalto K, Berntson L, Fasth A, Herlin T, Ekelund M, Peltoniemi S, Toftedal P, Nielsen S, Leinonen S, Bangsgaard R, Nielsen R, Rygg M, Nordal E and for the Nordic Study Group of Pediatric Rheumatology (NoSPeR)

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Uveitis in Juvenile Idiopathic Arthritis

18-Year Outcome in the Population-based Nordic Cohort Study

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Purpose: To assess the long-term outcome of uveitis in juvenile idiopathic arthritis (JIA).

Design: Population-based, multicenter, prospective JIA cohort, with a cross-sectional assessment of JIA-associated uveitis (JIA-U) 18 years after the onset of JIA.

Participants: A total of 434 patients with JIA, of whom 96 had uveitis, from defined geographic areas of Denmark, Finland, Norway, and Sweden.

Methods: Patients with onset of JIA between January 1997 and June 2000 were prospectively followed for 18 years. Pediatric rheumatologists and ophthalmologists collected clinical and laboratory data.

Main Outcome Measures: Cumulative incidence of uveitis and clinical characteristics, JIA and uveitis disease activity, ocular complications, visual outcome, and risk factors associated with the development of uveitis-related complications.

Results: Uveitis developed in 96 (22.1%) of 434 patients with JIA. In 12 patients (2.8%), uveitis was diagnosed between 8 and 18 years of follow-up. Systemic immunosuppressive medication was more common among patients with uveitis (47/96 [49.0%]) compared with patients without uveitis (78/338 [23.1%]). Active uveitis was present in 19 of 78 patients (24.4%) at the 18-year visit. Ocular complications occurred in 31 of 80 patients (38.8%). Short duration between the onset of JIA and the diagnosis of uveitis was a risk factor for developing ocular complications (odds ratio [OR], 1.4; 95% confidence interval [CI], 1.1−1.8). Patients with a diagnosis of uveitis before the onset of JIA all developed cataract and had an OR for development of glaucoma of 31.5 (95% CI, 3.6−274). Presence of antinuclear antibodies (ANAs) was also a risk factor for developing 1 or more ocular complications (OR, 3.0; 95% CI, 1.2−7.7). Decreased visual acuity (VA) <6/12 was found in 12 of 135 eyes (8.9%) with uveitis, and 4 of 80 patients (5.0%) with JIA-U had binocular decreased VA <6/12.

Conclusions: Our results suggest that uveitis screening should start immediately when the diagnosis of JIA is suspected or confirmed and be continued for more than 8 years after the diagnosis of JIA. Timely systemic immunosuppressive treatment in patients with a high risk of developing ocular complications must be considered early in the disease course to gain rapid control of ocular inflammation. *Ophthalmology 2020;■:1−11 © 2020 by the American Academy of Ophthalmology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).*

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Juvenile idiopathic arthritis (JIA) is a chronic rheumatic disease of unknown etiology that develops in children and adolescents before the age of 16 years. Uveitis, inflammation of the uvea, is the most common extra-articular manifestation in JIA.[1,2] The reported occurrence of uveitis in JIA varies considerably between different studies.[3-5] Point prevalence is commonly reported between 10% and 15%.[3,5,6] In a Finnish JIA cohort, the cumulative incidence was 24% during the first 7 years of JIA,[4] and in a Canadian cohort, 13% developed uveitis during a mean follow-up time of 6.9 years.[5] Both lower and higher occurrences of uveitis in JIA are reported in other studies.[7,8] Chronic anterior uveitis is the most frequent type of uveitis associated with JIA. Because of the asymptomatic nature of JIA-associated uveitis (JIA-U), all children with JIA should be routinely screened by an ophthalmologist.[9] Early identification and timely treatment of uveitis are crucial to prevent complications that may lead to visual impairment

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and, in some cases, blindness.[10,11] Recently, evidence has emerged for a treatment strategy for JIA-U, where early introduction of immunomodulating treatment and rapid control of the uveal inflammation aim to reduce the risk of developing ocular complications and visual loss.[12,13]

There are few long-term prospective studies on uveitis in JIA.[4,14,15] Studies have shown that the majority of patients with JIA-U develop uveitis within the first 4 years after the onset of JIA[5,16,17] and that high-grade uveitis and active uveal inflammation are associated with higher complication rates.[11,13,18,19] At diagnosis, ocular complications are seen in up to 21% to 76% of eyes with JIA-U,[11,13] and further complications are reported to occur during the course with a complication rate of 0.33 per eye per year.[18] However, our knowledge is limited regarding long-term complications and complications in patients who develop uveitis late in the course of JIA.[14,16]

Previous studies have reported that female gender, young age at onset of JIA, oligoarticular JIA, and the presence of antinuclear antibodies (ANAs) and human leukocyte antigen (HLA)-B27 are risk factors for the development of uveitis in JIA.[3,5,20] Reported risk factors for ocular complications in established uveitis are male gender, the onset of uveitis before arthritis, short interval between the onsets of JIA and uveitis, and the presence of ocular complications early in the disease course.[6,21] However, there are inconsistencies between studies concerning risk factors of ocular complications in JIA-U.

Our study describes the long-term clinical outcome in JIA-U in terms of cumulative incidence, the use of immunosuppressive treatment, visual outcome, ocular complications, and risk factors associated with the development of ocular complications.

Methods

Study Design

The Nordic JIA cohort is a prospective multicenter population-based study with 12 participating centers from specific geographic areas of Denmark, Finland, Norway, and Sweden. We included 510 consecutive patients with onset of JIA between January 1, 1997, and June 30, 2000. Onset of JIA was defined as the first episode of arthritis. Juvenile idiopathic arthritis was classified according to the International League of Associations for Rheumatology criteria.[22] To reflect a population-based sample, the study included all referred children from defined catchment areas in each country. During the inclusion period, letters were repeatedly sent to primary healthcare providers, child health centers, and orthopedic, pediatric, and rheumatology specialists in the catchment areas to ensure the referral of all eligible patients.[23] The healthcare systems in the Nordic countries are mostly free of charge for children aged less than 16 years, making it feasible to conduct a population-based study. The baseline study visit took place at a median of 7 months (interquartile range [IQR], 6−8 months) after the onset of JIA. Thereafter, at a median of 98 months, the 8-year follow-up study took place, with 440 participants at this follow-up. All patients with a baseline visit were invited to the 18-year follow-up. Among the 510 patients with a baseline inclusion, 434 were followed for 18 years and 329 (75.8%) attended a study visit at a department of pediatrics; of these, 273 (62.9%) attended a study visit at a department of ophthalmology. The remaining 105 patients (24.2%) participated in the 18-year follow-up study through a standardized telephone interview where we used the same questionnaires as for the patients who attended the visit in person (Fig 1). During the observation period, the patients were screened for uveitis. For the first 2 years, the interval between the ophthalmologic examinations was scheduled every 2 to 3 months; thereafter, the intervals were longer depending on the time since onset of JIA and JIA category. The screening followed local programs based on international recommendations.[9,10,24]

Data Collection

Demographics, JIA and uveitis disease characteristics, and blood samples were collected. Laboratory tests analyzed in this study included HLA-B27, rheumatoid factor (RF), and immunofluorescence ANAs. Because no universal screening dilutions have been established, ANA was considered positive according to the cutoff value developed at the local laboratory related to the specific ANA kits used. The cutoff value was ≥1/320 in Finland; ≥1/160 in Copenhagen, Aarhus, and some parts of Sweden; and ≥1/80 in Tromsø, Trondheim, and other parts of Sweden. Laboratory values from disease onset were used but supplemented from the 18-year visit in case of missing values.

For assessment of clinical remission in JIA, we applied Wallace et al's[25,26] provisional criteria for inactive disease, requiring no active arthritis, absence of systemic features due to JIA, normal erythrocyte sedimentation rate or C-reactive protein, normal global assessment on a visual analog scale from 0 to 10, absence of active uveitis, and morning stiffness lasting ≤15 minutes. The criterion for remission on medication is inactive disease on medication for 6 successive months, and the criterion for remission off medication is inactive disease for at least 12 months without treatment for JIA.

Characteristics of uveitis were recorded following the Standardization of Uveitis Nomenclature (SUN) Working Group criteria.[27] The uveitis was recorded as an anterior, intermediate,

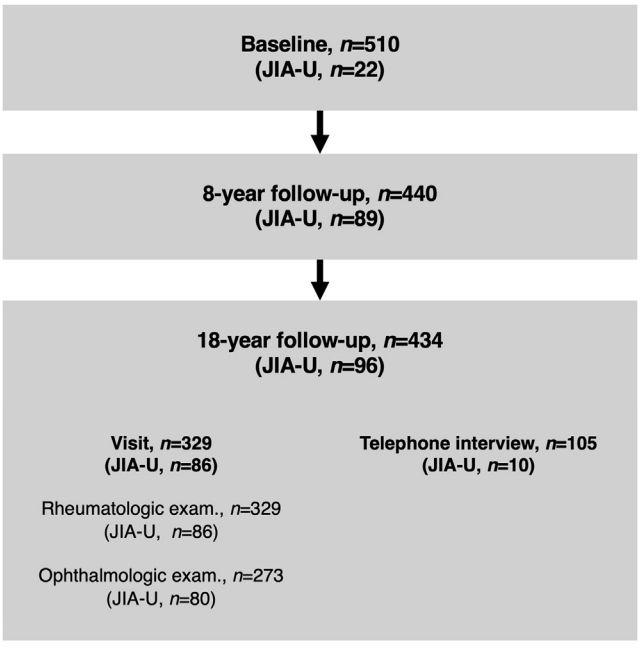

Figure 1. Flowchart of the study population throughout the observation period of 18 years. Total number of patients with juvenile idiopathic arthritis (JIA) and JIA-associated uveitis (JIA-U) at baseline, 8-year, and 18-year follow-up visits.

posterior, or pan uveitis, and as symptomatic or asymptomatic disease. The course of uveitis was defined as acute, recurrent, or chronic, as limited or persistent in duration, and as having a sudden or insidious onset.[27] The activity of uveitis in SUN grades and intraocular complications were recorded at the 18-year follow-up visit. Systemic medication was registered as previous if used in the period up to the 18-year follow-up and present if used at the 18-year visit. Systemic medication included synthetic disease-modifying antirheumatic drugs (sDMARDs) and biologic disease-modifying antirheumatic drugs (bDMARDs).

Ophthalmologic Assessment

The 18-year ophthalmologic examination included measurement of best-corrected visual acuities (BCVAs) monocular and binocular in Snellen fraction with a Snellen chart or a letter or number chart. We used the definition of visual impairment defined by the World Health Organization:[28] mild visual impairment as visual acuity (VA) <6/12, moderate visual impairment as VA <6/18, severe visual impairment as VA <6/60, and blindness as VA <3/60. Slit-lamp examination was performed for assessment of uveitis activity, which was defined as the presence of cells/mm^2 field in the anterior chamber, following the criteria of the SUN Working Group.[27] We defined uveitis course as acute if there was less than 3 months with uveitis activity and treatment, recurrent if there were recurrent episodes and at least 3 months without uveitis activity and treatment, and chronic if there was less than 3 months without uveitis activity and treatment. Information on ocular complications and ocular surgery was collected. We defined glaucoma as pathologic cupping of the optic disc or visual field defects in the presence of intraocular pressure >21 mmHg or history of glaucoma surgery. In the case of missing information in any variable, we excluded the patient from that particular assessment.

Statistical Analysis

We used medians and IQRs to describe demographics and clinical characteristics, and univariate logistic regression analysis with odds ratios (ORs) to assess baseline variables as risk factors of ocular complications in JIA-associated uveitis. Differences between groups were analyzed using Pearson's chi-square test and 2-proportion z-test for dichotomized variables, and continuous variables were analyzed using the Mann−Whitney U test. $P < 0.05$ was considered as significant. We performed a Kaplan−Meier analysis for the time interval between the onset of JIA and the diagnosis of uveitis, where the dates of uveitis diagnoses were obtained from the local screening programs. Separate Kaplan−Meier curves were constructed for patients who had uveitis-associated ocular complications at 18 years and patients without ocular complications at 18 years.

We constructed 2 heat maps. In the first, clinical characteristics were plotted in rows and eyes in columns. By using hierarchical clustering, rows and columns were ordered so that similar variables appeared next to each other, and afterward the heat map was annotated in the lower panel with ocular complications. In the second heat map, complications were plotted in rows and patients in columns. After applying hierarchical clustering, the map was annotated with previously reported risk factors for ocular complications (Fig S1).[6,21]

We did not perform imputation for missing data, and we included only patients with information on the assessed variable. Statistical analyses were performed with Stata/MP version 15 (StataCorp LP, College Station, TX) and Wolfram (Champaign, IL) Mathematica version 11.1.1.0.

Ethical Approval and Consent to Participate

Written informed consent was obtained from all patients. The medical research ethics committees and data protection authorities in the respective participating countries approved the study. The study was conducted according to the guidelines of the Declaration of Helsinki.

Results

At the 18-year follow-up, 96 (22.1%) of the 434 patients with JIA had uveitis. The cumulative incidence of JIA-U was 44 of 143 (30.8%) in Finland, 22 of 111 (19.8%) in Denmark, 19 of 103 (18.4%) in Norway, and 11 of 77 (14.3%) in Sweden. Finland had significantly more patients with JIA-U compared with the other countries in the cohort ($P = 0.002$, Pearson's chi-square).

Uveitis was detected in 89 of 440 patients (20.2%) during the first 8 years of follow-up. Additionally, 12 patients (2.8%) were diagnosed with uveitis between the 8-year[20] and 18-year follow-ups. Five patients with uveitis were lost to follow-up during this period. Of the 96 patients with uveitis at the 18-year follow-up, 80 attended the ophthalmology visit (83.3%) (Fig 1). All patients who were diagnosed with uveitis before JIA and 9 of the 12 patients diagnosed with uveitis between the 8-year and 18-year follow-ups were among the 80 patients with JIA-U examined by the ophthalmologist.

The median age at the diagnosis of uveitis was 5.8 years (IQR, 3.8−11.7 years). The age at onset of JIA was lower for patients with uveitis compared with those without uveitis ($P = 0.006$, Mann−Whitney U test). For patients developing uveitis, the median time from the onset of JIA to the diagnosis of uveitis was 1.6 years (IQR, 0.4−5.0 years). The maximum time from the onset of JIA to the diagnosis of uveitis was 17.6 years. Uveitis was diagnosed before arthritis in 8 of 96 patients (8.3%). These 8 were diagnosed with uveitis at a median of 0.3 years (IQR, 0.2−1.8 years) before the onset of JIA. The majority of patients with uveitis, 59 of 96 (61.5%), were female (Table 1).

The distribution of uveitis in the different categories of JIA was as follows: enthesitis-related arthritis in 14 of 45 patients (31.1%), RF-negative polyarthritis in 21 of 71 patients (29.6%), psoriatic arthritis in 8 of 28 patients (28.6%), extended oligoarthritis in 19 of 85 patients (22.4%), undifferentiated arthritis in 13 of 66 patients (19.7%), and persistent oligoarthritis in 21 of 119 patients (17.6%). We did not detect uveitis in any of the patients with RF-positive polyarthritis or systemic-onset JIA.

We did not find any significant differences in gender or ANA positivity among the patients with or without uveitis at the 18-year visit. Human leukocyte antigen B27 was significantly more common in patients with uveitis than without ($P = 0.005$, Pearson's chi-square) (Table 1). There was no significant difference in ANA or HLA-B27 among the patients from Finland compared with the other Nordic countries.

Clinical Presentation of Uveitis and Disease Activity

Among the 80 patients with JIA-U who attended the 18-year ophthalmology visit, 58 of 77 (75.3%) had bilateral uveitis, and 19 of 77 (24.7%) had unilateral uveitis. A total of 135 eyes in 77 patients were affected by uveitis. In 3 of the 80 examined patients, the information regarding whether the uveitis was unilateral or bilateral was missing. Anterior uveitis was found in 68 of 71 patients (95.8%). One patient had intermediate uveitis, and 2 patients had panuveitis. Thirty-eight of 75 patients (50.7%) had a chronic

Table 1. Characteristics of the Total Juvenile Idiopathic Arthritis Cohort and Patients with or without Uveitis at the 18-Year Follow-up Study

Characteristics	Total JIA Cohort n = 434	JIA without Uveitis n = 338	JIA-Associated Uveitis n = 96	P Value
Female, n (%)	297/434 (68.4)	238/338 (70.4)	59/96 (61.5)	0.096
Age at JIA onset, yrs	5.7 (2.6–9.8)	6.2 (2.9–10.1)	4.5 (1.9–8.7)	0.006
Age at uveitis diagnosis, yrs	–	–	5.8 (3.8–11.7)*	
Age at 18-yr visit, yrs	23.4 (20.8–27.1)	23.5 (20.4–27.4)	21.6 (19.1–26.1)	0.003
Follow-up time, yrs	17.6 (16.7–18.4)	17.7 (16.8–18.6)	17.4 (16.5–18.2)	0.029
ANA positive, n (%)	142/384 (37.0)	101/291 (35.0)	41/93 (44.1)	0.103
HLA-B27 positive, n (%)	93/433 (21.5)	63/337 (18.7)	30/96 (31.3)	0.005
Cumulative joint count	7.0 (3.0–13.0)	6.5 (2.0–13.0)	8.5 (4.0–14.0)	0.027
Patient PA	0.5 (0.0–3.0)†	1.0 (0.0–3.5)‡	1.0 (0.0–4.0)*	0.057
Patient GA	0.5 (0.0–2.5)†	0.5 (0.0–2.0)‡	1.0 (0.0–3.0)*	0.013
JADAS27	1.0 (0.0–4.0)†	0.5 (0.0–3.5)‡	2.0 (0.0–6.0)*	0.001
JIA categories, n (%)				
Systemic JIA	14 (3.2)	14 (3.2)	0	–
Persistent oligoarthritis	119 (27.4)	98 (29.0)	21 (21.8)	0.087
Extended oligoarthritis	85 (19.6)	66 (19.5)	19 (19.9)	0.049
RF-negative polyarthritis	71 (16.4)	50 (14.8)	21 (21.9)	0.019
RF-positive polyarthritis	6 (1.4)	6 (1.4)	0	–
Psoriatic arthritis	28 (6.5)	20 (5.9)	8 (8.3)	0.026
Enthesitis-related arthritis	45 (10.4)	31 (9.2)	14 (14.6)	0.017
Undifferentiated arthritis	66 (15.2)	54 (15.7)	13 (13.5)	0.070

ANA = antinuclear antibody; GA = global assessment; HLA = human leukocyte antigen; JADAS27 = juvenile arthritis disease activity score based on evaluation of 27 joints; JIA = juvenile idiopathic arthritis; PA = pain assessment; RF = rheumatoid factor.
Values are median interquartile range (IQR) if not otherwise specified. *P* value for comparison of JIA with and without uveitis, by Pearson's chi-square for categoric variables, and Mann–Whitney *U* test for continuous variables. Numbers assessed: *n = 89, †n = 403, and ‡n = 315.
Self-reported pain on a visual analogue scale (range 0–10). Self-reported global assessment of well-being on a visual analogue scale (range 0–10).

course of uveitis, and 28 of 75 patients (37.3%) had a recurrent course. Nine of 75 patients (12.0%) had an acute course with sudden onset and limited duration (<3 months) of the episode of uveitis activity and treatment (Table 2). Six of the 9 patients with acute course uveitis were HLA-B27 positive, and 5 patients had a HLA-B27 positive enthesitis-related arthritis.

At the 18-year follow-up visit, there were no detectable cells in the anterior chamber (SUN 0) in 59 of 78 (75.6%) of the assessed patients with uveitis. Standardization of Uveitis Nomenclature 0.5+ to 1+ was found in 18 of 78 (23.1%) and SUN 2+ in 1 of 78 (1.3%) of the examined patients with JIA-U. None of the patients had >SUN 2+. Among the 19 patients with anterior chamber cells at the visit, 13 (68.4%) had at least 1 ocular complication. A faint flare (1+) was found in 14 of 78 (17.9%), and a moderate flare (2+) was found in 4 of 78 (5.1%) of the examined patients with uveitis (Table 2).

The proportion with active JIA disease according to the provisional criteria reported by Wallace et al[25,26] for inactive disease was significantly higher in patients with JIA-U (45/86 [52.3%]) compared with those without uveitis (86/243 [35.4%]) ($P = 0.005$, Pearson's chi-square). The rate of remission without medication was lower among patients with uveitis (16/86 [18.6%]) compared with patients without uveitis (100/243 [41.2%]) ($P = 0.005$, Pearson's chi-square). The rate of remission on medication (inactive disease, including the absence of active uveitis for at least 6 continuous months, while the patient is on medication) was higher among patients with JIA-U, 14 of 86 (16.3%) compared with 23 of 243 (9.4%) for patients without uveitis, but this was not a significant difference ($P = 0.09$, Pearson's chi-square). Inactive disease but not yet fulfilling remission criteria was found in 11 of 86 (12.8%) patients with JIA-U and in 34 of 243 (14.0%) of the patients with JIA without uveitis.

Medication

At the baseline visit (median 7 months after onset of JIA), 25 of 96 (26.0%) of the patients with JIA-U were treated with synthetic disease-modifying antirheumatic drugs (sDMARDs). sDMARDs were used in 51 of 96 patients (53.1%) up to the 1-year visit (median 13 months after onset of JIA) and in 72 of 96 patients (75.0%) in the period up to the 8-year visit (median 98 months after onset of JIA). None of the patients with JIA-U were taking bDMARDs (infliximab or adalimumab) at baseline. Eight were treated with bDMARDs (infliximab, n = 7, adalimumab, n = 1) between the baseline and the 1-year visit, and 21 patients used bDMARDs (infliximab, n = 16, adalimumab, n = 5) within 8 years after onset of JIA.

Three of 8 patients with uveitis and ocular complications treated with bDMARDs within the 1-year visit were diagnosed with uveitis prior to JIA. Twelve of 21 patients treated with bDMARDs within the 8-year visit were diagnosed with uveitis during the first year after onset of JIA.

During the 18-year observation period, a total of 76 of 96 patients with uveitis (79.2%, 95% confidence interval [CI], 71.0–87.0) were treated with any sDMARDs compared with 223 of 378 patients without uveitis (59.0%, 95% CI, 54.0–64.0) ($P < 0.001$, 2-proportion *z*-test). Any bDMARDs were given to 52 of 96 patients with uveitis (54.2%, 95% CI, 44.0–64.0) and 76 of 335 patients without uveitis (22.7%, 95% CI, 18.0–27.0) ($P < 0.001$, 2-proportion *z*-test). Table S1 (available at www.aaojournal.org) shows detailed information on the different sDMARDs and bDMARDs. Among the 19 patients with active uveitis at the 18-year visit, 17 (89.5%) had been treated with sDMARDs or bDMARDs at some point during the 18-year observation period. Of the 59 patients with inactive uveitis (SUN 0) at the 18-year visit,

Table 2. Clinical Presentation of Juvenile Idiopathic Arthritis–Associated Uveitis According to the Standardization of Uveitis Nomenclature

Clinical presentation	Patients, n (%)
Uveitis localization, n = 71	
Anterior uveitis	68 (95.8)
Intermediate uveitis	1 (1.4)
Posterior uveitis	0
Pan uveitis	2 (2.8)
Uveitis symptoms, n = 76	
Mostly symptomatic	21 (27.6)
Mostly nonsymptomatic	55 (72.4)
Best judgment of onset of uveitis episodes, n = 72	
Sudden onset	14 (19.4)
Insidious onset	58 (80.6)
Best judgment of the duration of uveitis episodes, n = 71	
Limited duration (<3 months)	27 (38.0)
Persistent duration (≥3 months)	44 (62.0)
Uveitis course, n = 75	
Acute course (<3 mos with uveitis activity and treatment)	9 (12.0)
Recurrent course (≥3 mos without uveitis activity and treatment)	28 (37.3)
Chronic course (<3 mos without uveitis activity and treatment)	38 (50.7)
Anterior chamber cells at the 18-yr follow-up, n = 78	
SUN 0 (<1 cell in field)	59 (75.6)
SUN 0.5+ to 1+ (1–15 cells in field)*	18 (23.1)
SUN 2+ (16–25 cells in field)	1 (1.3)
Anterior chamber flare at the 18-yr follow-up, n = 78†	
SUN 0 (none flare)	59 (75.6)
SUN 1+ (faint flare)	14 (17.9)
SUN 2+ (moderate flare)	4 (5.1)

SUN = Standardization of Uveitis Nomenclature.
*Anterior chamber cells SUN 0.5+ to 1+ were grouped together in the study database; thus, it is not possible to divide into 2 separate groups (0.5+ and 1+).
†None of the patients had anterior chamber cells or flare SUN 3+ or SUN 4+.

50 (84.7%) had been treated with sDMARDs or bDMARDs during the observation period.

At the 18-year visit, 32 of 96 patients (33.3%) with uveitis were treated with sDMARDs compared with 55 of 338 patients (16.3%) without uveitis ($P < 0.001$, Pearson's chi-square). Biologic disease-modifying antirheumatic drugs were given to 34 of 96 (35.4%) of the patients with uveitis at the time of the visit and 50 of 338 (14.8%) of the patients without uveitis ($P < 0.001$, Pearson's chi-square). The use of any disease-modifying antirheumatic drugs (DMARDs) was significantly more common among patients with uveitis (47/96, 49.0%) at the 18-year visit compared with patients without uveitis (78/338, 23.1%) ($P < 0.001$, Pearson's chi-square) (Table S1). In 33.7% of the patients with JIA-U uveitis was reported to be the main reason for ongoing systemic immunomodulating treatment. Local treatment with any eyedrops were used by 29 of 92 (31.5%) of patients with JIA-U at the visit. Among the 19 patients with active uveitis at the visit, 14 (73.7%) were using sDMARDs or bDMARDs. Of the 59 patients with uveitis without active uveitis (SUN 0) at the 18-year visit, 29 (49.2%) had ongoing treatment with sDMARDs or bDMARDs.

Among the patients who had registered ocular complications at the 18-year visit, 6 of 31 (19.4%) used bDMARDs within 1 year of follow-up compared with 1 of 59 (1.7%) of the patients with uveitis who did not develop complications. This number was 13 of 31 (41.9%) and 5 of 59 (8.5%), respectively, within 8 years of follow-up. Of the patients who had ocular complications at the 18-year visit, 25 of 31 (80.6%) had used bDMARDs at some point during the 18-year observation period compared with 27 of 59 (45.8%) of the patients with uveitis who did not develop complications.

Ocular Complications and Visual Acuity

We found 1 or more ocular complications in 31 of 80 patients (38.8%) with uveitis attending the 18-year ophthalmology visit. Forty-two of 135 (31.1%) uveitis eyes were affected by at least 1 complication (Table 3). The most frequent ocular complications were cataract and glaucoma. Cataract was found in 25 of 80 (31.3%), of whom 21 of 25 (84.0%) had undergone cataract surgery. Among the patients who had cataract surgery, 16 patients also had glaucoma, 10 had synechiae, 8 had macular edema, 6 had band keratopathy, and 3 had epiretinal membrane, hypotony, and phthisis. Glaucoma occurred in 22 of 80 patients (27.5%), of whom 18 of 22 (82.0%) had undergone glaucoma surgery. Fifteen patients underwent surgery for both cataract and glaucoma. Four patients presented with an ocular complication at the baseline visit, 20 patients developed at least 1 complication during the first 8 years of follow-up, and 7 of the previously unaffected patients developed a uveitis-related complication between the 8-year and 18-year follow-up visits.

Eight patients were diagnosed with uveitis before JIA. All of them developed a cataract, and 7 were also diagnosed with glaucoma. In contrast, all patients with uveitis without ocular complications had their uveitis diagnosed after the onset of JIA. The timepoint for uveitis diagnosis for patients without complications was spread throughout the observation period, as presented in the Kaplan–Meier plots (Fig 2). An association was found between ocular complications and the starting point of uveitis with a median time of 0.4 years (IQR, 0.1–1.1 years) between the onset of JIA and the diagnosis of uveitis for the patients who developed ocular complications and 1.9 years (IQR, 0.5–4.1 years) for the patients who did not develop uveitis-related complications ($P < 0.001$, Mann–Whitney U test). Complications were most frequent among patients with anterior uveitis (28/68; 41.2%), asymptomatic uveitis (24/55; 43.6%), and a chronic course (23/38; 60.5%) or insidious onset of uveitis (27/58; 46.6%) (Fig 3).

In our cohort, 87.5% had been diagnosed with uveitis within 8 years after the onset of JIA (Fig 2). Among the 12 patients with onset of uveitis between the 8-year and 18-year follow-ups, only 1 patient developed uveitis-related complications. The age at uveitis diagnosis was available for 6 of the 12 patients (median age 22.9 years; IQR, 17.4–26.7 years). Four patients had persistent oligoarthritis, 2 patients had extended oligoarthritis, 1 patient had RF-negative polyarthritis, 1 patient had psoriatic arthritis, 1 patient had enthesitis-related arthritis, and 3 patients had undifferentiated arthritis. Nine patients were male, and 5 patients were HLA-B27 positive. Information on the clinical presentation of the uveitis was available for 9 of the 12 patients. Four patients had acute uveitis, 3 patients had recurrent uveitis, and 2 patients had chronic uveitis. Five had symptomatic uveitis.

We found worst-eye visual impairment with monocular BCVA <6/12 in 8 of 80 patients (10.0%) with uveitis examined by the ophthalmologist at the 18-year follow-up visit. Four of these 8 patients had BCVA >6/12 when tested with both eyes open, and thus binocular BCVA <6/12 in 4 of 80 patients (5.0%). Two patients had no light perception in both eyes, and 3 patients had no

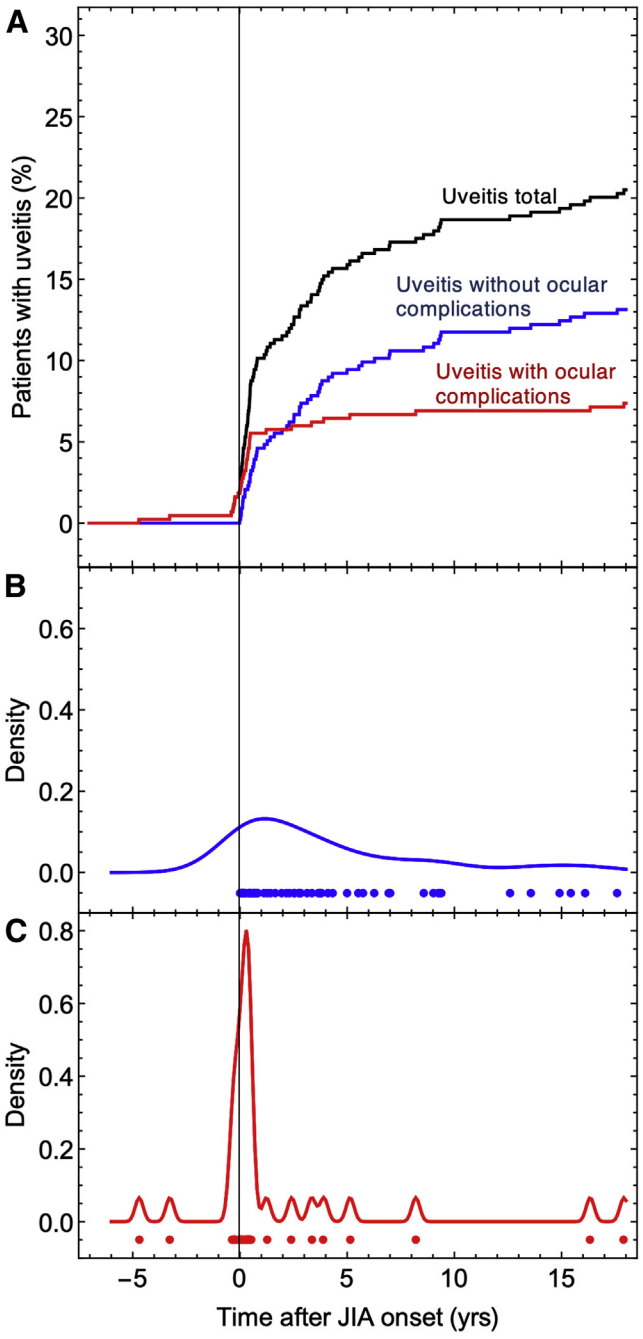

Figure 2. Time for diagnosis of uveitis during the 18-year observation period in the Nordic juvenile idiopathic arthritis (JIA) cohort for the patients who developed and did not develop ocular complications. **A,** Kaplan–Meier curve for the time points for diagnosis of uveitis in the total JIA cohort (**black curve**), patients with uveitis who did not develop ocular complications (**blue curve**), and patients with uveitis who developed ocular complications (**red curve**). Ocular complications were assessed at the 18-year follow-up, and time points for diagnosis of uveitis were collected from ophthalmological screening. **B,** Density histogram for the onset time points of uveitis among the patients who remain complication free, with each **blue dot** representing 1 uveitis case. **C,** Density histogram for the onset time points of uveitis with ocular complications, with each **red dot** representing 1 uveitis case.

light perception in 1 eye (Table 3). Binocular BCVA <6/12 was found in 4 of the 21 patients who had undergone cataract surgery, and 2 of the patients who were blind at the 18-year visit had both undergone cataract surgery.

Risk Factors Associated with Ocular Complications

A short time interval between the onset of JIA and diagnosis of uveitis, including both positive and negative values, was a significant risk factor for at least 1 complication related to uveitis in univariate logistic regression (OR, 1.4; 95% CI, 1.1–1.8). Another significant risk factor for ocular complications was ANA positivity (OR, 3.0; 95% CI, 1.2–7.7). All 8 patients with a diagnosis of uveitis before the onset of JIA developed cataract, and the risk of glaucoma was high when uveitis was diagnosed before JIA (OR, 31.5; 95% CI, 3.6–274). We did not find any significant predictors of ocular complications in analyses of gender, age at diagnosis of uveitis, age at onset of JIA, different JIA categories, or uveitis development 8 to 18 years after onset of JIA. The distribution of ocular complications relative to these assessed variables is presented in the heat map in Fig S1 (available at www.aaojournal.org).

Discussion

In our Nordic JIA cohort, enrolled from pediatric rheumatology practices, the cumulative incidence of uveitis was 22.1% during the 18 years of 434 prospectively followed patients with JIA. Uveitis-related complications occurred in 38.8%, and decreased VA <6/12 occurred in 12 of 135 eyes (8.9%) with JIA-U.

The reported prevalence of uveitis in JIA varies considerably between different studies and populations.[4,6,9,14,15,29-35] Several studies presenting uveitis prevalence are retrospective or registry-based, with a broad range of follow-up times, making it difficult to compare results. Other reasons for the variability in reported uveitis prevalence are differences in what is actually reported, such as point prevalence or period prevalence, study design, cohort compositions such as referral cohorts from which the patients are recruited, and genetic differences between populations. Some of the highest prevalence is reported from the Nordic countries,[3,4,20] and it has been suggested that children with European descent, especially with Nordic descent, have a higher risk of uveitis in JIA.[3,36] In other population-based studies from Spain, Czech Republic, Germany, and Estonia, the cumulative incidence of uveitis varied between 4.0% and 12.0%, but the follow-up period in these studies were shorter than in our study.[31-35]

The overall recently reported prevalence of uveitis appears to be decreasing compared with the 1990s and 2000s.[37,38] Kotaniemi et al[38] reported a decrease in the cumulative incidence of uveitis in JIA from 25.0% to 18.0% in 2 separate cohorts collected in 1990 to 1993 and 2000 to 2003. Likewise, Tappeiner et al[37] reported a decrease in uveitis from 33.6% to 23.9% between 2002 and 2013. In their study, the use of DMARDs was more common in the more recent cohort. In a later publication, they reported that methotrexate treatment started during

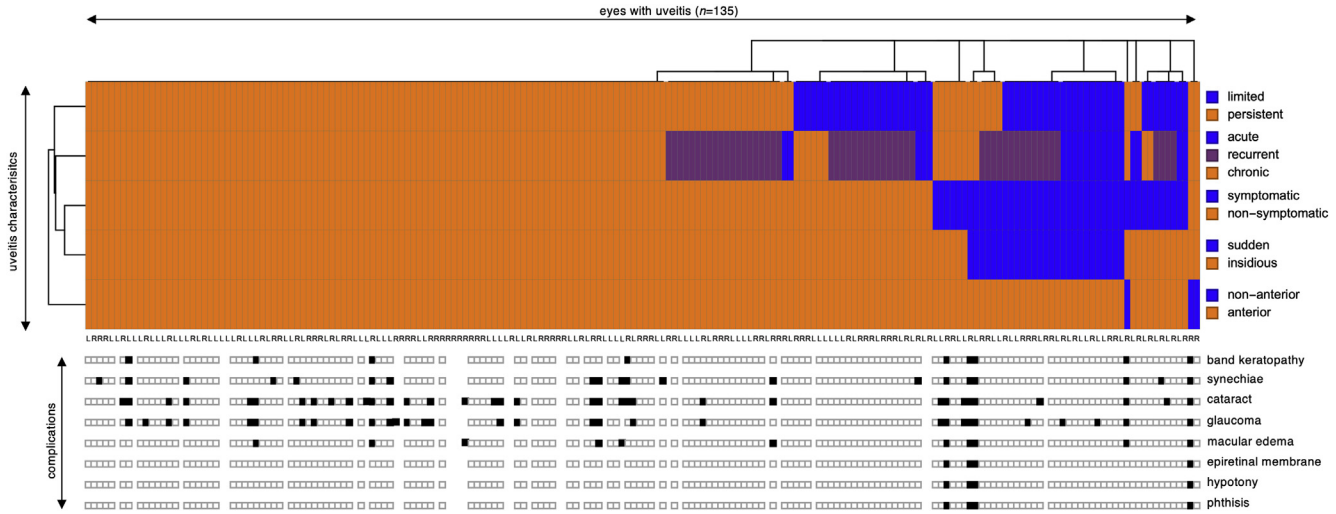

Figure 3. Heat map visualization of uveitis clinical characteristics per eye according to ocular complications. Uveitis clinical characteristics (rows) of each eye (columns) are ordered so that similar variables appear next to each other. The heat map is annotated (lower panel) with ocular complications. Uveitis characteristics; there is a cluster in orange to the left in the heat map consisting of eyes with persistent, chronic, nonsymptomatic, insidious, and anterior uveitis. Most complications occur for eyes that belong to this group. The blue color consists of limited, acute, symptomatic, sudden, and nonanterior (intermediate or pan) localization of the uveitis. The purple color is eyes with recurrent uveitis course. Ocular complications; **black square** represents each 1 eye with an ocular complication. L = left eye; R = right eye.

the first year after the onset of JIA was associated with a lowered risk of uveitis and that a combination treatment of methotrexate and anti-tumor necrosis factor was associated with an even lower risk of JIA-U.[39] In our study, the occurrence of uveitis remains high. This might partly be explained by the slightly less common sDMARD treatment in our study at the last study visit compared with the study by Tappeiner et al[37] and by the fact that our patients had onset of JIA in 1997–2000 when treatment with biologics was less common. Synthetic disease-modifying antirheumatic drug treatment was ongoing at 18 years of follow-up in our study in 25.7% of patients with JIA with or without uveitis, compared with 47.2% in the study by Tappeiner et al.[37] Treatment with bDMARDs was ongoing at the 18-year visit in our study in 24.9% of patients, compared with 21.8% of patients in the study by Tappeiner et al.[37] The difference in the rate of sDMARD treatment may be explained by the longer follow-up time in our study. Remission of uveitis (in terms of no detectable cells in the anterior chamber and no

Table 3. Ocular Complications in Juvenile Idiopathic Arthritis–Associated Uveitis among Patients Examined by an Ophthalmologist at the 18-Year Follow-up Visit

	Patients, n (%) n = 80	**Uveitis Eyes, n (%) n = 135**
Ocular complications		
At least 1 ocular complication	31 (38.8)	42 (31.1)
Cataract	25 (31.3)	32 (23.7)
Glaucoma	22 (27.5)	30 (22.2)
Synechiae	14 (17.5)	19 (14.1)
Macular edema	8 (10.0)	9 (6.7)
Band keratopathy	7 (8.8)	9 (6.7)
Epiretinal membrane	3 (3.8)	4 (3.0)
Hypotony	3 (3.8)	4 (3.0)
Phthisis	3 (3.8)	4 (3.0)
BCVA, binocular and monocular worst eye		
Mild visual impairment 6/18 ≤ BCVA <6/12	1 (1.3),* 2 (2.5)†	3 (2.2)
Moderate visual impairment 6/60 ≤ BCVA <6/18	1 (1.3),* 2 (2.5)†	3 (2.2)
Severe visual impairment 3/60 ≤ BCVA <6/60	0,* 1 (1.3)†	1 (0.7)
Blindness <3/60‡	2 (2.5),* 3 (3.8)†	5 (3.7)

BCVA = best-corrected visual acuity.
*Binocular.
†Monocular worst eye.
‡One patient with blindness had trauma to the eye.

flare) at the 18-year visit was more common among our patients (75.6%) compared with 42.0% in the study by Kotaniemi et al[38] and 65.3% by Tappeiner et al.[37]

In our study, the median time from the onset of JIA to the diagnosis of uveitis was 1.6 years, whereas some previous studies report a mean time of 1.1 to 1.8 years and a median time of 5.5 months.[4,5,9] Moreover, among study participants diagnosed with uveitis, 8.3% developed uveitis before JIA, and 80.0% had uveitis within 4 years after the onset of JIA. Uveitis reportedly develops before JIA in 3% to 7%[3,30] and during the first 4 years after onset of JIA in up to 91%.[4,5,9] These discrepancies with other studies may be explained by different definitions of the onset date of JIA. In our study, this was not the date of the physician's diagnosis of arthritis, but the date of the first evident clinical sign of arthritis, such as an obvious swelling or limp, even if reported the first time by the patients/parents and only later confirmed by a physician.

In contrast to most recent studies suggesting that uveitis rarely develops more than 7 years after the onset of JIA,[4,5,9] 12.5% of the patients with JIA-U in our cohort had onset of uveitis after the 8-year follow-up. Our results are in line with those of Zak et al,[14] who reported an increase in uveitis occurrence and complications from 1979 to 1980 to 1996 to 1997. Our study suggests that continuing the uveitis screening in patients with JIA after 7 to 8 years of diagnosis might be beneficial because approximately half of the late uveitis cases were asymptomatic. A lack of previous long-term prospective cohort studies may have led to an underestimation of the number of late uveitis cases and the overall cumulative incidence of uveitis.[5,13] Other prospective, long-term follow-up studies are needed to better assess the risk of late onset of uveitis in JIA.

In our study, 38.8% of the patients with JIA-U developed at least 1 ocular complication during the 18 years of observation. The rate of complications is lower than in previous reports 2 or more decades ago.[15,16,40] However, complications are more prevalent in our study compared with other recent studies from Europe.[37-39] Kotaniemi et al[38] presented an overall ocular complication rate of 21.0% in 2000−2003. The German prospective study by Tappeiner et al[37] found a decrease in ocular complications from 33.6% to 23.9% in the period between 2002 and 2013. Our high prevalence of complications might be explained mainly by the long follow-up because 7 of 31 (22.6%) of the ocular complications occurred in the period between 8 and 18 years of follow-up.[15,16,37,38,40] Earlier studies have shown that both treatment with synthetic and biologic DMARDs, and low uveitis activity are associated with lower occurrence of poor vision and ocular complications.[11,18,19,39] The comparatively high complication prevalence in our study may be explained partly by the recruitment period in the era before the early start of bDMARDs was an established treatment strategy. In our study, complications are more common in the group of patients who are diagnosed with uveitis before or shortly after onset of JIA. For patients who develop complications, the use of bDMARDs increased from 16% to 77% from 1 year to 18 years after the onset of JIA. However, most of our patients (75.6%) had quiescence of uveitis with no detectable cells in the anterior chamber at the 18-year visit.

In general, comparisons of studies on uveitis-related complications are challenging because of selection bias. Studies with shorter follow-up time may underreport the rate of complications, whereas studies from retrospective tertiary centers may report a higher rate of complications because they include the more severe uveitis cases. Cohorts selected from tertiary ophthalmology clinics may have more ocular complications than those collected from pediatric rheumatology centers. On the other hand, in many Nordic countries, tertiary pediatric rheumatology centers and tertiary ophthalmology clinics are often located at the same hospital, meaning that the selection of patients will not differ. In short, early introduction of DMARDs as a strategy for treatment of arthritis seems to reduce both the risk of uveitis and its complications.[39] Well-established ophthalmologic screening programs[9,10] may also contribute to the reduced ocular complications, presumably by earlier diagnosis before complications have occurred and timely treatment of the ocular inflammation. We did not find a significant association between the development of ocular complications and male gender or young age at the onset of uveitis.[21,41] However, we confirmed that developing uveitis before JIA, having a short duration between onset of JIA and diagnosis of uveitis, and having ANA positivity are risk factors for developing ocular complications. Notably, all patients who developed uveitis before JIA had ocular complications.

Long-term poor visual outcome has been associated with a diagnosis of uveitis before JIA, short interval between the diagnosis of arthritis and uveitis, high-grade uveal inflammation, and the presence of ocular complications early in the disease course and history of intraocular surgery.[6,11,13,21] Despite a relatively high rate of complications, the proportion of patients with unfavorable visual outcome in our study was lower or in line with previous reports.[2,4,17,40] Haasnoot et al[17] found in their study from 2016 that 4% had a visual impairment or were legally blind (≤20/200) at the age of 18 years and that 33% had at least 1 eye with VA ≤20/50. In our study, 2.5% of the patients with JIA-U were blind in both eyes and 3.8% were blind in the worst eye, and 5.0% in our study had a binocular VA <6/12. Kotaniemi et al[4] found that 3 of 104 children (2.9%) with JIA-U had a VA ≤20/60 after a mean follow-up time of 4.5 years, whereas we found a BCVA <6/18 for both eyes in 3 patients (3.8%) and in the worst eye for 6 patients (7.5%) after a median follow-up time of 17.6 years.

Study Strengths and Limitations

There are several strengths of this study. To our knowledge, this is one of few long-term prospective population-based studies on JIA-associated uveitis. This means that our results are generalizable to patients in the population with JIA, not just the patients with more severe JIA-U who are usually managed at tertiary ophthalmology centers. Despite the long observation period of 18 years, the proportion of patients lost to follow-up is relatively small, and we have

reliable ophthalmologic data for 83% of the patients with uveitis 18 years after JIA onset. The study is conducted according to the International League of Association for Rheumatology classification, the American College of Rheumatology disease activity criteria, and the SUN Working Group criteria, enabling comparison with other studies in the field. A limitation of the study is that we do not have information on the precise timepoints when patients started topical corticosteroids, the treatment starting point, or the indication (arthritis or uveitis) for treatment with systemic corticosteroids or DMARDs. Also, the inclusion period of the study was at the beginning of the biologic era. Thus, it may not reflect the effect of early implementation of immunomodulating treatment on uveitis outcomes. At the 18-year visit, 15% were lost to follow-up, and because patients with more severe disease are likely to attend follow-ups, this may lead to biases and an overestimation of the cumulative uveitis incidence. For instance, the cumulative incidence of uveitis may be 96 of 510 (18.8%) rather than 96 of 434 (22.1%) if all uveitis cases attended the 18-year follow-up. On the other hand, we may also have lost some late diagnosed uveitis cases, which implies that the true cumulative incidence might be somewhere between those figures. There is some missing information for specific uveitis variables, reducing the total number of assessable patients. The relatively small sample size in subgroups may limit identification of relevant risk factors for complications. Future work should focus on longer follow-up and developing prediction rules for prediction of severe uveitis course to enable targeted screening and treatment strategies adapted to high-risk subgroups.

In conclusion, this unique long-term prospective population-based study found that a considerable proportion of patients with uveitis still develop sight-threatening complications in young adulthood. The patients at highest risk of complications are those who develop uveitis before JIA or closely after the onset of JIA. Screening by an ophthalmologist must start urgently in all children when JIA is suspected and diagnosed. Our study shows that uveitis may develop up to 18 years after the onset of JIA. We suggest screening to be extended for a longer period than recommended in most established screening programs to identify late-onset uveitis.[9,10,12] The high prevalence of uveitis and ocular complications emphasizes the need for interdisciplinary care, with early consideration of systemic immunosuppressive treatment. Ophthalmologists and pediatric rheumatologists should collaborate closely to minimize the risk of visual impairment with potentially severe implications for quality of life in young adults with JIA.

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Abbreviations and Acronyms:
ANA = antinuclear antibody; **BCVA** = best-corrected visual acuity; **bDMARD** = biologic disease-modifying antirheumatic drug; **CI** = confidence interval; **DMARD** = disease-modifying antirheumatic drug; **HLA** = human leukocyte antigen; **IQR** = interquartile range; **JIA** = juvenile idiopathic arthritis; **JIA-U** = juvenile idiopathic arthritis associated uveitis; **OR** = odds ratio; **RF** = rheumatoid factor; **sDMARD** = synthetic disease-modifying antirheumatic drug; **SUN** = Standardization of Uveitis Nomenclature; **VA** = visual acuity.

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