Clinical Epidemiological Studies for Improving Patient Care in Juvenile Idiopathic Arthritis

Joeri William van Straalen

Stellingen

Behorende bij het proefschrift:

"Clinical Epidemiological Studies for Improving Patient Care in Juvenile Idiopathic Arthritis"

1. Clinical decision making in JIA can be supported by validated prediction tools.
This thesis

2. Collaboration in JIA research is beneficial and can be accomplished without the exchange of individual patient data.
This thesis

3. Real-world evidence is equally important as evidence from clinical trials.
This thesis

4. Clinicians should always consider more frequent ophthalmologic screening for uveitis in JIA patients after MTX discontinuation.
This thesis

5. Remote monitoring of disease activity is a safe and feasible approach for reducing the number of hospital visits in JIA patients with inactive disease, saving time and costs for both patients, their parents and hospitals.
This thesis

6. It's easy to lie with statistics, but it's hard to tell the truth without them.
Charles Wheelan

7. The pursuit of science is a never-ending journey into the unknown, fueled by curiosity and guided by reason.
Neil Armstrong

8. Science investigates; religion interprets. Science gives man knowledge, which is power; religion gives man wisdom, which is control. Science deals mainly with facts; religion deals mainly with values. The two are not rivals. They are complementary.
Dr. Martin Luther King Jr.

9. The greatest wealth is health.
Virgil

10. Toeval is logisch.
Johan Cruijff

Joeri William van Straalen
Utrecht, 12 oktober 2023

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Clinical Epidemiological Studies for Improving Patient Care in Juvenile Idiopathic Arthritis
ISBN/EAN: 978-94-6469-508-3
DOI: https://doi.org/10.33540/1824

Cover design, lay-out and printing: ProefschriftMaken
The research described in this thesis was financially supported by FOREUM Foundation for Research in Rheumatology.

Clinical Epidemiological Studies

for Improving Patient Care in Juvenile Idiopathic Arthritis

Klinisch epidemiologische studies
ter verbetering van de patiëntenzorg bij jeugdreuma
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

donderdag 12 oktober 2023 des middags te 4.15 uur

door

Joeri William van Straalen

geboren op 30 januari 1995
te Hoorn

Promotor:	Prof. dr. N.M. Wulffraat
Copromotoren:	Dr. S. de Roock Dr. J.F. Swart
Beoordelingscommissie:	Prof. dr. D.E. Grobbee (voorzitter) Prof. dr. L.J. Bont Prof. dr. E.A.M. Sanders Prof. dr. A.V. Ramanan Dr. J.M. van den Berg

Voor mijn ouders.

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1

Clinical epidemiology and juvenile idiopathic arthritis

CLINICAL EPIDEMIOLOGY AND JUVENILE IDIOPATHIC ARTHRITIS

Clinical epidemiology

Epidemiology is the study of how often diseases and health-related states occur in different groups of people and why[1]. It is traditionally applied in the area of public health and infectious diseases, but it can also be extended to other fields such as veterinary medicine (veterinary epidemiology) and pharmacology (pharmacoepidemiology). Clinical epidemiology is the practice of applying epidemiological methods to questions relevant for patient care[2]. Clinical epidemiological research should therefore reflect the actual clinical practice in terms of study design, presentation and utilization of results. Broadly, this field can be separated into four categories: 1) diagnostic research which focusses on distinguishing patients with a disease of interest from patients without this disease, 2) etiologic research which aims to identify valid causal factors of clinical outcomes of interest, 3) prognostic research which aims to predict a specific course of a disease, and 4) therapeutic or intervention research which assesses the effect of an intervention on clinical outcomes. These major categories of clinical epidemiological research can be summarized in the DEPTh model (Table 1). This model can be used to design and understand clinical research, but also to recognize clinical problems in daily practice and search for evidence to deal with these[2].

Table 1. DEPTh model for main categories of clinical epidemiological research.

Type of research question	Descriptive/ causal	Aim (clinical challenge)	Relevance
Diagnostic research	Descriptive	To predict the probability of presence of target disease from clinical and nonclinical profile	Relevance for patient and physician to establish diagnosis and guide management
Etiologic research	Causal	To causally explain occurrence of target disease from determinant	Research relevance, may indicate means of prevention and causal intervention
Prognostic research	Descriptive	To predict the course of disease from clinical and nonclinical profile	Relevance for patient and physician to learn about the future and guide management
Therapeutic/ intervention research	Causal and descriptive	1. To causally explain the course of disease as influenced by treatment 2. To predict the course of disease given treatment (options) and clinical and nonclinical profile	1. Relevance for research and drug development/ registration 2. Relevance for patient and physician to decide on optimal treatment

From: *Grobbee DE & Hoes AW. Clinical Epidemiology: Principles, Methods, and Applications for Clinical Research, Second Edition. Jones & Bartlett Publishers; 2014.*

In general, there are four main study designs for data-collection in epidemiological research: 1) cross-sectional studies which provide a snap-shot of a study population by collecting exposures and outcomes at the same time, 2) case-control studies in which study groups are identified based on the outcome after which exposures are

retrospectively collected, 3) cohort studies in which study groups are identified based on exposure (such as a disease) after which outcomes are measured during follow-up and 4) randomized controlled trials (RCTs) or clinical trials which assign study participants to one or more interventions of interest after which outcomes are measured during follow-up[2,3]. While the latter design actively intervenes in the natural course or routine care of a study participant, the first three designs are merely observational, which increases generalizability of study results but often poses a challenge for inferring causality. And while the latter two designs measure exposures and outcomes in the total study cohort (census), the first two designs (might) measure exposures and outcomes in just a sample of the total study cohort. This can be a valid and efficient procedure, but there is a risk of selecting a biased sample. As can be seen, each study design has its relative strengths and weaknesses in providing answers to specific (clinical) research questions (Table 2).

Table 2. Characteristics of main study designs in epidemiological research.

Descriptor	Cross-sectional	Case-control	Cohort	RCT/clinical trial
Time between exposure and outcome measurement	No	Yes	Yes	Yes
Census or sampling	Can be both	Sampling	Census	Census
Intervention	No	No	No	Yes
Main strengths	Quick and cheap, suitable for diagnostic research	Efficient, suitable for rare outcomes	Suitable for rare exposures, real-world evidence	Suitable for causal research, straightforward analysis
Main limitations	No causal inference, risk of poor timing of measurements	Risk of selection bias, no absolute risk estimates	Costly and time consuming, risk of confounding	Costly and time-consuming, poor generalizability

Adapted from: *Grobbee DE & Hoes AW. Clinical Epidemiology: Principles, Methods, and Applications for Clinical Research, Second Edition. Jones & Bartlett Publishers; 2014.* RCT = randomized controlled trial

Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) is defined as arthritis of unknown cause persisting for more than six weeks before the age of 16[4–6]. The International League of Associations for Rheumatology (ILAR) has identified seven categories of JIA with distinct clinical and laboratory features[7] (Table 3), although an improved classification system is under development[8]. Roughly one in a thousand children worldwide suffers from this chronic condition, making it the commonest form of paediatric onset rheumatic disease[9]. As with many autoimmune diseases, the cause of JIA is unknown, but it is believed to be a combination of environmental exposures in genetically susceptible individuals[4]. This hypothesis is supported by varying prevalence rates of JIA categories across the world[10] and evidence that relatives of children with JIA have a higher prevalence of certain

autoimmune diseases[11]. JIA patients present with symptoms such as pain, fatigue and impaired physical functioning, which overlap with other inflammatory disorders or non-inflammatory chronic musculoskeletal pain syndrome (CMPS), an even more common diagnosis in paediatric rheumatology[12–15]. A diagnosis of JIA is furthermore supported by morning stiffness, fever (in case of systemic arthritis), a family history of autoimmune disease and joint swelling upon physical examination.

Table 3. Characteristics of different JIA categories in order of prevalence.

JIA category	% of JIA	Onset	Typical clinical characteristics
Oligoarthritis	27-56%	Early childhood, female predominance	Asymmetric arthritis in <5 large joints, ANA positive, risk of chronic uveitis
RF negative polyarthritis	11-28%	Female predominance	Arthritis in ≥5 large and small joints, RF negative
Undifferentiated arthritis	11-21%	Heterogeneous	Heterogeneous
Systemic arthritis	4-17%	No gender predominance	Spiking fever, rash, organomegaly, serositis, risk of MAS
Enthesitis-related arthritis	3-11%	Late childhood, male predominance	Spondyloarthritis, HLA-B27 positive, familial autoimmune disease, risk of acute uveitis
Psoriatic arthritis	2-11%	Female predominance	Psoriasis, nail pitting, dactylitis, ANA positive, HLA-B27 positive, familial autoimmune disease
RF positive polyarthritis	2-7%	Late childhood, female predominance	Arthritis in ≥5 small joints, RF positive

Adapted from: *Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet. 2007;369(9563):767-778. doi:10.1016/S0140-6736(07)60363-8.* ANA = antinuclear antibodies; HLA = human leucocyte antigen; JIA = juvenile idiopathic arthritis; MAS = macrophage activation syndrome; RF = rheumatoid factor

Following a treat-to-target approach[16], the main aim of JIA treatment is to reduce disease activity. Commonly used immunosuppressive drugs are non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular as well as systemic corticosteroids, conventional synthetic and biological disease-modifying antirheumatic drugs (DMARDs)[17]. These drugs are usually prescribed in a step-up strategy and trial and error approach, taking into account the JIA category, disease activity and response to treatment[4,9]. A commonly used disease activity measure in the treat-to-target strategy for JIA is the clinical Juvenile Arthritis Disease Activity Score (cJADAS), which consists of a physician global assessment of disease activity (PGA), patient/parent assessment of well-being and count of the number of joints with active inflammation[18]. Because of immunosuppressive therapy, JIA patients are at an increased risk of infections[19,20] and there are concerns that vaccines are less safe and effective.

Nevertheless, due to developments in the treatment of JIA over the last two decades such as the introduction and large scale use of biological DMARDs, clinical remission has become a realistic target for the majority of patients diagnosed with JIA[21]. Still, the disease

can persist into adulthood and has the potential to inflict permanent articular and extra-articular damage. Children with JIA furthermore suffer from a decreased health-related quality of life (HRQOL) compared to healthy peers[4,22].

In addition, many patients suffer from comorbidities (defined as any active, past or transient, distinct additional illness), which complicate the therapeutic approach to JIA[23]. These comorbidities might be unrelated to JIA, related to a common underlying etiological pathway (uveitis, macrophage activation syndrome (MAS)) or related to treatment (opportunistic infections, malignancies)[24], as stated earlier. Examples of relatively common comorbidities in JIA are uveitis, psoriasis, autoimmune thyroid disease (AITD), inflammatory bowel disease (IBD) and type 1 diabetes mellitus[25–28]. However, contrary to adult rheumatoid arthritis (RA), the burden of comorbidity in JIA is largely unknown.

JIA-associated uveitis

Uveitis is the most common comorbidity in JIA, affecting roughly one in every six JIA patients[29–31]. This condition involves inflammation of the uveal components of the eye, which comprise the iris, choroid and retina[25,32]. Broadly, two types of uveitis can be distinguished: chronic anterior uveitis and acute anterior uveitis. Acute anterior uveitis presents with evident symptoms such as unilateral eye pain and redness and mainly affects human leucocyte antigen (HLA)-B27 positive male patients with enthesitis-related arthritis (ERA). Chronic uveitis on the other hand is often bilateral and clinically silent. Chronic uveitis is more prevalent and often observed in young, female and antinuclear antibodies (ANA) positive oligoarthritis patients[25,32]. If not treated in a timely manner, JIA-associated uveitis (both acute and chronic) can lead to significant visual impairment, including glaucoma, cataracts and synechiae[33].

For this reason, several screening guidelines for JIA-associated chronic uveitis exist[30,32–34]. This screening is performed by an ophthalmologist upon slit lamp examination and screening frequencies are based on the aforementioned risk factors for chronic uveitis (Table 4). Uveitis most often develops in the first four years after arthritis onset, but may occasionally appear up to ten years thereafter. Hence, screening should be initiated immediately after JIA diagnosis and must be continued for seven years[30]. Current screening guidelines only categorize patients into a "high", "low" or "intermediate" risk group[35]. Therefore, screening for JIA-associated uveitis could be improved by individualized risks. If uveitis is diagnosed in a patient with JIA, treatment includes topical glucocorticoids and if needed systemic therapy with methotrexate (MTX) or MTX combined with adalimumab (ADA)[33,36–38]. It is not known if drug therapy for arthritis also has a preventive effect on the occurrence of uveitis in JIA. Some evidence indicates a protective effect for MTX and ADA[39–43], but this effect should be confirmed in further studies.

Table 4. Heiligenhaus modifications of the American Section of Rheumatology and Ophthalmology guidelines for the routine screening for uveitis in JIA patients.

JIA subgroup	ANA	Age at JIA onset (yrs)	JIA duration (yrs)	Recommended screening intervals (months)
OA, RF–PA, PsA, AA	+	≤6	≤4	3
OA, RF–PA, PsA, AA	+	≤6	>4	6
OA, RF–PA, PsA, AA	+	≤6	≥7	12
OA, RF–PA, PsA, AA	+	>6	≤2	6
OA, RF–PA, PsA, AA	+	>6	>2	12
OA, RF–PA, PsA, AA	-	≤6	≤4	6
OA, RF–PA, PsA, AA	-	≤6	>4	12
OA, RF–PA, PsA, AA	-	>6	n.a.	12
ERA	n.a.	n.a.	n.a.	12
RF+PA, Sys A	n.a.	n.a.	n.a.	12
Patients with uveitis	n.a.	n.a.	n.a.	According to uveitis course

From: *Heiligenhaus A, Niewerth M, Ganser G, Heinz C, Minden K; German Uveitis in Childhood Study Group. Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nation-wide study in Germany: suggested modification of the current screening guidelines. Rheumatology (Oxford). 2007;46(6):1015-1019. doi:10.1093/rheumatology/kem053.* AA = other arthritis; ERA = enthesitis-related arthritis; JIA = juvenile idiopathic arthritis; n.a. = not applicable; OA = oligoarthritis; PsA = psoriatic arthritis; RF-PA = rheumatoid factor negative polyarthritis; RF+PA = rheumatoid factor positive polyarthritis; Sys A = systemic arthritis

Observational data collection in JIA

After the introduction of biological DMARDs for the management of JIA, several national and international registries have been set up with the aim of capturing long-term observational data from routine hospital visits on drug efficacy, adverse events and patient-reported outcome measures (PROMs)[44]. Examples include the United Kingdom "Biologics for Children with Rheumatic Diseases" (BCRD) study[45], the German "Biologics in Paediatric Rheumatology Registry" (BiKeR)[46], the United States and Canada "Childhood Arthritis and Rheumatology Research Alliance" (CARRA) registry[47] and the international "Pharmacovigilance in JIA patients treated with biologic agents and/or MTX" (Pharmachild) registry[48]. The latter is the largest JIA registry worldwide and currently includes >9,000 patients who are treated in 85 mainly tertiary care centres belonging to the Paediatric Rheumatology International Trials Organisation (PRINTO) from 31 countries around the world (Figure 1). Pharmachild collects demographic, clinical and laboratory data, information on drug exposure and adverse events and Juvenile Arthritis Multidimensional Assessment Reports (JAMARs)[44]. The JAMAR assesses PROMs in JIA, including functional status, pain, disease activity, HRQOL, well-being and satisfaction with disease status[49], and has been validated in 54 languages[50]. PROMs are an essential component in a holistic treat-to-target approach to the care of JIA patients[16,51], since disease activity does not always

directly translate to patient satisfaction. Furthermore, these measures have the potential to be used as input for clinical practice, such as treat-to-target and home-monitoring for disease activity. Note that fatigue is not included in the set of outcome variables of JIA, in spite of the clinical burden it can pose.

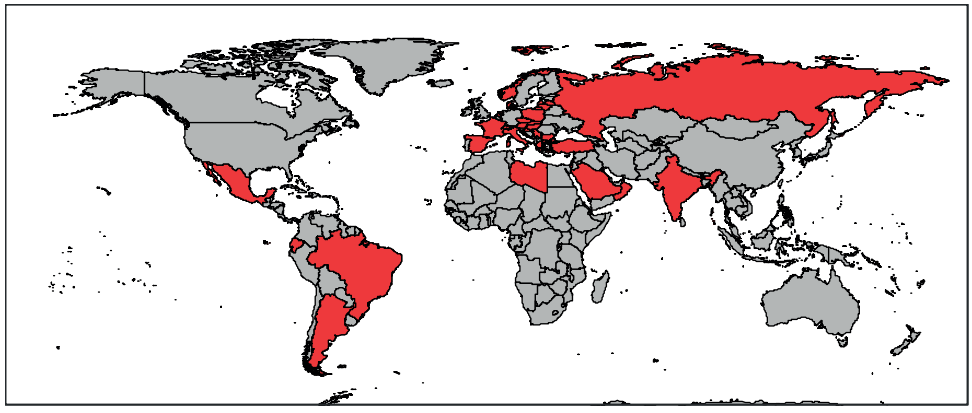

Figure 1. Countries of centres participating in the international Pharmachild registry (in red).

In the Netherlands, the largest paediatric rheumatology department is located within the Wilhelmina Children's Hospital of the University Medical Centre Utrecht, which also contributes patient data to Pharmachild since 2012. The Wilhelmina Children's Hospital furthermore collects anonymous routine healthcare data for research purposes which are extracted from electronic health records using the research data platform (RDP)[18]. This platform was set up in 2011 and currently contains information of >900 patients with JIA. The RDP is therefore an important source of real-world evidence for answering unsolved questions in the care of JIA. This type of evidence resembles more closely the actual clinical practice than intervention trials[52].

Aims and outline of this thesis

In this thesis, I analysed retrospective and prospectively collected routine hospital visit data from the RDP of the Wilhelmina Children's Hospital paediatric rheumatology department, Pharmachild and collaborating registries on several topics related to the care of children with JIA. These patients commonly visit their paediatric rheumatologist once every three months, but there are no strict guidelines for increasing this visit interval. To this end, the "Testing an increased visit interval scheme using web-based self-evaluation in patients with JIA" (THUIS)-study was set up at the Wilhelmina Children's Hospital. Throughout the thesis, I used traditional and advanced epidemiological methods (such as random effects models, bootstrapping, propensity score analysis, multiple imputation, time-varying analyses, model recalibration and regularization) and a variety of epidemiological study designs to provide the best possible answers to clinically relevant questions in the management of patients with JIA. The following questions have been addressed:

- What is the probability of an individual patient referred to the paediatric rheumatologist with specific symptoms to be diagnosed with JIA and not CMPS?
- How often do comorbidities and familial autoimmune diseases occur in JIA patients?
- What is the probability of an individual JIA patient to develop (chronic) uveitis?
- What factors are associated with an increased risk of developing IBD and AITD in JIA?
- What is the effect of MTX therapy on the development of uveitis in JIA?
- Does treatment with ADA have a different effect on well-being in JIA patients than treatment with etanercept (ETN)?
- Is the meningococcal ACWY (MenACWY) vaccine safe and immunogenic in JIA and IBD patients treated with anti-tumour necrosis factor (TNF) agents?
- Can home monitoring of PROMs in JIA patients be used to safely extend the interval of visiting the paediatric rheumatologist?

In order to answer these questions, the following studies were conducted.

Part II: Diagnosis

In Chapter 2, I present a diagnostic prediction model based on PROMs for distinguishing JIA from CMPS in patients with corresponding symptoms. In Chapter 3, I give an overview of the prevalence of different autoimmune diseases and associated factors in parents of JIA patients from the Pharmachild registry.

Part III: Comorbidity

In Chapter 4, I report the occurrence of four comorbidities of interest (MAS, uveitis, varicella and tuberculosis (TB)) in JIA patients from Pharmachild, the United Kingdom JIA

Biologic Registries (BCRD/BSPAR-ETN) and German biologic registries (BiKeR/JuMBO). In Chapter 5, I provide an optimism-adjusted prognostic prediction model for the ever-risk of developing chronic or acute uveitis in JIA. In Chapter 6, I describe the development of a prediction model for chronic uveitis in JIA at different disease durations and subsequent external validation in the UK Childhood Arthritis Prospective Study (CAPS) and German Inception Cohort of Newly diagnosed patients with juvenile idiopathic arthritis (ICON) cohorts. In Chapter 7, I report independent risk factors for AITD in JIA that could be used for preventive screening. In Chapter 8, I present independent risk factors for IBD in JIA and quantified its incidence on different drug therapies.

Part IV: Treatment and management

In Chapter 9, I describe the effect of (different dosages of) MTX therapy on developing uveitis in JIA and whether or not this effect alters after a therapy stop. In Chapter 10, I report a real-world comparison of the effects of ADA and ETN on patient-reported well-being in JIA. In Chapter 11, I provide long-term immunogenicity and safety results of the MenACWY vaccine in patients with JIA and IBD treated with anti-TNF agents. In Chapter 12, I outline the methodology and interim results of the THUIS study: a clinical non-inferiority trial at the Wilhelmina Children's Hospital which aims to demonstrate that JIA patients with inactive disease can safely skip one 3-monthly hospital control visit by home-monitoring their disease activity using the JAMAR and EuroQol five-dimensional youth questionnaire with five levels (EQ-5D-Y-5L). Ultimately, I summarize all research findings from the previous chapters and discuss broader implications and future perspectives in Chapter 13.

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PART II

Diagnosis

CHAPTER 2

2

A diagnostic prediction model for separating chronic musculoskeletal pain syndrome and juvenile idiopathic arthritis

Joeri W. van Straalen[1,2], Martine van Stigt Thans[1,2], Nico M. Wulffraat[1,2], Sytze de Roock[1,2], and Joost F. Swart[1,2]

[1]Department of Paediatric Immunology and Rheumatology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, the Netherlands
[2]Faculty of Medicine, Utrecht University, Utrecht, the Netherlands

J Pediatr. 2022;251:164-171.e6.

ABSTRACT

Objectives

To develop and validate a diagnostic prediction model that can early distinguish between juvenile idiopathic arthritis (JIA) and chronic musculoskeletal pain syndrome (CMPS), two common diagnoses in paediatric rheumatology, based on patient-reported outcomes.

Study design

This retrospective cohort study evaluated if the Juvenile Arthritis Multidimensional Assessment Report (JAMAR) performs well in distinguishing JIA from CMPS. We analysed JAMARs that were completed by patients (n = 287) at first visit to the paediatric rheumatology department of the Wilhelmina Children's Hospital in Utrecht, the Netherlands. Relevant JAMAR items for predicting a diagnosis of JIA were selected in a penalized multivariable model suitable for clinical application. The model was subsequently validated in new data from the same centre.

Results

A total of 196 JAMARs (97 JIA, 99 CMPS) were collected in the model development data and 91 JAMARs (48 JIA, 43 CMPS) in the validation data. Variables in the prediction model that were strongest associated with a diagnosis of JIA instead of CMPS were asymmetric pain/swelling in the shoulder (OR: 2.34), difficulty with self-care (OR: 2.41), skin rash (OR: 2.07) and asymmetric/pain swelling in the knee (OR: 2.29). Calibration and discrimination (AUC = 0.83, 95% CI: 0.74 – 0.92) of the model in the validation data were good.

Conclusions

The JAMAR is an interesting tool to help distinguishing JIA from CMPS in patients with corresponding symptoms. We present an easy to use, adjusted and validated model to early separate these two diagnoses based on patient-reported outcomes for proper referral and treatment.

Keywords: Juvenile Arthritis Multidimensional Assessment Report; chronic musculoskeletal pain syndrome; juvenile idiopathic arthritis; patient-reported outcomes; paediatric rheumatology; prediction model

Corresponding editorial: Weiss JE. Prediction Model for Juvenile Idiopathic Arthritis: Challenges and Opportunities. J Pediatr. 2022 Dec;251:46-49. doi: 10.1016/j.jpeds.2022.07.045.

INTRODUCTION

Two common diagnoses made in children referred to the paediatric rheumatologist for a suspected rheumatic disease are juvenile idiopathic arthritis (JIA) and chronic musculoskeletal pain syndrome (CMPS)[1–4]. JIA is defined as all forms of arthritis of unknown cause persisting for >6 weeks starting below the age of 16[5]. The International League of Associations for Rheumatology (ILAR) classifies seven JIA subtypes with distinct clinical and laboratory characteristics[6]. CMPS is an idiopathic non-inflammatory condition of chronic musculoskeletal pain, which is defined as ongoing pain in the bones, joints and soft tissues persisting for ≥3 months[1,3,7,8]. Several paediatric forms of CMPS can be distinguished, some of which have more specific diagnostic criteria. These comprise generalized pain syndrome (including juvenile primary fibromyalgia), complex regional pain syndrome, local pain syndromes and lower back pain[1,8].

JIA and CMPS patients present with heterogeneous and overlapping symptoms[1,7,9,10]. Patient history and physical examination by experienced physicians are needed to distinguish JIA from CMPS, with a family history of certain autoimmune diseases (e.g. psoriasis, uveitis and spondyloarthropathy), morning stiffness and joint swelling or limitation arguably pointing towards JIA. Since the management and prognosis of JIA and CMPS are very different, it is important to early separate them for proper referral. Delay in the treatment of JIA could lead to contractures, overgrowth of the affected bone and joint damage[5,11], while a delay in the management of CMPS could result in musculoskeletal disequilibrium and negatively impact psychological well-being[4,12]. Therefore, it would be of interest if these two diagnoses could be separated early using patient-reported outcomes only.

The aim of this study was to 1) assess if a combination of patient-reported items from the Juvenile Arthritis Multidimensional Assessment Report (JAMAR) would perform well in distinguishing JIA from CMPS in patients with corresponding symptoms and 2) present a validated prediction model for separating these two diagnoses in clinical practice.

METHODS

Patients

This was a retrospective cohort study using data from the paediatric rheumatology outpatient clinic of the Wilhelmina Children's Hospital in Utrecht, the Netherlands, a tertiary care centre. Since 2012, it has been standard care for all referred patients to complete an electronic version of the JAMAR shortly prior to first visit to the outpatient clinic. This questionnaire was developed in 2011 with the aim of assessing health status

in JIA patients and includes 15 parent or patient-centred items including well-being, pain, functional status, disease activity, joint disease and drug side effects[13]. Data about first visits of referred patients were extracted from electronic medical records and the paediatric rheumatology registry of the Wilhelmina Children's Hospital. The paediatric rheumatology registry was created in 2011 and has since collected clinical and laboratory data from >900 patients. For this study, we used the following inclusion criteria at first visit: aged <18 years old, no immunosuppressive treatment and having been diagnosed (after follow-up) with either JIA or CMPS after having completed a JAMAR questionnaire (within a range of three weeks from first visit). Patients receiving immunosuppressive treatment were excluded since it is likely that they had already been diagnosed with JIA elsewhere. For developing the diagnostic prediction model, we used data from patients that completed a JAMAR before July 1st, 2018. These included 196 eligible patients, of which 97 (49.5%) were diagnosed with JIA. The model was subsequently validated using new data collected from July 1st, 2018 – May 28th, 2020. These included 91 eligible patients, of which 48 (52.7%) were diagnosed with JIA.

Outcome and predictors

The outcome predicted in this study was a diagnosis of JIA (instead of CMPS). JIA was diagnosed as per ILAR criteria and CMPS was diagnosed if there was persistent musculoskeletal pain for at least three months in the absence of any underlying cause. Due to the retrospective nature of the data, no specific diagnostic criteria for different forms of CMPS were used. Potential CMPS patients were selected from the paediatric rheumatology registry using the following diagnosis codes: "arthralgia", "myalgia", "myofascial pain syndrome/tendinitis", "foot osteochondrosis", "patellofemoral pain syndrome", "low back pain" and "orthopaedic condition – not further specified". Two researchers (MvST and JS) independently reviewed descriptions of diagnoses for correctness. CMPS patients were further classified as having "local pain" in case of at maximum one painful joint group and "generalized pain" in case of ≥2 painful joint groups.

Predictors included in the study were age at first visit, sex and separate items of the JAMAR. For patients aged <12 with both an available child and parent version of the JAMAR, we used the parent version. For patients aged ≥12, we used the child version. JAMAR items about drug therapy and previous visits were irrelevant due to the study design and thus not analysed. We hypothesized that asymmetric joint involvement would be associated with JIA rather than CMPS. Therefore, we combined JAMAR items about patient-reported pain or swelling in joints on the left and right side into variables with three categories: no pain or swelling, pain or swelling on the left or right side (i.e. asymmetric pain/swelling) and pain or swelling on both the left and right side (i.e. symmetric pain/swelling). In order to avoid fitting an overfit model, individual juvenile arthritis functional score (JAFS) and paediatric rheumatology quality of life scale (JQL) items were dichotomized into the

following categories: "no difficulty/never" (score 0) versus "some difficulty/sometimes or worse" (scores 1-3). Age at first visit, VAS well-being, VAS pain and VAS disease activity were treated as continuous variables and linearity with the logit outcome was visually assessed.

Model development and validation

For all variables in the model development data, we performed a univariable logistic regression analysis. Variables with a *P* value of <0.10 were subsequently fitted in a multivariable penalized logistic regression model for diagnosing JIA. The number of self-reported painful or swollen joints (range 0 – 18) was not considered for inclusion into the multivariable model in order to preserve independence of predictor variables. The multivariable model was fitted using least absolute shrinkage and selection operator (LASSO) regression on complete cases. LASSO regression is a statistical technique suitable for data with many variables that adds a penalty to model coefficients by shrinking them towards zero[14]. This technique simultaneously performs regularization by making model coefficients less optimistic and variable selection by setting coefficients of variables that are unimportant in predicting the outcome to exactly zero. As a result, predictions from a LASSO regression will be less extreme due to overfitting, which might benefit future predictions in new patients. The degree of shrinking model coefficients towards zero in LASSO regression is determined by the λ parameter and for this study we used the value of λ that minimized prediction error in ten-fold cross validation[14]. For every patient in the model development and validation data, a predicted probability for JIA was calculated using the shrunken coefficients from the LASSO model. Performance of the model in the development and validation data was assessed by the area under the receiver operating characteristic curve (AUC) and a calibration plot of mean predicted probabilities versus frequencies of the outcome within quintiles of the data.

As a secondary analysis, we repeated all model building and validation procedures for patients in the model development and validation datasets with only 1) oligoarthritis and local pain syndrome and 2) polyarthritis and generalized pain syndrome.

All analyses were performed with R version 3.6.3[15] with the glmnet, rms and pROC packages. We adhered to the guidelines for Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD)[16].

RESULTS

Characteristics of patients in model development data

A flowchart of patients included in the model development and validation data is provided in Figure 1. In the group of patients used for developing the prediction model, JIA patients were significantly more often male (30.1% vs. 17.2%) and reported more often skin rash (20.6% vs. 7.1%) and difficulty with self-care (50.0% vs. 34.4%) compared to patients diagnosed with CMPS (Table 1). On the other hand, CMPS patients were older (median 14.8 vs. 11.5 years) and reported more often symmetric joint involvement and a painful or swollen lower back (27.3% vs. 12.4%) and neck (41.4% vs. 15.5%). The latter was also reflected in a higher frequency of reported difficulty looking up (19.4% vs. 7.4%) and over the shoulder (23.2% vs. 10.5%) compared to JIA patients. Furthermore, the median number of self-reported painful or swollen joints was significantly higher in CMPS patients (4, IQR: 2 – 7) than in JIA patients (2, IQR: 1 – 4). Overall, both JIA and CMPS patients in the model development data reported much pain, as observed from VAS pain scores (median 5.5, IQR: 3.0 – 7.3) and the dichotomized question 5 from the paediatric rheumatology quality of life scale (97.4%). Extended characteristics of patients in the model development data are reported in Supplementary Table 1.

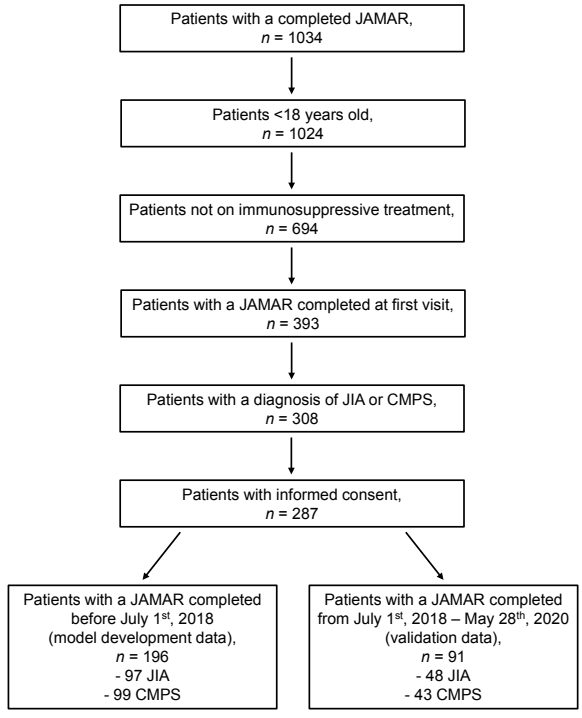

Figure 1. Flowchart of patients included in the model development and validation data. CMPS: chronic musculoskeletal pain syndrome, JAMAR: juvenile arthritis multidimensional assessment report, JIA: juvenile idiopathic arthritis.

Table 1. Characteristics with *P* <0.10 of patients in the model development data (*N* = 196).

Characteristic	JIA (*N* = 97)	CMPS (*N* = 99)	*P*-value
Demographics			
Age at first visit, median (IQR), y	11.5 (5.4 – 14.7)	14.8 (12.2 – 16.1)	<0.01
Girls, No. (%)	67 (69.1%)	82 (82.8%)	0.03
JAMAR items			
Functional ability during past four weeks, No. (%)			
Difficulty carrying out activities with fingers (JAFS 6)	27 (28.1%) *N* = 96	47 (48.0%) *N* = 98	<0.01
Difficulty squeezing with hands (JAFS 8)	25 (26.3%) *N* = 95	38 (38.4%)	0.07
Difficulty putting hands behind neck (JAFS 12)	7 (7.6%) *N* = 92	18 (18.2%)	0.04
Difficulty looking over shoulder (JAFS 13)	10 (10.5%) *N* = 95	23 (23.2%)	0.02
Difficulty looking up (JAFS 14)	7 (7.4%) *N* = 94	19 (19.4%) *N* = 98	0.02
VAS pain, median (IQR)	5.0 (2.5 – 7.0)	6.0 (3.5 – 7.5)	0.09
Number of painful/swollen joints, median (IQR)	2 (1 – 4)	4 (2 – 7)	<0.01
Pain/swelling in finger(s), No. (%)			
No	71 (73.2%)	59 (59.6%)	Reference
Asymmetric	10 (10.3%)	10 (10.1%)	0.70
Symmetric	16 (16.5%)	30 (30.3%)	0.02
Pain/swelling in shoulder(s), No. (%)			
No	85 (87.6%)	80 (80.8%)	Reference
Asymmetric	8 (8.2%)	4 (4.0%)	0.32
Symmetric	4 (4.1%)	15 (15.2%)	0.02
Pain/swelling in hip(s), No. (%)			
No	89 (91.8%)	71 (71.7%)	Reference
Asymmetric	4 (4.1%)	10 (10.1%)	0.06
Symmetric	4 (4.1%)	18 (18.2%)	<0.01
Pain/swelling in knee(s), No. (%)			
No	36 (37.1%)	41 (41.4%)	Reference
Asymmetric	36 (37.1%)	14 (141%)	<0.01
Symmetric	25 (25.8%)	44 (44.4%)	0.20
Pain/swelling in ankle(s), No. (%)			
No	72 (74.2%)	61 (61.6%)	Reference
Asymmetric	11 (11.3%)	7 (7.1%)	0.58
Symmetric	14 (14.4%)	31 (31.3%)	0.01
Pain/swelling in neck, No. (%)	15 (15.5%)	41 (41.4%)	<0.01
Pain/swelling in lower back, No. (%)	12 (12.4%)	27 (27.3%)	0.01

Table 1. Continued.

Characteristic	JIA (*N* = 97)	CMPS (*N* = 99)	*P*-value
Skin rash, No. (%)	20 (20.6%) *N* = 96	7 (7.1%)	<0.01
VAS disease activity, median (IQR)	4.5 (2.5 – 6.5)	3.0 (1.5 – 6.0)	0.08
Attending school, No. (%)	76 (78.4%)	94 (94.9%)	<0.01
Quality of life during past four weeks, No. (%)			
Difficulty with self-care (JQL 1)	45 (50.0%) *N* = 90	32 (34.4%) *N* = 93	0.02
Felt sad/depressed (JQL 6)	48 (51.1%) *N* = 94	65 (66.3%) *N* = 98	0.03
Difficulty concentrating (JQL 9)	50 (55.6%) *N* = 90	66 (67.3%) *N* = 98	0.10

CMPS: chronic musculoskeletal pain syndrome, IQR: interquartile range, JAFS: juvenile arthritis functional score, JIA: juvenile idiopathic arthritis, JQL: paediatric rheumatology quality of life scale, VAS: visual analogue scale.

Development of prediction model

Following univariable logistic regression analysis, a *P* value of <0.10 was observed in the model development data for the following variables: age at first visit, sex, difficulty carrying out activities with fingers, difficulty squeezing with hands, difficulty putting hands behind neck, difficulty looking over shoulder, difficulty looking up, VAS pain score, pain/swelling in the finger(s), pain/swelling in the shoulder(s), pain/swelling in the hip(s), pain/swelling in the knee(s), pain/swelling in the ankle(s), pain/swelling in the neck, pain/swelling in the lower back, skin rash, VAS disease activity, school attendance, difficulty with self-care, felt sad/depressed and difficulty concentrating. These variables were subsequently fitted in a multivariable logistic LASSO regression, which forced the following variables to be excluded: difficulty carrying out activities with fingers, difficulty squeezing with hands, difficulty looking up, VAS pain score, pain/swelling in the lower back, pain/swelling in the fingers, symmetric pain/swelling in the shoulders, asymmetric pain/swelling in the ankle, school attendance and difficulty concentrating. According to the model, a diagnosis of JIA was most associated with asymmetric pain/swelling in the shoulder, asymmetric pain/swelling in the knee, skin rash and difficulty with self-care (Table 2). A diagnosis of CMPS was most associated with female sex, older age at first visit, pain swelling in the neck, pain/swelling in the hip(s), symmetric pain/swelling in the knees and symmetric pain/swelling in the ankles. The model was based on 170 patients due to missing data for 26 patients.

Table 2. Coefficients of multivariable LASSO prediction model for a diagnosis of JIA instead of CMPS.

Variables	Coefficients	OR
Intercept	2.48	11.96
Female sex	-0.77	0.46
Age at first visit, y	-0.17	0.84
Difficulty putting hands behind neck (JAFS 12)	-0.09	0.91
Difficulty looking over shoulder (JAFS 13)	-0.17	0.85
Pain/swelling in neck	-0.71	0.49
Asymmetric pain/swelling in shoulder	0.85	2.34
Asymmetric pain/swelling in hip	-0.70	0.49
Symmetric pain/swelling in hips	-1.00	0.36
Asymmetric pain/swelling in knee	0.83	2.29
Symmetric pain/swelling in knees	-0.44	0.64
Symmetric pain/swelling in ankles	-0.42	0.66
Skin rash	0.73	2.07
VAS disease activity	0.07	1.07
Difficulty with self-care (JQL 1)	0.88	2.41
Felt sad/depressed (JQL 6)	-0.16	0.85

LASSO: least absolute shrinkage and selection operator, JAFS: juvenile arthritis functional score, JIA: juvenile idiopathic arthritis, JQL: paediatric rheumatology quality of life scale, OR: odds ratio.

The equation for calculating the probability of JIA for an individual patient following the model has the form of:

$$P(\text{JIA}) = \frac{1}{1 + e^{-(\beta 0 + \beta 1 * x1 + \beta 2 * x2 + \cdots + \beta n * xn)}}$$

Where β0 is the model intercept, β1 through βn are the model coefficients and x1 through xn are the observed patient values for the variables as displayed in Table 2.

The prediction model demonstrated good discrimination (AUC = 0.89, 95% CI: 0.84 – 0.93) in the development data (Figure 2). Some miscalibration was observed due to the shrinkage of coefficients. At a cut-off threshold of 70% for the predicted probability of JIA in the model development data, the model had a negative predictive value of 95% and a positive predictive value of 67%.

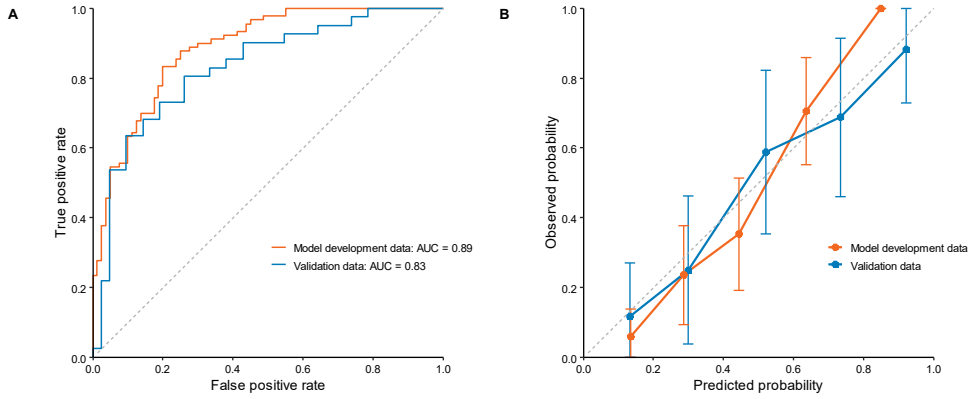

Figure 2. Prediction model performance in development and validation data. A: ROC curves of false positive and true positive rates for different thresholds of predicted probabilities. B: calibration plots of mean predicted probabilities versus frequencies of the outcome within quintiles of the data. Vertical bars indicate 95% confidence intervals. AUC: area under the curve.

Validation of prediction model

Compared to the model development data, similar effects across JIA and CMPS patients were observed in the model validation group (Supplementary Table 2). For both the validation and model development data, the majority of JIA patients had oligoarthritis and the majority of CMPS patients had generalized pain (Table 3). Predictions in the validation data were calculated for 83 patients due to eight patients with missing data. Calibration and discrimination (AUC = 0.83, 95% CI: 0.74 – 0.92) in the validation data were good. At the cut-off threshold of 70% for the predicted probability of JIA the model had a negative predictive value of 85% and a positive predictive value of 66%.

Table 3. Distribution of subtypes of included JIA and CMPS patients.

	Model development data (*N* = 196)	**Validation data (*N* = 91)**
JIA, No. (%)		
Total	97 (100.0%)	48 (100.0%)
Enthesitis-related arthritis	14 (14.4%)	2 (4.2%)
Oligoarthritis	53 (54.6%)	33 (66.7%)
Psoriatic arthritis	9 (9.3%)	0 (0.0%)
RF- polyarthritis	8 (8.2%)	5 (10.4%)
RF+ polyarthritis	7 (7.2%)	2 (4.2%)
Systemic arthritis	3 (3.1%)	6 (12.5%)
Undifferentiated arthritis	3 (3.1%)	1 (2.1%)
CMPS, No. (%)		
Total	99 (100.0%)	43 (100.0%)
Local pain[1]	27 (27.3%)	13 (30.2%)
Generalized pain[2]	72 (72.7%)	30 (69.8%)

Abbreviations: CMPS, chronic musculoskeletal pain syndrome, JIA, juvenile idiopathic arthritis, RF, rheumatoid factor. [1]one painful joint group. [2]two or more painful joint groups.

Secondary analysis

When restricting our analyses to oligoarthritis and local pain syndrome patients in the model development and validation data, the following were the best predictor variables for separating JIA from CMPS on multivariable analysis: age at first visit, difficulty running on flat ground, difficulty walking up five steps, difficulty jumping forward, difficulty squatting, pain/swelling in the knee(s), morning stiffness, VAS disease activity, school attendance and difficulty with self-care. The prediction model demonstrated excellent discrimination in the model development (AUC = 0.93, 95% CI: 0.87 – 0.99) and validation data (AUC = 0.86, 95% CI: 0.75 – 0.97) and overall acceptable calibration (Supplementary Figure 1). Subsequently, when restricting our analyses to polyarthritis and generalized pain syndrome patients in the model development and validation data, the following were the best predictor variables for separating JIA from CMPS on multivariable analysis: age at first visit, difficulty opening a door, pain/swelling in the toe(s), pain/swelling in the neck and difficulty with self-care. This prediction model demonstrated good discrimination in the model development (AUC = 0.87, 95% CI: 0.75 – 0.98) and validation data (AUC = 0.86, 95% CI: 0.72 – 1.0) and overall good calibration.

Clinical application

For clinical practice, predictions from our prediction model can easily be obtained from a risk calculator (Appendix; available on the *Journal of Pediatrics* website at https://www.jpeds.com/article/S0022-3476(22)00344-4/fulltext). For non-digital use, a nomogram was constructed from which predicted risks of JIA can be calculated as a function of the model parameters (Figure 3).

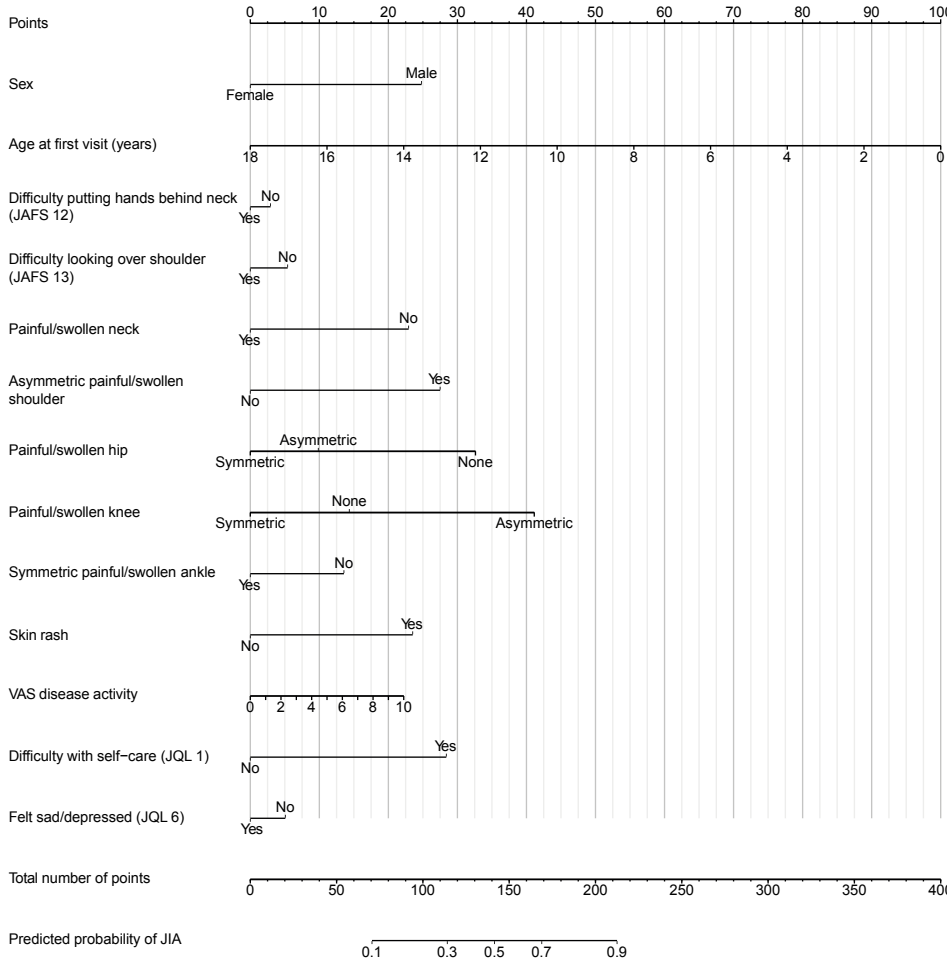

Figure 3. Nomogram of predicted probabilities for JIA instead of CMPS. For every observation of model variables on the left (Sex, …, JQL 6), read off the corresponding number of points from the top axis. Add up all points to read off the corresponding predicted probability of JIA using the bottom two axes. For example, for a female patient, aged 4, with difficulty putting her hands behind the neck, no difficulty looking over the shoulder, no painful/swollen neck, an asymmetric painful/swollen shoulder, no painful/swollen hips, no painful/swollen knees, no painful/swollen ankles, no skin rash, a VAS disease activity of 8, difficulty with self-care and who did not feel sad/depressed, the total number of points is 0 + 78 + 0 + 6 + 23 + 28 + 33 + 14 + 14 + 0 + 18 + 28 + 5 = 247, which corresponds to a predicted probability of JIA instead of CMPS of >90%.

DISCUSSION

In this study, we showed that the JAMAR questionnaire performs well in separating JIA and CMPS at first visit to paediatric rheumatology. JAMAR items that were strongly associated with a diagnosis of JIA instead of CMPS on multivariable analysis were male sex, young age, patient-reported asymmetric pain or swelling in the shoulder or knee, skin rash and difficulty with self-care. CMPS patients reported more often symmetrical joint involvement and pain/swelling in the neck and lower back than JIA patients.
We decided to only include patients with a diagnosis of JIA or CMPS since these patients form the majority of our target domain, i.e. patients with signs and symptoms suspect of JIA. Patients referred to the paediatric rheumatologist with other diseases such as systemic lupus erythematosus or auto inflammatory conditions generally present with distinct symptoms. According to our data, the number of patients at first visit to paediatric rheumatology that will be diagnosed with CMPS is roughly equal to the number of patients that will be diagnosed with JIA.

Previous studies comparing children with CMPS to children with JIA are scarce. Two studies reported that CMPS patients were older at onset of symptoms and more often female than patients with JIA[10] or other rheumatic diseases[7]. It has also been described that CMPS patients report more pain than JIA patients[10,17]. These findings are in line with the findings of the present study, although the VAS pain score was not a significant variable in predicting a diagnosis of JIA on multivariable analysis. One previous study also presented a tool for predicting the final diagnosis in children with musculoskeletal complaints and indicated the pattern of joint swelling over time, the duration of morning stiffness, the frequency of pain and precipitating factors to be independently correlated with chronic arthritis[18]. This tool, however, was based on predictors from a detailed medical history instead of patient-reported outcomes.

Several important variables in the prediction model can be explained by the existing literature. A systematic review reported that musculoskeletal pain is more common in girls than in boys and increases with age[19]. Furthermore, asymmetric involvement of large joints such as the knee and shoulder is common in oligoarthritis, the largest ILAR category of JIA[5,11]. Skin rash as a predictor of JIA can be attributed to a diagnosis of systemic or psoriatic JIA[6,20]. In our model development data, 100% (3/3) of systemic JIA and 44% (4/9) of psoriatic JIA patients reported skin rash. According to our model, difficulty with self-care was another important variable associated with JIA and we observed that this was most often reported by systemic JIA (3/3; 100%) and polyarticular JIA (12/15; 80%) patients in the model development data. Examples of self-care activities mentioned in the JAMAR are eating, getting dressed and washing, which especially require sufficient functioning of the wrists and hands. Patients with polyarticular and systemic JIA most often reported

involvement of these joint groups in our data, which is in line with previous literature[5,21]. We speculate that difficulty with self-care distinguishes children with JIA from children with CMPS because the joints of the latter group are not limited due to increased intra-articular fluid or swollen joint capsules. Other important predictors for CMPS were pain/swelling in the neck and hip. Pain in these joints is incorporated in several diagnostic criteria for fibromyalgia syndrome[22]. Nevertheless, literature about involvement of the neck/hip in juvenile CMPS is scarce[1,19]. Lastly, symmetrical pain/swelling was observed more often in CMPS patients than JIA patients for all examined joints. This confirmed our pre-specified hypothesis that asymmetric joint involvement would be associated with JIA rather than CMPS. In line with our finding, a study including 33 patients with juvenile fibromyalgia syndrome reported that pain was symmetrical in 79% of the patients[23].

As described earlier, some predictors in our model are likely associated with different subtypes of JIA and CMPS. Indeed, different predictor variables were selected in our secondary analyses restricted to focal or diffuse complaints, compared to our main analysis. Nevertheless, the aim of the current study was to present a model that is able to distinguish between joint pain with an inflammatory and non-inflammatory cause and not explain differences between subtypes of JIA and CMPS. Our model enables physicians to properly refer patients in an early stage for further diagnostics and treatment.

The prediction model performed well in both the model development and validation data in terms of discrimination and calibration and yielded high negative predictive values and reasonable positive predictive values at a cut-off threshold of 70% for the predicted probability of JIA. This threshold therefore seems appropriate for ruling out a diagnosis of JIA with some risk that also CMPS patients will be falsely "diagnosed" with JIA by the model. This misclassification is not problematic, since a diagnosis of JIA will subsequently have to be confirmed by the paediatric rheumatologist following physical examination, which is already standard care.

We are convinced that the current model will not only be useful for paediatric rheumatologists but also general paediatricians, since most children are referred to the paediatric rheumatology unit by the latter group[24]. This goes to show that also general paediatricians often face the challenge of distinguishing JIA and CMPS. In fact, the authors argue that paediatric rheumatologists only observe the tip of the iceberg.

This study has strengths and limitations. A major strength is that for almost 300 patients information was available about JAMARs completed before a diagnosis of JIA or CMPS was made, which is a standard procedure in our hospital. The final prediction model demonstrated high discriminative power in the validation data, was adjusted for overfitting using LASSO regression and can easily be consulted by physicians using

a digital risk calculator. Furthermore, the JAMAR is a commonly used instrument in the care and follow-up (2 – 4 times per year) of JIA patients around the world and has been validated in 54 languages across 52 countries[25]. On the other hand, the JAMAR has not been validated in other diagnoses and therefore its use in CMPS patients should be further investigated and validated. Another limitation of this study is that we could not differentiate between CMPS patients with amplified musculoskeletal pain syndromes and orthopaedic conditions due to limited descriptions of CMPS diagnoses. Also, our model was not validated in a non-Western hospital. It is known that the distribution of ILAR categories varies around the world[26], and therefore it is uncertain if our model performs similarly in a non-Western setting. The clinical relevance of the model furthermore depends on the number of available paediatric rheumatologists in the target setting and the time they have to see patients.

For future research, it might be interesting to add information about the duration of complaints until first visit, which was not available in our study. Previous literature stated that this duration is on average longer than a year for CMPS patients[27] but only several months for JIA patients[28]. In order for the JAMAR questionnaire to even better discriminate between JIA and CMPS, the authors remark that the items about "joint pain or swelling" might be separated into two categories: "joint pain" and "joint swelling". The latter category is likely to be more associated with JIA than CMPS as a result of active joint inflammation.

In conclusion, we showed that the JAMAR is an interesting tool for distinguishing JIA from CMPS in children with corresponding symptoms. We present an easy to use, adjusted and validated model with the aim to early separate JIA and CMPS based on patient-reported outcomes for proper referral and treatment.

ACKNOWLEDGEMENTS

The authors thank all patients and their parents or guardians for consenting to this research. We furthermore thank all paediatric rheumatologists from the Wilhelmina Children's Hospital for the acquisition of patient data.

Permission for use of JAMAR and its translations must be obtained in writing from PRINTO, Genoa, Italy. All JAMAR-related inquiries should be directed to at printo@gaslini.org. Permission for use of CHAQ and CHQ derived-material is granted through the scientific cooperation of the copyright holder ICORE of Woodside CA and HealthActCHQ Inc. of Boston, Massachusetts USA. All CHQ-related inquiries should be directed to licensing@healthactchq.com. All CHAQ-related inquiries should be directed to gsingh@stanford.edu.

FUNDING

This work was supported by a research grant from FOREUM Foundation for Research in Rheumatology and by longstanding research support from the Dutch Arthritis Foundation (ReumaNederland), grant number LLP10. The study sponsors had no role in the study design, the collection, analysis and interpretation of data, the writing of the report and the decision to submit the manuscript for publication.

COMPETING INTERESTS

All authors declare that they have no conflict of interest.

ETHICS APPROVAL

This study was classified by the institutional review board of the UMC Utrecht as exempt of the Medical Research Involving Human Subjects Act (21/774) and was carried out in compliance with the Helsinki Declaration. All included patients provided informed consent for the use of their data for scientific purposes.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Extended characteristics of patients in the model development data (N = 196).

Characteristic	JIA (*N* = 97)	CMPS (*N* = 99)	*P*-value
Demographics			
Age at first visit, median (IQR), y	11.5 (5.4 – 14.7)	14.8 (12.2 – 16.1)	<0.01*
Girls, No. (%)	67 (69.1%)	82 (82.8%)	<0.03*
JAMAR items			
Functional ability during past four weeks, No. (%)			
Difficulty running on flat ground (JAFS 1)	60 (63.2%) *N* = 95	53 (53.5%)	0.18
Difficulty walking up 5 steps (JAFS 2)	49 (51.6%) *N* = 95	44 (44.4%)	0.32
Difficulty jumping forward (JAFS 3)	56 (60.9%) *N* = 92	52 (53.6%) *N* = 97	0.31
Difficulty squatting (JAFS 4)	62 (66.0%) *N* = 94	63 (64.3%) *N* = 98	0.81
Difficulty bending down (JAFS 5)	41 (43.2%) *N* = 95	45 (45.9%) *N* = 98	0.70
Difficulty carrying out activities with fingers (JAFS 6)	27 (28.1%) *N* = 96	47 (48.0%) *N* = 98	<0.01*
Difficulty opening and closing fists (JAFS 7)	19 (19.8%) *N* = 96	25 (25.5%) *N* = 98	0.34
Difficulty squeezing with hands (JAFS 8)	25 (26.3%) *N* = 95	38 (38.4%)	0.07*
Difficulty opening a door (JAFS 9)	15 (17.0%) *N* = 88	13 (13.1%)	0.46
Difficulty opening a tap or jar (JAFS 10)	22 (24.4%) *N* = 90	27 (27.3%)	0.66
Difficulty stretching out arms (JAFS 11)	12 (12.8%) *N* = 94	14 (14.1%)	0.78
Difficulty putting hands behind neck (JAFS 12)	7 (7.6%) *N* = 92	18 (18.2%)	0.04*
Difficulty looking over shoulder (JAFS 13)	10 (10.5%) *N* = 95	23 (23.2%)	0.02*
Difficulty looking up (JAFS 14)	7 (7.4%) *N* = 94	19 (19.4%) *N* = 98	0.02*
Difficulty biting (JAFS 15)	1 (1.1%) *N* = 95	3 (3.1%) *N* = 98	0.35
VAS pain, median (IQR)	5.0 (2.5 – 7.0)	6.0 (3.5 – 7.5)	0.09*
Number of painful/swollen joints, median (IQR)	2 (1 – 4)	4 (2 – 7)	<0.01*
Pain/swelling in finger(s), No. (%)			
No	71 (73.2%)	59 (59.6%)	Reference
Asymmetric	10 (10.3%)	10 (10.1%)	0.70
Symmetric	16 (16.5%)	30 (30.3%)	0.02*

Supplementary Table 1. Continued.

Characteristic	JIA (*N* = 97)	CMPS (*N* = 99)	*P*-value
Pain/swelling in wrist(s), No. (%)			
No	74 (76.3%)	71 (71.7%)	Reference
Asymmetric	13 (13.4%)	9 (9.1%)	0.48
Symmetric	10 (10.3%)	19 (19.2%)	0.11
Pain/swelling in elbow(s), No. (%)			
No	86 (88.7%)	87 (87.9%)	Reference
Asymmetric	7 (7.2%)	5 (5.1%)	0.57
Symmetric	4 (4.18%)	7 (7.1%)	0.40
Pain/swelling in shoulder(s), No. (%)			
No	85 (87.6%)	80 (80.8%)	Reference
Asymmetric	8 (8.2%)	4 (4.0%)	0.32
Symmetric	4 (4.1%)	15 (15.2%)	0.02*
Pain/swelling in hip(s), No. (%)			
No	89 (91.8%)	71 (71.7%)	Reference
Asymmetric	4 (4.1%)	10 (10.1%)	0.06*
Symmetric	4 (4.1%)	18 (18.2%)	<0.01*
Pain/swelling in knee(s), No. (%)			
No	36 (37.1%)	41 (41.4%)	Reference
Asymmetric	36 (37.1%)	14 (14.1%)	<0.01
Symmetric	25 (25.8%)	44 (44.4%)	0.20
Pain/swelling in ankle(s), No. (%)			
No	72 (74.2%)	61 (61.6%)	Reference
Asymmetric	11 (11.3%)	7 (7.1%)	0.58
Symmetric	14 (14.4%)	31 (31.3%)	<0.01*
Pain/swelling in toe(s), No. (%)			
No	79 (81.4%)	83 (83.8%)	Reference
Asymmetric	9 (9.3%)	11 (11.1%)	0.75
Symmetric	9 (9.3%)	5 (5.1%)	0.27
Pain/swelling in neck, No. (%)	15 (15.5%)	41 (41.4%)	<0.01*
Pain/swelling in lower back, No. (%)	12 (12.4%)	27 (27.3%)	0.01*
Morning stiffness, No. (%)	69 (71.9%) *N* = 96	65 (65.7%)	0.35
Fever, No. (%)	7 (7.2%)	5 (5.1%)	0.53
Skin rash, No. (%)	20 (20.8%) *N* = 96	7 (7.1%)	<0.01*
VAS disease activity, median (IQR)	4.5 (2.5 – 6.5)	3.0 (1.5 – 6.0)	0.08*

Supplementary Table 1. Continued.

Characteristic	JIA (*N* = 97)	CMPS (*N* = 99)	*P*-value
State of illness, No. (%)			
Remission	6 (6.3%)	2 (2.1%)	Reference
Persistent activity	75 (78.9%)	74 (78.7%)	0.19
Relapse	14 (14.7%) *N* = 95	18 (19.1%) *N* = 94	0.13
Attending school, No. (%)	76 (78.4%)	94 (94.9%)	<0.01*
Quality of life during past four weeks, No. (%)			
Difficulty with self-care (JQL 1)	45 (50.0%) *N* = 90	30 (32.3%) *N* = 93	0.02*
Difficulty taking a 15 minute walk or walking up stairs (JQL 2)	72 (76.6%) *N* = 94	81 (84.4%) *N* = 96	0.18
Difficulty carrying out activities that require a lot of energy (JQL 3)	76 (78.4%) *N* = 93	87 (88.8%) *N* = 98	0.17
Difficulty doing at-school activities or playing with friends (JQL 4)	63 (73.3%) *N* = 86	74 (76.3%) *N* = 97	0.64
Had pain (JQL 5)	90 (94.7%) *N* = 95	99 (100.0%)	0.99
Felt sad/depressed (JQL 6)	48 (51.1%) *N* = 94	65 (66.3%) *N* = 98	0.03*
Felt nervous/anxious (JQL 7)	42 (44.2%) *N* = 95	46 (48.4%) *N* = 95	0.56
Trouble getting along with other children (JQL 8)	16 (17.0%) *N* = 94	19 (19.8%) *N* = 96	0.62
Difficulty concentrating (JQL 9)	50 (55.6%) *N* = 90	66 (67.3%) *N* = 98	0.10*
Felt dissatisfied with appearance or abilities (JQL 10)	29 (35.4%) *N* = 82	44 (45.4%) *N* = 97	0.18
VAS well-being, median (IQR)	3.5 (1.0 – 6.0)	3.8 (1.0 – 6.4)	0.56
Satisfied with illness, No. (%)	12 (12.6%) *N* = 95	11 (11.2%) *N* = 98	0.76

Abbreviations: CMPS, chronic musculoskeletal pain syndrome, IQR, interquartile range, JAFS, juvenile arthritis functional score, JIA, juvenile idiopathic arthritis, JQL, paediatric rheumatology quality of life scale, VAS, visual analogue scale.

*variables with P <0.10 were included in multivariable logistic LASSO regression.

Supplementary Table 2. Characteristics of patients in the validation data (N = 91).

Characteristic	JIA (*N* = 48)	CMPS (*N* = 43)
Demographics		
Age at first visit, median (IQR), y	11.4 (5.1 – 14.7)	15.3 (12.2 – 16.3)
Girls, No. (%)	25 (52.1%)	36 (83.7%)
JAMAR items		
Functional ability during past four weeks, No. (%)		
Difficulty running on flat ground (JAFS 1)	26 (55.3%) *N* = 47	27 (62.8%)
Difficulty walking up 5 steps (JAFS 2)	20 (43.5%) *N* = 46	23 (53.5%)
Difficulty jumping forward (JAFS 3)	25 (53.2%) *N* = 47	21 (50.0%) *N* = 42
Difficulty squatting (JAFS 4)	29 (60.4%)	29 (67.4%)
Difficulty bending down (JAFS 5)	22 (46.8%) *N* = 47	23 (53.5%)
Difficulty carrying out activities with fingers (JAFS 6)	12 (25.0%)	16 (37.2%)
Difficulty opening and closing fists (JAFS 7)	10 (21.3%) *N* = 47	10 (23.3%)
Difficulty squeezing with hands (JAFS 8)	13 (27.1%)	15 (34.9%)
Difficulty opening a door (JAFS 9)	9 (19.6%) *N* = 46	2 (4.7%)
Difficulty opening a tap or jar (JAFS 10)	10 (22.7%) *N* = 44	12 (27.9%)
Difficulty stretching out arms (JAFS 11)	7 (14.9%) *N* = 47	5 (11.6%)
Difficulty putting hands behind neck (JAFS 12)	5 (10.4%)	2 (4.7%)
Difficulty looking over shoulder (JAFS 13)	3 (6.5%) *N* = 46	12 (27.9%)
Difficulty looking up (JAFS 14)	2 (4.2%)	8 (18.6%)
Difficulty biting (JAFS 15)	3 (6.2%)	2 (4.7%)
VAS pain, median (IQR)	4.0 (1.0 – 7.0)	6.0 (4.3 – 8.0)
Number of painful/swollen joints, median (IQR)	1.5 (1.0 – 4.0)	4.0 (1.5 – 7.5)
Pain/swelling in finger(s), No. (%)		
No	36 (75.0%)	27 (62.8%)
Asymmetric	4 (8.3%)	3 (7.0%)
Symmetric	8 (16.7%)	13 (30.2%)
Pain/swelling in wrist(s), No. (%)		
No	33 (68.8%)	27 (62.8%)
Asymmetric	11 (22.9%)	3 (7.0%)
Symmetric	4 (8.3%)	13 (30.2%)

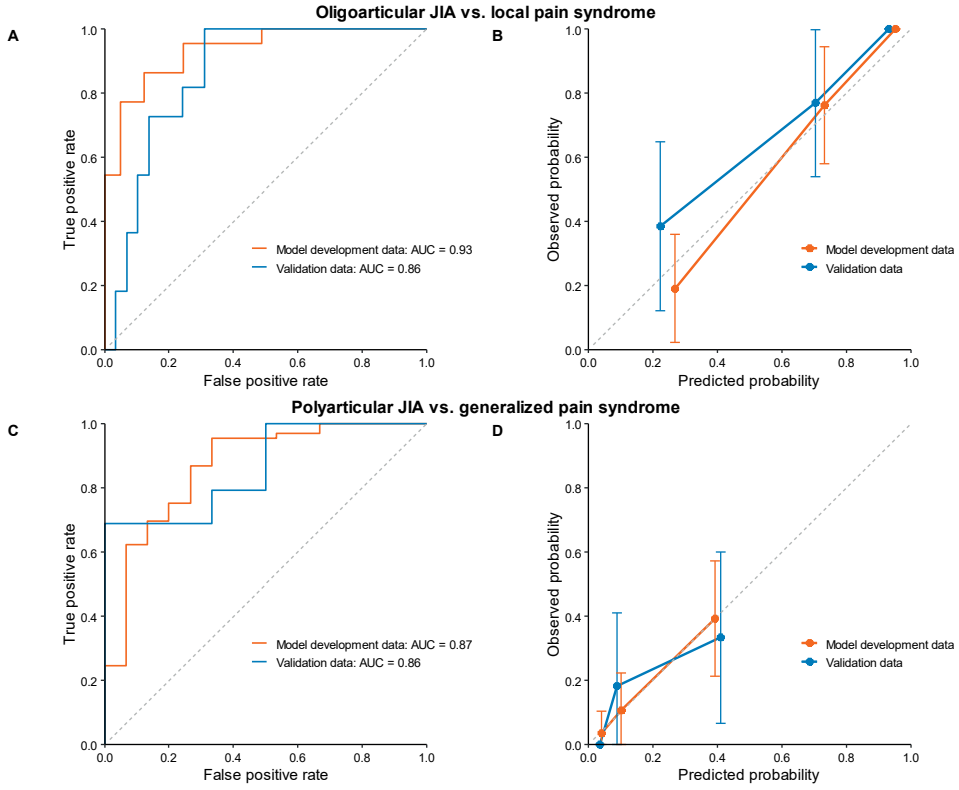
Supplementary Table 2. Continued.

Characteristic	JIA (*N* = 48)	CMPS (*N* = 43)
Pain/swelling in elbow(s), No. (%)		
No	42 (87.5%)	37 (86.0%)
Asymmetric	2 (4.2%)	2 (4.7%)
Symmetric	4 (8.3%)	4 (9.3%)
Pain/swelling in shoulder(s), No. (%)		
No	41 (85.4%)	29 (67.4%)
Asymmetric	4 (8.3%)	3 (7.0%)
Symmetric	3 (6.2%)	11 (25.6%)
Pain/swelling in hip(s), No. (%)		
No	46 (95.8%)	34 (79.1%)
Asymmetric	1 (2.1%)	2 (4.7%)
Symmetric	1 (2.1%)	7 (16.3%)
Pain/swelling in knee(s), No. (%)		
No	13 (27.1%)	23 (53.5%)
Asymmetric	24 (50.0%)	4 (9.3%)
Symmetric	11 (22.9%)	16 (37.2%)
Pain/swelling in ankle(s), No. (%)		
No	37 (77.1%)	29 (67.4%)
Asymmetric	9 (18.8%)	4 (9.3%)
Symmetric	2 (4.2%)	10 (23.3%)
Pain/swelling in toe(s), No. (%)		
No	45 (93.8%)	38 (88.4%)
Asymmetric	1 (2.1%)	2 (4.7%)
Symmetric	2 (4.2%)	3 (7.0%)
Pain/swelling in neck, No. (%)	5 (10.4%)	22 (51.2%)
Pain/swelling in lower back, No. (%)	3 (6.2%)	13 (30.2%)
Morning stiffness, No. (%)	33 (68.8)	30 (71.4%) *N* = 42
Fever, No. (%)	8 (16.7%)	1 (2.3%)
Skin rash, No. (%)	10 (20.8%)	4 (9.3%)
VAS disease activity, median (IQR)	4.5 (1.0 – 6.5)	5.0 (2.3 – 7.5)
State of illness, No. (%)		
Remission	4 (8.3%)	0 (0.0%)
Persistent activity	36 (75.0%)	34 (81.0%)
Relapse	8 (16.7%)	8 (19.0%) *N* = 42
Attending school, No. (%)	36 (75.0%)	42 (97.7%)

Supplementary Table 2. Continued.

Characteristic	JIA (*N* = 48)	CMPS (*N* = 43)
Quality of life during past four weeks, No. (%)		
Difficulty with self-care (JQL 1)	20 (44.4%) *N* = 45	15 (35.7%) *N* = 42
Difficulty taking a 15 minute walk or walking up stairs (JQL 2)	32 (68.1%) *N* = 47	37 (86.0%)
Difficulty carrying out activities that require a lot of energy (JQL 3)	36 (80.0%) *N* = 45	38 (88.4%)
Difficulty doing at-school activities or playing with friends (JQL 4)	24 (55.8%) *N* = 43	35 (83.3%) *N* = 42
Had pain (JQL 5)	45 (93.8%)	43 (100.0%)
Felt sad/depressed (JQL 6)	22 (47.8%) *N* = 46	29 (69.0%) *N* = 42
Felt nervous/anxious (JQL 7)	22 (46.8%) *N* = 47	25 (62.5%) *N* = 40
Trouble getting along with other children (JQL 8)	7 (14.9%) *N* = 47	12 (27.9%)
Difficulty concentrating (JQL 9)	28 (58.3%)	31 (72.1%)
Felt dissatisfied with appearance or abilities (JQL 10)	13 (31.0%) *N* = 42	18 (42.9%) *N* = 42
VAS well-being, median (IQR)	3.5 (1.4 – 6.0)	5.0 (2.8 – 7.0)
Satisfied with illness, No. (%)	6 (12.5%)	7 (17.1%) *N* = 41

Abbreviations: CMPS, chronic musculoskeletal pain syndrome, IQR, interquartile range, JAFS, juvenile arthritis functional score, JIA, juvenile idiopathic arthritis, JQL, paediatric rheumatology quality of life scale, VAS, visual analogue scale.



Supplementary Figure 1. Performance of prediction models from secondary analyses for oligoarthritis vs. local pain syndrome and polyarthritis vs. generalized pain syndrome. A and C: ROC curves of false positive and true positive rates for different thresholds of predicted probabilities. B and D: calibration plots of mean predicted probabilities versus frequencies of the outcome within tertiles of the data. Vertical bars indicate 95% confidence intervals. AUC: area under the curve. JIA: juvenile idiopathic arthritis.

CHAPTER 3

3

Prevalence of familial autoimmune diseases in juvenile idiopathic arthritis: results from the international Pharmachild registry

Joeri W. van Straalen[1,2], Sytze de Roock[1,2], Gabriella Giancane[3,4], Ekaterina Alexeeva[5,6], Elena Koskova[7], Pablo Mesa-del-Castillo Bermejo[8], Francesco Zulian[9], Adele Civino[10], Davide Montin[11], Nico M. Wulffraat[1,2], Nicolino Ruperto[12] and Joost F. Swart[1,2] for the Paediatric Rheumatology International Trials Organisation (PRINTO)

[1]Department of Paediatric Immunology and Rheumatology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, the Netherlands
[2]Faculty of Medicine, Utrecht University, Utrecht, the Netherlands
[3]IRCCS Istituto Giannina Gaslini, Clinica Pediatrica e Reumatologia, Genoa, Italy
[4]Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili (DiNOGMI), Università degli Studi di Genova, Genoa, Italy
[5]Federal State Autonomous Institution "National Medical Research Centre of Children's Health" of the Ministry of Health of the Russian Federation, Moscow, Russian Federation
[6]Federal State Autonomous Educational Institution of Higher Education, I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation, Moscow, Russian Federation
[7]Department of Paediatric Rheumatology, National Institute of Rheumatic Diseases, Piestany, Slovakia.
[8]Rheumatology, Paediatrics, Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain
[9]Department of Woman and Child Health, University of Padua, Padua, Italy
[10]UO Pediatria - Sez. Reumatologia e Immunologia pediatrica, P.O. "Vito Fazzi", Lecce, Italy
[11]Immunology and Rheumatology Unit, Regina Margherita Children Hospital, Turin, Italy
[12]UOSID Centro trial, IRCCS Istituto Giannina Gaslini, Genoa, Italy

ABSTRACT

Background

Little is known about the disposition to autoimmune diseases (ADs) among children diagnosed with JIA. In this study, we provide a comprehensive overview of the prevalence of and factors associated with ADs in parents of children with juvenile idiopathic arthritis (JIA).

Methods

Prevalence rates of ADs and 95% Poisson confidence intervals were calculated for parents of JIA patients from the international Pharmachild registry and compared with general population prevalence rates as reported in the literature. Demographic, clinical and laboratory features were compared between JIA patients with and without a family history of AD using χ^2 and Mann-Whitney *U* tests.

Results

8,673 patients were included and the most common familial ADs were psoriasis, autoimmune thyroid disease, rheumatoid arthritis and ankylosing spondylitis. The prevalence of several ADs was higher in parents of the included JIA patients than in the general population. Clinical Juvenile Arthritis Disease Activity Scores at study entry and last follow-up were not significantly different between patients with (n = 1,231) and without a family history of AD (n = 7,442). Factors associated with familial AD were older age at JIA onset ($P < 0.01$), Scandinavian residence ($P < 0.01$), enthesitis-related arthritis, psoriatic arthritis and undifferentiated arthritis ($P < 0.01$), ANA positivity ($P = 0.03$) and HLA-B27 positivity ($P < 0.01$).

Conclusions

Familial AD proves to be a risk factor for JIA development and certain diseases should therefore not be overlooked during family health history at the diagnosis stage. A family history of AD is associated with the JIA category but does not influence the severity or disease course.

Keywords: juvenile idiopathic arthritis; familial autoimmune diseases; paediatric rheumatology; registry; epidemiology

BACKGROUND

Juvenile idiopathic arthritis (JIA) is an umbrella term that comprises seven subtypes of arthritis of unknown cause that begin before the age of 16 years and last for more than 6 weeks [1]. Six out of seven subtypes are considered an autoimmune disease (AD), except for systemic JIA, which resembles more an autoinflammatory disease[1]. ADs are known to cluster within families and share common pathogenic mechanisms and genetic factors[2,3]. However, little is known about the relationship between JIA and familial ADs. A previous study reported that 32% of 4,677 JIA patients had at least one first-degree relative with an AD[4]. Furthermore, JIA patients with a family history of AD were reported to have higher disease activity and more often enthesitis-related arthritis (ERA) and psoriatic arthritis than JIA patients without such family history[5,6]. Frequently described ADs in relatives of JIA patients are insulin-dependent diabetes mellitus (IDDM), JIA, rheumatoid arthritis (RA), autoimmune thyroid disease (AITD), spondyloarthropathy and psoriasis[4–11]. Nonetheless, the few studies about familial autoimmunity in JIA are either based on a limited number of patients, do not report prevalence rates within families or only report pre-selected ADs.

The objective of this study is to provide a comprehensive overview of the occurrence of and factors associated with ADs in parents of children with JIA from a large international registry[12] and to compare prevalence rates with those reported in the general population.

METHODS

Patients

Patients were included from the international observational Pharmachild registry. Pharmachild started in 2011 with the objective of studying safety and effectiveness of drug therapies in JIA. Patients are included from Paediatric Rheumatology International Trials Organisation (PRINTO) centres from 31 countries worldwide. The registry includes patients with a diagnosis of JIA as per International League of Associations for Rheumatology (ILAR) criteria that are being treated with nonsteroidal anti-inflammatory drugs (NSAIDs), intraarticular steroids, systemic steroids, and/or conventional synthetic (cs-) or biological (b-) disease-modifying antirheumatic drugs (DMARD) as decided by the treating physician. Additional information about the Pharmachild registry is previously reported[12]. The extracted Pharmachild data were locked on 12 November, 2020. Patients without available information for family history of AD were excluded from the current study.

Outcome and characteristics

Three researchers (JS, JvS and SdR) reviewed reported diseases in first degree relatives (i.e. mother and father) of the included JIA patients in order to ensure only definite diagnoses of ADs were included. Reported ADs were classified into the following categories: psoriasis, AITD, RA, ankylosing spondylitis, inflammatory bowel disease (IBD), JIA, asthma, IDDM, systemic lupus erythematosus, vitiligo, celiac disease, multiple sclerosis, uveitis, sarcoidosis, reactive arthritis, Sjögren's syndrome, rheumatic fever, vasculitides, Still's disease, familial Mediterranean fever, other autoimmune arthritis, other connective tissue disease and other AD. In addition, the following patient characteristics were collected: sex, geographic region, ethnicity, age at JIA onset, ILAR category of JIA, rheumatoid factor (RF) status, human leukocyte antigen (HLA) B27 status, antinuclear antibodies (ANA) status, number of active joints and clinical Juvenile Arthritis Disease Activity Score (cJADAS) at study entry and last visit and observation period (calculated from disease onset until last visit). Patients were grouped into the following geographic regions based on the country of the centre in which they were treated: Western Europe, Central and Eastern Europe, Scandinavia, Northern Africa and the Middle East, Latin America and Southern Asia[13]. Ethnicity was reported at inclusion by the treating physician from a fixed set of categories. RF status was determined from two measurements at least three months apart according to ILAR criteria. Since not all patients had two available ANA tests, only the first test was used to determine ANA status. The cJADAS is a composite measure for disease activity that takes into account the number of active joints, physician global assessment of disease activity and parent/patient global assessment of well-being[14]. The latter two components of the cJADAS are measured on a 21-circle visual analogue scale ranging from 0 – 10[15].

Statistical analysis

Characteristics of patients with a family history of AD and those without were compared using the χ^2 test for categorical variables and Mann-Whitney *U* test for numerical variables. Pairwise comparisons of categories of geographic region, ethnicity and ILAR subtypes were performed with Bonferroni correction. For each AD category, prevalence rates among parents and corresponding 95% Poisson confidence intervals were calculated. Prevalence rates of ADs in the general population were collected from the literature. For this, we included data from worldwide literature reviews or surveillance studies. ILAR categories of patients with different familial ADs were compared using the Fisher's exact test. All comparative analyses were performed on complete cases and a *P*-value of <0.05 was considered statistically significant. All analyses were performed with R version 4.0.0.

RESULTS

Patient characteristics

At the cut-off date, a total of 9,111 JIA patients were enrolled in Pharmachild, of which 438 (4.8%) had no available information about parental ADs and were excluded from further analyses. For the remaining cohort of 8,673 JIA patients, the total observation period was 43,800 years with a median duration of 4.0 years (IQR: 1.8 – 7.3). The median duration from disease onset until study entry was 139 days (IQR: 55 – 458). The majority of patients were treated in European centres (n = 7,590; 87.5%) (Table 1). An overview of the classification of treatment centre countries into geographic regions is provided in Supplementary Table 1. Of all included patients, 1,231 (14.2%, 95% CI: 13.5 – 14.9%) had a family history of AD. Out of these, 1,107 (89.9%) had a family history of one AD, 116 (9.4%) had a family history of two ADs and 8 (0.6%) had a family history of three or more ADs. Patients with a family history of AD more often had ERA, psoriatic arthritis and undifferentiated arthritis than patients without a family history of AD ($P < 0.01$), were more often ANA ($P = 0.03$) and HLA-B27 positive ($P < 0.01$) and had an older age at JIA onset ($P < 0.01$). Patients without a family history of JIA more often had systemic arthritis. Furthermore, the proportion of patients from Scandinavia and Southern Europe was higher in patients with a family history of AD than in patients without such family history ($P < 0.01$). The same effect was observed for patients of European Caucasian and Northern African or Middle Eastern ethnicity ($P < 0.01$). No significant differences in sex, RF status and disease activity were observed.

Table 1. Characteristics of JIA patients with and without a family history of AD in parents (n = 8,673).

Characteristic	No family history of AD (n = 7,442)	Family history of AD (n = 1,231)	*P*-value
Female, n (%)	5,060 (68.0%)	847 (68.8%)	0.59
Age at JIA onset, median (IQR)	5.2 (2.4 – 9.8)	6.3 (2.5 – 10.8)	<0.01*
Geographic region, n (%)			<0.01*[a]
Central and Eastern Europe	2,091 (28.1%)	210 (17.1%)	
Latin America	663 (8.9%)	50 (4.1%)	
Northern Africa and Middle East	157 (2.1%)	44 (3.6%)[b, c]	
Scandinavia	685 (9.2%)	177 (14.4%)[b, c]	
Southern Asia	153 (2.1%)	16 (1.3%)[d, e]	
Southern Europe	2,384 (32.0%)	497 (40.4%)[b, c]	
Western Europe	1,309 (17.6%)	237 (19.3%)[b, c, e]	
Ethnicity, n (%)			<0.01*[a]
European Caucasian	5,654 (85.6%)	1,008 (89.1%)	
Hispanic	267 (4.0%)	21 (1.9%)[f]	
Indian	132 (2.0%)	12 (1.1%)	

Table 1. Continued

Characteristic	No family history of AD (n = 7,442)	Family history of AD (n = 1,231)	*P*-value
Multiethnic	93 (1.4%)	14 (1.2%)	
Northern African or Middle Eastern	281 (4.3%)	60 (5.3%)[g]	
Southeast Asian	59 (0.9%)	6 (0.5%)	
Sub-Saharan African	75 (1.1%)	5 (0.4%)	
Other	47 (0.7%)	5 (0.4%)	
	n = 6,608	n = 1,131	
ILAR category, n (%)			<0.01*[a]
ERA	777 (10.4%)	178 (14.5%)	
Oligoarthritis	2,934 (39.4%)	319 (25.9%)[h]	
Polyarthritis RF-	2,045 (27.5%)	228 (18.5%)[h]	
Polyarthritis RF+	335 (4.5%)	38 (3.1%)[h]	
Psoriatic arthritis	144 (1.9%)	146 (11.9%)[h, i, j, k]	
Systemic arthritis	898 (12.1%)	51 (4.1%)[h, i, j, l]	
Undifferentiated arthritis	309 (4.2%)	271 (22.0%)[h, i, j, k, m]	
Laboratory characteristics, n (%)			
ANA positive	2853 (40.9%)	514 (44.3%)	0.03*
	n = 6,970	n = 1,160	
RF positive)	356 (5.4%)	49 (4.5%)	0.26
	n = 6,629	n = 1,088	
HLA-B27 positive	865 (19.4%)	229 (28.6%)	<0.01*
	n = 4,467	n = 800	
Disease activity, median (IQR)			
Active joints at study entry	0 (0 – 2)	0 (0 – 2)	0.18
	n = 3,143	n = 583	
cJADAS at study entry	2.0 (0.0 – 7.0)	2.0 (0.0 – 7.0)	0.61
	n = 2,713	n = 519	
Active joints at last visit	0 (0 – 1)	0 (0 – 1)	0.74
	n = 3,143	n = 583	
cJADAS at last visit	1.0 (0.0 – 5.0)	1.0 (0.0 – 5.0)	0.82
	n = 2,713	n = 519	
Observation period in years, median (IQR)	4.0 (1.8 – 7.3)	3.9 (1.8 – 7.0)	0.24

AD: autoimmune disease, ANA: antinuclear antibodies, cJADAS: clinical JADAS, ERA: enthesitis-related arthritis, HLA: human leukocyte antigen, IQR: interquartile range, ILAR: International League of Associations for Rheumatology, JIA: juvenile idiopathic arthritis, RF: rheumatoid factor

*$P < 0.05$, [a]*P*-value indicates overall difference between categories, [b]significantly different from Central and Eastern Europe, [c]significantly different from Latin America, [d]significantly different from Northern Africa and Middle East, [e]significantly different from Scandinavia, [f]significantly different from European Caucasian, [g]significantly different from Hispanic, [h]significantly different from ERA, [i]significantly different from oligoarthritis, [j]significantly different from polyarthritis RF-, [k]significantly different from polyarthritis RF+, [l]significantly different from psoriatic arthritis, [m]significantly different from systemic arthritis

Table 2. Prevalence rates of ADs in parents of included JIA patients (n = 17,346).

Disease	Frequency	Prevalence per 100,000 (95% Poisson CI)	Global prevalence per 100,000
Psoriasis	369	2,127 (1,916 – 2,356)	140 – 1,990[16]
Autoimmune thyroid disease	275	1,585 (1,404 – 1,784)	GD:0 – 2,000[17] HT: 0 – 7,000[17]
Rheumatoid arthritis	141	813 (684 – 959)	300 – 700[18]
Ankylosing spondylitis	136	784 (658 – 927)	20 – 350[19]
Inflammatory bowel disease	68	392(304 – 497)	UC: 2 – 505[20] CD: 1 – 322[20]
Juvenile idiopathic arthritis	51	294 (219 – 387)	21[21]
Asthma	48	277 (204 – 367)	4,300[22]
Insulin-dependent diabetes mellitus	38	219 (155 – 301)	39 – 96[23]
Systemic lupus erythematosus	31	179 (121 – 254)	0 – 241[24]
Vitiligo	29	167 (112– 240)	100 – 1,200[25]
Other autoimmune arthritis	28	161 (107– 233)	-[a]
Celiac disease	27	156 (103 – 226)	400 – 800[26]
Other autoimmune disease	25	144 (93 – 213)	-[a]
Uveitis	17	98 (57 – 157)	9 – 730[27]
Multiple sclerosis	16	92 (53 – 150)	2 – 164.6[28]
Sarcoidosis	15	87 (48 – 143)	2 – 160[29]
Reactive arthritis	12	69 (36 – 121)	0 - 200[19]
Other connective tissue disease	11	63 (32 – 114)	-[a]
Sjögren's syndrome	10	58 (28 – 106)	61[30]
Rheumatic fever	8	46 (20 – 91)	-[b]
Vasculitides	5	29 (9 – 68)	-[a]
Still's disease	4	23 (6 – 59)	1 – 6.8[31]
Familial Mediterranean fever	2	12 (1 – 42)	-[c]

AD: autoimmune disease, CD: Crohn's disease, CI: confidence interval, GD: Graves' disease, HT: Hashimoto's thyroiditis, UC: ulcerative colitis

[a]heterogeneous group of diseases, [b]not a chronic disease, [c]mainly affects ethnic groups from the eastern Mediterranean region

Prevalence rates of familial ADs

A total of 1,366 ADs were reported in the parents (n = 17,346) of the included JIA patients. An overview of the classification of reported ADs is provided in Supplementary Table 2. The most common diseases were psoriasis (n = 369; 2.1%), AITD (n = 275; 1.6%), RA (n = 141; 0.8%) and ankylosing spondylitis (n = 136; 0.8%). Prevalence rates of several ADs in parents of the included JIA patients were raised compared to reported prevalence rates in the general population, most notably ankylosing spondylitis, JIA and IDDM (Table 2). The observed prevalence of asthma and celiac disease was notably lower than the prevalence in the general population. The prevalence rates of separate diseases in the "other autoimmune disease" group are listed in Supplementary Table 3. The distribution

of ILAR categories amongst included JIA patients was significantly different for several familial ADs (Table 3). Of clinical relevance were the observations that patients with a family history of ankylosing spondylitis oftentimes had ERA or undifferentiated arthritis ($P < 0.01$), while patients with a family history of psoriasis oftentimes had psoriatic or undifferentiated arthritis ($P < 0.01$). For patients with different familial ADs, the absolute frequencies of ILAR categories are visualized in Figure 1.

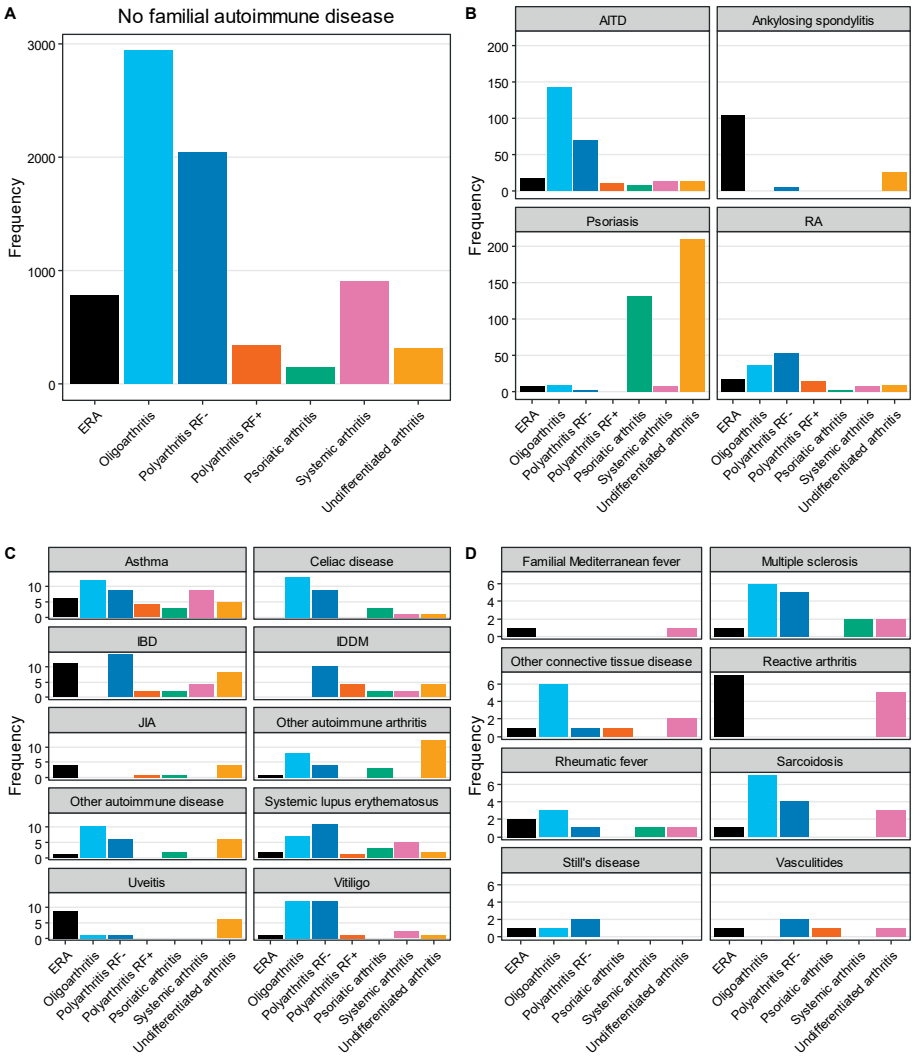


Figure 1. JIA categories of patients with and without familial autoimmune diseases. A: absolute frequencies of JIA categories for patients without familial autoimmune diseases. B-D: absolute frequencies of JIA categories for patients with different familial autoimmune diseases, each panel is displayed on a different scale. AITD: autoimmune thyroid disease, ERA: enthesitis-related arthritis, IBD: inflammatory bowel disease, IDDM: insulin-dependent diabetes mellitus, JIA: juvenile idiopathic arthritis, RA: rheumatoid arthritis, RF: rheumatoid factor.

DISCUSSION

The objective of this study was to present prevalence rates of ADs in parents of JIA patients and identify factors associated with such family history. According to our study, the prevalence rates of several ADs in parents of JIA patients are higher than those in the general population, with the most frequent familial ADs in JIA being psoriasis, AITD, RA and ankylosing spondylitis. Factors associated with a family history of AD in JIA are the geographic region, ethnicity, age at JIA onset, ILAR category, ANA status and HLA-B27 status.

In this study, the observed proportion of JIA patients with a family history of AD in first-degree relatives (14.2%, 95% CI: 13.5 – 14.9%) was lower than in previous studies (21.4 – 31.8%)[4,11]. This is possibly explained by the method of reporting familial autoimmunity in Pharmachild, differences in the target population and/or the definition of first-degree relatives. In Pharmachild, familial ADs are registered using self-reporting by the patient or parent, which might have led to an underestimation of the absolute prevalence of familial AD in JIA. Pharmachild furthermore defines a first-degree relative as the mother or father of a patient, whereas other definitions also include siblings. In addition, Pharmachild captures whether or not first degree relatives of JIA patients have a history of AD but does not distinguish between mother and father. Because of this, we could not report an overall prevalence of AD in parents since one parent can have a history of multiple ADs. Based on the number of JIA patients with a family history of AD (n = 1,231) in parents (n = 17,346) and the total number of reported ADs (n = 1,366), the overall prevalence of AD in parents would have to be little over 7.1 % for the current study. This number is still higher than the reported prevalence of AD in the general population of nearly 5%[2,3,32], which is in accordance with previous studies[7,11,33,34]. To our knowledge, no overall prevalence rate for AD has yet been reported for parents of JIA patients.

We observed several differences in characteristics of JIA patients with and without a family history of AD. A small study by Tronconi *et al*[8] did not find an association between a family history of AD and the subtype and age at onset of JIA. On the contrary, the current study observed that patients with psoriatic arthritis, undifferentiated arthritis and ERA reported relatively often a family history of AD as opposed to patients with systemic arthritis and oligoarthritis, which is also in line with two previous studies[4,6]. The association between HLA-B27 and a family history of AD corresponds with the observed effect for JIA category, given that, 73.7% of ERA patients and 38.3% of undifferentiated arthritis patients in our study were HLA-B27 positive. The association of familial AD with psoriatic arthritis and ERA can be explained by the ILAR criteria of these categories, which includes a family history of psoriasis for psoriatic arthritis, and a family history of ankylosing spondylitis, ERA, sacroiliitis with IBD, Reiter's syndrome or acute anterior uveitis for ERA[35]. Also, the

high frequency of familial AD in the undifferentiated arthritis group is likely due to the fact that many JIA patients are assigned to this group because of a family history of psoriasis, which serves as an exclusion criterion for all other JIA categories except psoriatic arthritis. It has previously been discussed whether or not this exclusion criterion should be revised[36]. Indeed, we observed that a family history of psoriasis was relatively common for patients with psoriatic and undifferentiated JIA and a family history of ankylosing spondylitis and uveitis for ERA. It was furthermore interesting to see that a family history of AITD was relatively common in JIA patients with oligoarthritis, given that several studies have reported a link between oligoarthritis and AITD in JIA[33,34,37,38]. On the other hand, a family history of AD was negatively associated with systemic arthritis in the current study. This can be explained by the autoinflammatory instead of autoimmune nature of this JIA category[1]. Previous studies have reported contradictory relationships between the age at JIA onset and a family history of AD[5,6,8,39–41]. In this study, familial AD was associated with older age at JIA onset. It is unclear what causes this effect, but it might be confounded by the category of JIA since oligoarthritis commonly presents at a young age and ERA during late childhood[42].We furthermore found that familial AD was associated with ANA positivity in the included JIA patients while previous studies report opposing results [5,39,40]. These differences might be due to the number and type of familial ADs investigated in each study. ANA are a marker of several ADs including AITD[43], which was a frequently reported AD in the parents of the included JIA patients. We also observed a statistically significant difference in the distribution of geographic regions. Patients from Scandinavia, Southern Europe, Western Europe, Northern Africa and the Middle East had relatively more often a family history of AD compared to patients from Central and Eastern Europe, Latin America and Southern Asia. The same effect was observed for patients of European Caucasian and Northern African or Middle Eastern ethnicity compared to patients of other ethnicities. These findings largely support existing epidemiological data on the worldwide distribution of AD, with higher relative frequencies in industrialized countries compared to developing countries[44]. Therefore, at the diagnosis stage of possible JIA, physicians might want to ask about a family history of AD especially in children of the before mentioned ethnicities with relatively increased prevalence. In the current study, we found no effect of familial autoimmunity on (the course of) disease activity in the included JIA patients. Previously, two studies reported that JIA patients with a family history of AD had higher disease activity and longer active disease duration than JIA patients without such family history[5,6]. This contradiction might be a result of differences in the target population and study design, given that one of the mentioned studies included a highly consanguineous JIA population from Saudi Arabia and the other study only included JIA patients from Iran in a case-control design. Nevertheless, other studies indicate a more severe disease course and unfavourable outcome for psoriatic arthritis patients compared to other JIA categories [45,46]. Also, it has been reported that a family history of AD is associated with the development of comorbidities in JIA[47,48], which was beyond the scope of the current study.

Amongst others, psoriasis, RA, ankylosing spondylitis, JIA, IDDM and Still's disease were more prevalent in parents of the included JIA patients than in the general population based on the available literature. Familial AD therefore proves to be a risk factor for JIA development. In a study of Finnish JIA patients, Pohjankoski *et al.* also observed higher prevalence rates of RA, spondyloarthropathy, psoriatic arthritis, JIA and IDDM in parents and full siblings of JIA patients compared to the general population[11]. The population prevalence rates for AITD reported in the literature varied to a large extent, most definitely due to differences in diagnostic criteria. Therefore, in the present study we could not conclude with certainty if AITD is more common in parents of JIA patients than in the general population. Nevertheless, a previous study reported that the prevalence of Hashimoto's thyroiditis in first and second-degree relatives was significantly higher for JIA patients compared to age-matched healthy controls[7]. All these findings are consistent with the hypothesis that clinically distinct ADs share common genetic susceptibility factors[4]. On the other hand, the prevalence of asthma and celiac disease in our data was decreased compared to the reported general population prevalence rates, perhaps due to the self-reporting mechanism of capturing familial autoimmunity data in Pharmachild. As an example, many children outgrow asthma[49] and might therefore not report this disease in adulthood. Pohjankoski *et al.* also reported no increased frequency of celiac disease in families of JIA patients compared to the general population[11].

Our study has a few limitations. First, it is likely that the absolute prevalence of familial autoimmunity in JIA is underestimated by our data since these were gathered using self-reporting by the patients and their parents, as described previously. In order to minimize the probability of recall bias, we focused only on parents and did not include ADs in second and third-degree relatives. Secondly, the majority of included patients were treated in European centres, which might also have influenced prevalence rates of familial ADs. Lastly, since it was not possible to distinguish between male or female parents in our data, we could not study a possible parent-of-origin effect. A previous study has reported that the prevalence of ADs among mothers of JIA patients was significantly higher than that of fathers, suggesting a maternal parent-of-origin effect wherein the sex of the parent with an AD influences the expression of JIA in offspring[50].

Nevertheless, we present the largest study on familial AD in JIA so far. We included patients from multiple countries around the world, making it possible to study geographical differences in prevalence rates. We furthermore present information for all reported familial ADs in parents of JIA patients from the Pharmachild registry, and did not focus on a pre-selected set of diseases. This study confirms previously reported associations with familial AD in JIA and demonstrates that a family history of AD is not related to the disease course. These study results might provide useful information for paediatric rheumatologists at the diagnosis stage of a child with (possible) JIA.

CONCLUSIONS

In conclusion, we provide for the first time a comprehensive overview of the frequency of different ADs in parents of JIA patients. Several of these diseases have an increased prevalence compared to the general population. Psoriasis, AITD, RA and ankylosing spondylitis were most often reported and should therefore not be overlooked during family health history at the diagnosis stage of a child with possible JIA. A family history of AD is particularly associated with psoriatic arthritis, undifferentiated arthritis and ERA but does not influence the severity or course of JIA.

ACKNOWLEDGEMENTS

The authors would like to thank all PRINTO centres for their contribution to the data collection and PRINTO personnel for data quality control. The authors furthermore express their acknowledgements to the European Reference Network for Immunodeficiency, Autoinflammatory, Autoimmune and Paediatric Rheumatic diseases (ERN-RITA). We also thank all patients and their parents or guardians for participating in Pharmachild.

FUNDING

This work was supported by a research grant from FOREUM Foundation for Research in Rheumatology. Pharmachild has been supported by funding from the Italian public hospital IRCCS Istituto Giannina Gaslini and a grant from the European Union (grant 260353).

COMPETING INTERESTS

NR has received honoraria for consultancies or speaker bureaus from the following pharmaceutical companies in the past three years: 2 Bridge, Amgen, AstraZeneca, Aurinia, Bayer, Brystol Myers and Squibb, Celgene, inMed, Cambridge Healthcare Research, Domain Therapeutic, EMD Serono, Glaxo Smith Kline, Idorsia, Janssen, Eli Lilly, Novartis, Pfizer, Sobi, UCB.

The IRCCS Istituto Giannina Gaslini (IGG), where NR works as full-time public employee has received contributions from the following industries in the last three years: Bristol Myers and Squibb, Eli-Lilly, F Hoffmann-La Roche, Novartis, Pfizer, Sobi. This funding has

been reinvested for the research activities of the hospital in a fully independent manner, without any commitment with third parties.
All other authors declare no conflicts of interest.

ETHICS APPROVAL

Pharmachild and all participating centres obtained approval from their respective ethics committees and were conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent/assent based on existing national regulations.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Classification of treatment centre countries of JIA patients into geographic regions.

Geographic region	Countries
Western Europe	Austria, France, the Netherlands and Switzerland
Southern Europe	Greece, Italy and Spain
Central and Eastern Europe	Bulgaria, Croatia, Czech Republic, Hungary, Latvia, Lithuania, Poland, Romania, Serbia, Slovakia and Russia
Scandinavia	Denmark and Norway
Northern Africa and the Middle East	Israel, Libya, Oman, Saudi Arabia and Turkey
Latin America	Argentina, Brazil, Ecuador and Mexico
Southern Asia	India and Singapore

Supplementary Table 2. Classification of reported autoimmune diseases in parents of included JIA patients.

Autoimmune disease category	Reported autoimmune diseases included
Psoriasis	Psoriasis
Autoimmune thyroid disease	Hashimoto's thyroiditis, Graves' disease
Rheumatoid arthritis	Rheumatoid arthritis
Ankylosing spondylitis	Ankylosing spondylitis
Inflammatory bowel disease	Crohn's disease, ulcerative colitis
Juvenile idiopathic arthritis	Juvenile idiopathic arthritis
Asthma	Asthma
Insulin-dependent diabetes mellitus	Insulin-dependent diabetes mellitus
Systemic lupus erythematosus	Systemic lupus erythematosus
Vitiligo	Vitiligo
Celiac disease	Celiac disease
Multiple sclerosis	Multiple sclerosis
Uveitis	Uveitis
Sarcoidosis	Sarcoidosis
Reactive arthritis	Reactive arthritis
Sjögren's syndrome	Sjögren's syndrome
Rheumatic fever	Rheumatic fever
Vasculitides	ANCA-associated vasculitis, Churg-Strauss syndrome, giant cell arteritis, Henoch-Schönlein purpura, leukocytoclastic vasculitis, microscopic polyangiitis, nodular vasculitis, polyarteritis nodosa, Takayasu's arteritis, Wegener's granulomatosis
Still's disease	Still's disease
Familial Mediterranean fever	Familial Mediterranean fever
Other autoimmune arthritis	Psoriatic arthritis, undifferentiated arthritis, unspecified arthritis
Other connective tissue disease	Scleroderma, mixed connective tissue disease
Other autoimmune disease	Eczema, alopecia areata, cutaneous lupus, immune thrombocytopenia, pemphigus, antiphospholipid antibody syndrome, autoimmune nephritis, autoimmune atrophic gastritis, autoimmune haemolytic anaemia, autoimmune hepatitis, Evans syndrome, miastenia, dermatomyositis

Supplementary Table 3. Prevalence rates of diseases from the "other autoimmune disease" category in parents of included JIA patients (n = 17,346).

Disease	Frequency	Prevalence per 100,000 (95% Poisson CI)
Eczema	6	34.6 (12.5 – 75.5)
Alopecia areata	3	17.3 (3.3 – 50.9)
Cutaneous lupus	3	17.3 (3.3 – 50.9)
Immune thrombocytopenia	2	11.5 (1.1 – 42.0)
Pemphigus	2	11.5 (1.1 – 42.0)
Antiphospholipid antibody syndrome	2	11.5 (1.1 – 42.0)
Autoimmune nephritis	1	5.8 (0.0 – 32.7)
Autoimmune atrophic gastritis	1	5.8 (0.0 – 32.7)
Autoimmune hemolyticanaemia	1	5.8 (0.0 – 32.7)
Autoimmune hepatitis	1	5.8 (0.0 – 32.7)
Evans syndrome	1	5.8 (0.0 – 32.7)
Miastenia	1	5.8 (0.0 – 32.7)
Dermatomyositis	1	5.8 (0.0 – 32.7)

PART III

Comorbidity

CHAPTER 4

4

Burden of comorbid conditions in children and young people with juvenile idiopathic arthritis: a collaborative analysis of 3 JIA registries

Lianne Kearsley-Fleet[1*], Jens Klotsche[2*], Joeri W. van Straalen[3*], Wendy Costello[4], Gianfranco D'Angelo[5], Gabriella Giancane[6], Gerd Horneff[7,8], Ariane Klein[7,8], Matilda Láday[9], Mark Lunt[1], Sytze de Roock[3], Nicolino Ruperto[6], Casper Schoemaker[3,10], Gordana Vijatov-Djuric[11,12], Jelena Vojinovic[13,14], Olga Vougiouka[15], Nico M. Wulffraat[3], UK JIA Biologics Registers Investigators Group, Paediatric Rheumatology International Trials Organisation (PRINTO), Kimme L. Hyrich[1,16], Kirsten Minden[2,17] and Joost F. Swart[3]

[1]Centre for Epidemiology Versus Arthritis, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom
[2]German Rheumatism Research Centre Berlin, Epidemiology unit, Germany
[3]Department of Paediatric Immunology and Rheumatology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Netherlands
[4]Irish Children's Arthritis Network (iCAN), Bansha, Co Tipperary, Ireland
[5]Ospedale Pediatrico G. Salesi di Ancona, Paediatrics, Ancona, Italy
[6]IRCCS Istituto Giannina Gaslini, Clinica Pediatrica e Reumatologia, Genoa, Italy
[7]Department of Paediatrics, Asklepios Kinderklinik Sankt Augustin, Sankt Augustin, Germany
[8]Department of Paediatric and Adolescent Medicine, Medical Faculty, University Hospital of Cologne, Cologne, Germany
[9]Spitalul Clinic Județean De Urgenta, Tîrgu-Mureș, Romania
[10]Dutch JIA Patient and Parent Organisation (member of ENCA), Rijen, Netherlands
[11]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia
[12]Institute for Child and Youth Health Care of Vojvodina, Department of Immunology, Allergology and Rheumatology, Novi Sad, Serbia
[13]University of Nis, Faculty of Medicine, Department of Paediatric Immunology and Rheumatology, University Clinic Centre, Nis, Serbia
[14]Clinical Centre Nis, Clinic of Paediatrics, Department of Paediatric Rheumatology, Nis, Serbia
[15]"P a A Kyriakou" Children's Hospital, 2nd Paediatric Department, Athens University School of Medicine, Athens, Greece
[16]NIHR Manchester BRC, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom
[17]Charité-Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Department of Paediatric Pulmonology, Immunology and Critical Care Medicine, Berlin, Germany

**Lianne Kearsley-Fleet, Jens Klotsche and Joeri W. van Straalen all contributed equally*

Rheumatology (Oxford). 2022;61(6):2524-2534.

ABSTRACT

Objectives

The burden of comorbidities is largely unknown in JIA. From 2000, national and international patient registries were established to monitor biologic treatment, disease activity and adverse events in patients with JIA. The aim of this analysis was to investigate in parallel, for the first time, three of the largest JIA registries in Europe/internationally – UK JIA Biologic Registers (BCRD/BSPAR-ETN), German biologic registers (BiKeR/JuMBO), multinational Pharmachild – to quantify the occurrence of selected comorbidities in patients with JIA.

Methods

Information on which data the registers collect were compared. Patient characteristics and levels of comorbidity were presented, focusing on four key conditions: uveitis, MAS, varicella, and history of tuberculosis. Incidence rates of these on methotrexate/biologic therapy were determined.

Results

8066 patients were registered into the three JIA registers with similar history of the four comorbidities across the studies; however, varicella vaccination coverage was higher in Germany (56%) versus UK/Pharmachild (16%/13%). At final follow-up, prevalence of varicella infection was lower in Germany (15%) versus UK/Pharmachild (37%/50%). Prevalence of TB (0.1-1.8%) and uveitis (15-19%) was similar across all registers. The proportion of systemic-JIA patients who ever had MAS was lower in Germany (6%) versus UK (15%) and Pharmachild (17%).

Conclusion

This analysis is the first and largest to investigate the occurrence of four important comorbidities in three JIA registries in Europe and the role of anti-rheumatic drugs. Combined, these three registries represent one of the biggest collection of cases of JIA worldwide and offer a unique setting for future JIA outcome studies.

Keywords: JIA; epidemiology; biologic therapy; DMARDs; outcome measures; viruses

Key messages:

- This study investigates comorbidities in eight-thousand children and young people with JIA across three large registers.
- Rates of comorbidities were similar, although varicella vaccination in populations impacted comparability of varicella infections.
- This shows how JIA registers can collaborate, with synchronized analyses, and can move towards harmonisation.

INTRODUCTION

Juvenile idiopathic arthritis (JIA), characterised by arthritis of unknown origin starting before 16 years old, is the most common form of childhood chronic rheumatic illness; prevalence varying between 16 to 150 per 100,000[1,2]. The International League of Associations for Rheumatology (ILAR) has identified seven JIA categories with distinct clinical symptoms and disease courses[3]. Many children and young people (CYP) with arthritis will continue to have active disease as adults, some with severe disability despite the dramatically improved disease outcomes observed since the introduction of biologic therapy. Childhood arthritis is costly to society, in both personal and economic terms. Patients with JIA show an impairment in health status and caregivers have a life burden[4].

Many CYP with JIA suffer from comorbidities, defined as distinct additional diseases that exist prior to or may occur during the clinical course of JIA[5], with some being transient resolving medical conditions and others remaining active and persistent. These may be related to JIA itself, such as uveitis or macrophage activation syndrome (MAS)[6,7], or treatment, such as an increase in serious infections[8,9]. Other conditions may be coincidental or share risk factors with JIA itself. These can add to the complexity of the patient, as overall impact of different diseases can contribute to the overall burden of illness for the patient (e.g. socioeconomic, cultural, environmental, patient behaviour characteristics)[10]. In adults with rheumatoid arthritis, comorbidity is common, with some studies suggesting that three-in-four patients will have a second or further diagnosis as well[11].

For JIA, the burden of comorbidities is largely unknown. Following biologic DMARDs introduction in the 2000s, several patient registries were established aiming to monitoring treatment, disease activity and adverse events (AEs) in CYP with JIA. The long follow-up time of these registries serve as an important source for real-world evidence on comorbidities. Through collaboration between different registries, a better understanding of the occurrence of comorbidities in CYP with JIA can be obtained by identifying key comorbidities and their prevalence in this patient population. Detailed information on the occurrence of key comorbidities in JIA can be of use for health care providers, health care authorities and health care insurance companies.

The aim of this project was to carry out a parallel analysis in three of the largest JIA registries to quantify the occurrence of selected comorbidities in CYP with JIA; uveitis, MAS, varicella (and herpes zoster) infection, and tuberculosis (TB). The specific objectives were to (1) compare methodology of each register in terms of capturing data on comorbidity, (2) describe the prevalence of the four comorbidities above and (3) quantify the incidence of these comorbidities that later develop under treatment by final follow-up.

METHODS

Comparison of registry methodology

This analysis included three of the largest JIA cohorts; United Kingdom (UK) JIA Biologics Registers, German biologic registers, international Pharmachild registry. Data from each registry were extracted (UK: 6-Jan-2021; Germany: 10-Nov-2019; Pharmachild: 12-Nov-2020) regarding target population of each cohort, patient recruitment, baseline data collection, baseline comorbidities data, follow-up data collection, and serious AE reporting.

Cohort descriptions

UK JIA Biologic Registers

The UK JIA Biologic Registers consist of two parallel registers; British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study (BSPAR-ETN; established 2004), and Biologics for Children with Rheumatic Diseases Study (BCRD; established 2010)[12]. These prospective multicentre observational cohort studies run in parallel, aiming to monitor drug safety and assess effectiveness of therapy in routine care of CYP with JIA in the UK. Patients register when they start either methotrexate or biologic therapy. Recruitment is encouraged although not mandatory.

Data are collected via online web-portal completed by treating physician or affiliated clinical research nurse at start of therapy (registration), six months, one year and then annually. Data includes patient demographics, disease activity (joint count, physician global assessment and inflammatory parameters), functional ability using Childhood Heath Assessment Questionnaire (CHAQ)[13], comorbidities, and anti-rheumatic therapies. The rheumatologist or research nurse reports new AEs on each follow-up form.

German Biologic Registers

BiKeR (biologics in paediatric rheumatology) and JuMBO (Juvenile Arthritis Methotrexate/ Biologics Long- Term Observation) are ongoing multicentre, prospective, observational cohort studies aiming to monitor the drug safety of DMARDs and assess effectiveness of therapy in routine care of patients with JIA in Germany.

Patients with JIA enrol in BiKeR at start of biologic therapy (since 2001) or methotrexate monotherapy (since 2005). JuMBO (established 2007) is the follow-up register where patients who have reached 18 years old in BiKeR, or left paediatric care, are further observed. The register ensures the long-term follow-up of JIA patients in adult rheumatologic care.

Data are collected via paper questionnaires. Patients are assessed in BiKeR by the paediatric rheumatologist at enrolment, three months, six months, and six-monthly thereafter.

The follow-up visits are scheduled six-monthly in JuMBO. Both registers collect patient demographics, disease activity (joint count, physician global assessment and inflammatory parameters), functional ability (CHAQ in BiKeR, Health Assessment Questionnaire (HAQ) in JuMBO), comorbidities, and anti-rheumatic therapies. The rheumatologist reports any new AEs on each follow-up form.

Pharmachild

Pharmacovigilance in JIA (Pharmachild) is an ongoing observational register (established 2011); the aim is to monitor drug safety and assess effectiveness of therapy in routine care of patients with JIA. Patients are enrolled from 87 member centres around the world that belong to the Paediatric Rheumatology International Trials Organisation (PRINTO)[8,14].

Data are collected either retrospectively from enrolment or both retrospectively and prospectively every six months. Data are collected via a web-based registration system completed by the treating physician, patient-reported outcomes are entered by the patients/parents directly into the system. Data collected includes patient demographics, disease activity (joint count, physician global assessment and inflammatory parameters) and a juvenile arthritis multidimensional assessment report (JAMAR)[15], comorbidities, and anti-rheumatic therapies. The rheumatologist reports any new AEs on each follow-up form.

All registries – adverse events and ethics

Patients in the UK JIA Biologics Registers and Pharmachild continue (yearly) follow-up into adulthood (>18 years old). All registries report history of comorbidities from a tick box list of pre-defined conditions at registration. Reported AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system. AEs may include comorbidities and adverse drug reactions. All registries and centres obtained ethics committee approval according to national requirements and parents/patients provided consent/assent as appropriate in accordance with the Declaration of Helsinki. For the UK, BSPAR-ETN was approved by the West Midlands Research Ethics Committee and BCRD was approved by the North West 7 REC Greater Manchester Central Ethics Committee. For Germany, BiKeR was approved by the ethics committee of the Medical Council of North Rhine- Westphalia, Duesseldorf, Germany and JuMBO was approved by the ethics committee of Charité University Medicine Berlin. All participating centres in Pharmachild provided institutional ethics committee approval.

Data analysis

Four key comorbidities/diseases were compared between the cohorts: uveitis, MAS, varicella (varicella and herpes zoster infection), and TB. These were chosen since they are considered important in relation to JIA and its treatment.

All patients were included from the UK registries. Only patients successfully transferred to JuMBO were included in the German registers to analyse occurrence of comorbidities in childhood, adolescence and adulthood in the same cohort, although patient characteristics were described at registration into BiKeR. For Pharmachild, patients with at least one prospective visit after registration were included. For all registries, baseline data were presented at the point of registration, including history of comorbidities at baseline. Proportions of patients with comorbidities (ever uveitis, MAS, TB, and varicella) at most recent study follow-up were also presented, including comorbidities reported at registration and thus refers to time from JIA diagnosis until most recent study follow-up.

Subsequently, incidence rates of the four comorbidities of interest on methotrexate or biologic therapy within the studies were investigated. Patients were included from first registration, and exposure censored at event of interest, or patient's last follow-up, whichever came first. An event on methotrexate was defined as an event on methotrexate therapy only; patients were censored three months following methotrexate cessation, start date of biologic, or last follow-up, whichever came first. An event on biologic was defined as an event on biologic or within three months of last dose (if stopped, regardless of other therapies). Patients could contribute to both analyses if they switched between treatments, providing they met the inclusion criteria for each of the comorbidity analyses (see below). The information about MAS prior to BiKeR enrolment is available since 2004. Incidence rates for the German registers were presented separately; so the paediatric cohort rates (BiKeR) could be compared with the other registers, and the adult cohort (JuMBO) could demonstrate rates in an adult JIA population.

The analyses were limited to first event of uveitis, MAS, varicella, or TB reported within each register. Patients with a history of uveitis, MAS, or TB already at registration into the registers were excluded for their respective incidence analyses. For varicella, separate incidence rates were reported for (a) varicella infection only, (b) herpes zoster infection only and (c) either varicella or herpes zoster infection. All patients were included in these analyses regardless of varicella vaccination (VZV) history or a well-noted history of varicella infection, with the except of those with missing data at baseline which were excluded. Percentage of varicella/herpes zoster infection resulting in hospitalisation were analysed to compare between seriousness of the infection on therapy. For MAS, incidence rates on therapy were reported for systemic-JIA patients only.

The MedDRA preferred term (PT) used to identify MAS was "Histiocytosis haematophagic". BiKeR/JuMBO and Pharmachild identified TB cases from MedDRA PTs "tuberculosis", "latent tuberculosis", "pulmonary tuberculosis" and "disseminated tuberculosis". Infection coding in the UK register (to site rather than organism) meant all events including causative organism as "Mycobacterium tuberculous" were included. All registers identified uveitis

from MedDRA PTs "uveitis", "iridocyclitis", "autoimmune uveitis" and "iritis". All registries used MedDRA PT "varicella" for varicella infection and "herpes zoster" for herpes zoster infection.

Statistical analysis

All registers reported data into predefined tables providing descriptive statistics of baseline demographic and clinical data. For Pharmachild, clinical data assessed within 31 days after registration were reported. Median and interquartile range (IQR) were reported for numerical data, frequencies and percentages were reported for categorical data. All registers reported incidence rates of comorbidities as the number of new events per 100 person years with 95% confidence intervals (CI). No formal statistical comparisons were undertaken.

RESULTS

Comparison of the three cohorts

The cohorts are presented in Supplementary Table 1, including populations, and data collection. All registers include JIA patients (per ILAR criteria) on methotrexate and biological therapy. While the UK and German registers are national, include patients starting these therapies, safety data are collected in Pharmachild, an international study, from disease onset either retrospectively or prospectively after registration. Moment of inclusion is therefore not necessarily at start of therapy. Furthermore, Pharmachild uses a more limited comorbidity tick-box list, although additional comorbidities are captured through the registrations full safety and event history form.

All studies collect patient demographics and most core outcome variables, including the ability to measure JADAS-71. While Pharmachild collects moderate, severe or serious AEs, the German and UK registers also collect mild AEs. The four comorbidities of interest in this manuscript – uveitis, MAS, varicella and TB – were all captured in a similar format at baseline across all cohorts. VZV information is collected from all cohorts although the UK only have vaccination data from July 2016 onwards.

Patient characteristics

A total of 8066 CYP with JIA from the three registers were included in this analysis; 2963 from the UK, 1541 from Germany, and 3562 into the prospective cohort of Pharmachild. Table 1 shows characteristics of patients registered into these studies. Overall, 68-70% of patients were female, although age at registration varied from 11 years (UK/Pharmachild), to 14 years (Germany). In addition, the UK had a lower disease duration at registration (1 year) versus Germany/Pharmachild (3 years).

Table 1: Characteristics of patients included from the three registers.

	UK JIA Biologics Registers registered by 6th January 2021	**BiKeR / JuMBO registered by 10th November 2019**	**Pharmachild prospective cohort registered by 12th November 2020**
Number of patients, n	2963	1541	3562
Female, n (%)	2014 (68%)	1046 (68%)	2476 (70%)
ILAR category, n (%)			
Oligoarthritis	880 (30%)	415 (27%)	1426 (40%)
Persistent	359 (12%)	137 (9%)	903 (25%)
Extended	521 (18%)	278 (18%)	523 (15%)
Polyarthritis RF -	962 (32%)	414 (27%)	913 (26%)
Polyarthritis RF +	242 (8%)	129 (8%)	148 (4%)
Systemic arthritis	259 (9%)	82 (5%)	370 (10%)
Psoriatic arthritis	189 (6%)	131 (8%)	120 (3%)
Enthesitis-related arthritis	253 (9%)	315 (20%)	333 (9%)
Undifferentiated arthritis	94 (3%)	54 (5%)	252 (7%)
Unknown	84 (3%)	1 (<1%)	-
At registration			
Age (years), median (IQR)	11 (6, 14)	14 (12, 16)	11 (7 – 14)
Disease duration (years) from diagnosis, median (IQR)	1 (0, 4) N=2894	3 (1, 7) N=1531	3 (1 – 6)
Disease Activity, median (IQR)			
Active joint count (71-joint)	4 (1, 8) N=2724	4 (2, 8) N=1537	1 (0, 4) N = 906
Limited joint count (71-joint)	3 (1, 6) N=2658	4 (2, 9) N=1537	1 (0, 4) N = 906
Physician Global Assessment (10cm)	3 (2, 5) N=1909	5 (3, 7) N=1513	2 (0, 4) N = 906
Parent (patient) Assessment of Well-being (10cm)	4 (1, 6) N=1978	5 (3, 7) N=1384	2 (0, 5) N = 668
Functional Ability	CHAQ (range 0-3): 0.9 (0.3, 1.5) N=1871	CHAQ (range 0-3): 0.5 (0.125, 1.00) N=1395	JAMAR: 2 (0, 6) N = 560
Pain VAS (10cm)	4 (1, 7) N=1899	4 (2, 7) N=1228	2(0, 5) N = 619
ESR (mm/h)	13 (5, 30) N=2444	16 (7, 35) N=1451	12 (6, 28) N = 710
CRP (mg/L)	5 (4, 15) N=2497	5.5 (2.1, 24) N=947	3 (1, 11) N = 728
JADAS-71	13 (7, 20) N=1337	15 (10, 20) N=1370	8 (2, 16) N = 510

Table 1: Continued

	UK JIA Biologics Registers registered by 6th January 2021	**BiKeR / JuMBO registered by 10th November 2019**	**Pharmachild prospective cohort registered by 12th November 2020**
Varicella vaccination, n (%)	95 (16%) N=609	136 (56%) N=241	376 (13%) N = 2934
History of comorbidities, n (%)			
Ever Uveitis	444 (16%) N=2738	204 (13%)	664 (19%) N = 3484
Ever MAS (sJIA only)	32 (24%) N=136	2 (3.9%) N=56	53 (14%) N = 366
Had Varicella infection	750 (32%)[b] N=2351	98 (11%) N=871	1120 (49%) N = 2279
Ever Tuberculosis	12 (0.6%) N=1900	0 (0.0%)	46 (1.5%)[a] N = 3005
Drugs, n (%)			
Methotrexate (monotherapy)	1092 (37%)	544 (35%)	1084 (30%)
Etanercept	1105 (37%)	885 (57%)	738 (20.7%)
Adalimumab	430 (15%)	86 (6%)	397 (11.1%)
Infliximab	123 (4%)	0 (0%)	47 (1.3%)
Anakinra	37 (1%)	1 (<1%)	65 (1.8%)
Rituximab	9 (<1%)	0 (0%)	1 (<1%)
Tocilizumab	138 (5%)	18 (2%)	117 (3%)
Abatacept	25 (1%)	3 (<1%)	104 (3%)
Golimumab	1 (<1%)	1 (<1%)	6 (<1%)
Baricitinib	1 (<1%)	0	0 (0%)
Secukinumab	3 (<1%)	0	0 (0%)
Canakinumab	0 (0%)	3 (<1%)	34 (1%)
At most recent follow-up			
Follow-up from JIA diagnosis (years, not necessarily in the study), median (IQR)	5 (3, 9) N=2926	14 (7, 18) N=1514	6 (3 – 9)
Mean (SD)	6.5 (4.6)	13.2 (6.1)	6.5 (4.5)
Age (years), median (IQR)	14 (10 – 17)	22 (19 – 25)	13 (9 – 17)

Table 1: Continued

	UK JIA Biologics Registers registered by 6th January 2021	BiKeR / JuMBO registered by 10th November 2019	Pharmachild prospective cohort registered by 12th November 2020
Comorbidities, n (%)			
Ever Uveitis	556 (19%)	238 (15%)	676 (19%) N = 3484
Ever MAS (sJIA only)	37 (15%) N=250	5 (6%) N=82	62 (17%) N = 366
Ever Varicella Infection	822 (37%)[b] N=2238	127 (15%) N=871	1166 (50%) N = 2312
Ever Tuberculosis	17 (0.6%)	2 (0.1%) N=1541	54 (1.8%)[a] N = 3006

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ILAR: International League of Associations for Rheumatology; JADAS: Juvenile Arthritis Disease Activity Score; JAMAR: Juvenile Arthritis Multidimensional Assessment Report; MAS: macrophage activation syndrome; RF: rheumatoid factor; sJIA: systemic juvenile idiopathic arthritis; VAS: visual analogue scale. [a]Including latent tuberculosis. [b]Identified at baseline as either ticked varicella infection, or were chicken pox immune (providing they had not had the vaccination).

Prevalence of most comorbidities at registration were similar across the studies; 13-19% had a history of uveitis, 0-1.5% had ever had TB. However, VZV coverage was higher in Germany (56% versus 13%-16%) resulting in a lower varicella infection at registration (11% versus 32%-49%). VZV coverage per country for Pharmachild is provided in Supplementary Table 2.

At final follow-up, prevalence of ever uveitis (15-19%), and ever TB (0.1-1.8%) was similar across all registers. Differences in varicella infection was again observed at final follow-up; 15% in Germany, 37% in UK, 50% in Pharmachild.

Incidence rates of comorbidities on therapy

Incidence of comorbidities were investigated for CYP within the registers on methotrexate and biologic therapy (Tables 2 and 3). Rate of uveitis varied between cohorts for patients on methotrexate therapy from 2.1 (UK) to 0.22 (Pharmachild) per 100 person years, whilst Germany reported no patients. Rates of uveitis on biologic therapy remained higher in the UK (0.75) versus Pharmachild (0.20) and BiKeR (0.14 per 100 person years). The German adult JIA (JuMBO) register reported a higher incidence of uveitis compared with the paediatric cohort (0.33 vs 0.14 per 100 person years). Rates of varicella and herpes zoster infection were also higher for the UK on methotrexate and biologic therapy; varicella infection on biologic therapy 1.7 versus 0.32 (Pharmachild) and 0.07 per 100 person years (BiKeR). The percentage of varicella or herpes zoster infections that resulted in hospitalization was higher in the UK register compared to the German registers and Pharmachild. No obvious

differences in hospitalizations for varicella or herpes zoster infections were observed between events on methotrexate and biologic therapy within any of the registers.

Table 2. Incidence of comorbidities on methotrexate monotherapy in the three registers.

	Pharmachild	**JuMBO**	**BiKeR**	**UK JIA Biologics Registers**
Total number of patients	2462[a]	544		1065
ILAR category, n (%)				
Oligoarthritis	988 (40%)	179 (33%)		372 (35%)
Persistent	*623 (25%)*	*100 (18%)*		*194 (18%)*
Extended	*365 (15%)*	*79 (15%)*		*178 (17%)*
Polyarthritis RF-	692 (28%)	140 (26%)		341 (32%)
Polyarthritis RF+	116 (5%)	30 (6%)		84 (8%)
Systemic arthritis	202 (8%)	15 (3%)		46 (4%)
Psoriatic arthritis	84 (3%)	57 (10%)		83 (8%)
Enthesitis-related arthritis	218 (9%)	104 (19%)		71 (7%)
Undifferentiated arthritis	162 (7%)	19 (3%)		35 (3%)
Unknown	0 (0%)	0 (0%)		33 (3%)
Total MTX exposure, years	1659	642	2226	2499

Table 2. Continued.

	Pharmcachild		JuMBO		BiKeR		UK JIA Biologics Registers	
	Rate per 100 person years (95% CI)	**Frequency, N**	**Rate per 100 person years (95% CI)**	**Frequency, N**	**Rate per 100 person years (95% CI)**	**Frequency, N**	**Rate per 100 person years (95% CI)**	**Frequency, N**
Uveitis	0.22 (0.05 – 0.64)	3 patients, N = 1967	-	No patients, N = 544	-	No patients, N = 544	2.2 (1.6 – 3.0)	41 patients, N = 952
MAS (sJIA only)	1.57 (0.04 - 8.74)	1 patient, N = 177	-	No patients, N=82	-	No patients, N=82	1.2 (0.2 – 8.3)	1 patient, N = 42
Varicella	0.55 (0.25 – 1.04)	9 patients, N = 2462	-	No patients, N = 544	-	No patients, N = 544	2.4 (1.8 – 3.1)	50 patients, N = 1065
Herpes zoster	0.12 (0.01 – 0.44)	2 patients, N = 2462	0.3 (0.03 – 1.1)	2 patients, N = 544	0.04 (0.001 – 0.24)	1 patient, N = 544	0.5 (0.3 – 1.0)	12 patients, N = 1065
Varicella + herpes zoster	0.67 (0.33 – 1.20)	11 patients, 1 (9%) hospitalized, N = 2462	0.3 (0.03 – 1.1)	2 patients, 0 (0%) hospitalized N = 544	0.04 (0.001 – 0.24)	1 patient, 0 (0%) hospitalized, N = 544	2.9 (2.3 – 3.8)	61 patients, 25 (41%) hospitalized, N = 1065
TB	0.18 (0.04 - 0.53)	3 patients, N = 2430	0.15 (0.02 - 1.11)	1 patient, N=544	-	No patients, N=544	-	No patients, N = 1062

ILAR:InternationalLeagueofAssociationsforRheumatology;MAS:macrophageactivationsyndrome;RF:rheumatoidfactor;sJIA:systemicjuvenileidiopathicarthritis;TB:tuberculosis

[a]Number of Pharmachild patients ever treated with methotrexate monotherapy is greater than the number reported on methotrexate monotherapy at registration (table 1).

Table 3. Incidence of comorbidities on biologic therapy in the three registers.

	Pharmachild	JuMBO	BiKeR	UK JIA Biologics Registers
Total number of patients	2475[a]	1256		2185
ILAR category, n (%)				
Oligoarthritis	834 (34%)	298 (24%)		579 (26%)
Persistent	430 (17%)	47 (4%)		*181 (8%)*
Extended	404 (16%)	251 (20%)		*398 (18%)*
Polyarthritis RF-	699 (28%)	345 (27%)		715 (33%)
Polyarthritis RF+	106 (4%)	125 (10%)		189 (9%)
Systemic arthritis	291 (12%)	84 (7%)		226 (10%)
Psoriatic arthritis	95 (4%)	93 (7%)		133 (6%)
Enthesitis-related arthritis	266 (11%)	266 (21)		212 (10%)
Undifferentiated arthritis	184 (7%)	45 (4%)		64 (3%)
Unknown	0 (0%)	0 (0%)		67 (3%)
Total biologic exposure, years	4778	1920	5180	6078

Table 3. Continued.

	Pharmachild	JuMBO	BiKeR	UK JIA Biologics Registers
Individual biologic exposure[b], years				
TNF-α inhibitors				
Adalimumab	1332	521	570	1176
Certolizumab	7	94	4	-
Etanercept	2260	571	4222	3193
Golimumab	50	110	20	6
Infliximab	125	154	56	686
IL-1 inhibitors				
Anakinra	112	25	66	132
Canakinumab	139	13	21	5
Other				
Abatacept	348	62	95	167
Baricitinib	<1	10	1	3
Rituximab	4	41	4	94
Secukinumab	-	13	2	-
Tocilizumab	400	306	120	794
Ustekinumab	-	-	-	4

Table 3. Continued.

	Pharmachild		JuMBO		BiKeR		UK JIA Biologics Registers BiKeR	
	Rate per 100 person years (95% CI)	**Frequency, N**	**Rate per 100 person years (95% CI)**	**Frequency, N**	**Rate per 100 person years (95% CI)**	**Frequency, N**	**Rate per 100 person years (95% CI)**	**Frequency, N**
Uveitis	0.20 (0.08 – 0.40)	7 patients, N = 1930	0.33 (0.17 – 0.60)	11 patients, N = 1256	0.14 (0.07 – 0.26)	10 patients, N = 1256	0.7 (0.5 – 1.0)	34 patients, N = 1781
MAS (sJIA only)	1.73 (0.75 - 3.40)	8 patients, N = 246	0.48 (0.07 - 3.39)	1 patient, N=82	0.15 (0.02 - 1.13)	1 patient, N=82	0.5 (0.2 – 1.4)	4 patients, N = 196
Varicella	0.32 (0.18 – 0.53)	15 patients, N = 2475	0.03 (0.001 – 0.17)	1 patient, N = 1256	0.07 (0.02 – 0.16)	5 patients, N = 1256	1.7 (1.4 – 2.0)	96 patients, N = 2185
Herpes zoster	0.38 (0.23 – 0.61)	18 patients, N = 2475	0.18 (0.07 – 0.40)	6 patients, N = 1256	0.14 (0.07 – 0.26)	10 patients, N = 1256	0.8 (0.6 – 1.1)	46 patients, N = 2185
Varicella + herpes zoster	0.70 (0.48 – 0.99)	33 patients, 3 (9%) hospitalized, N = 2475	0.21 (0.08 – 0.44)	7 patients, 1 (14%) hospitalized, N = 1256	0.21 (0.12 – 0.35)	15 patients, 2 (13%) hospitalized, N = 1256	2.5 (2.1 – 2.9)	139 patients, 55 (40%) hospitalized, N = 2185
TB	0.11 (0.03 - 0.25)	5 patients, N = 2436	0.03 (0.004 - 0.22)	1 patient, N=1256	-	No patients, N=1256	0.05 (0.02 – 0.15)	3 patients, N=2185

ILAR:InternationalLeagueofAssociationsforRheumatology;MAS:macrophageactivationsyndrome;RF:rheumatoidfactor;sJIA:systemicjuvenileidiopathicarthritis;TB:tuberculosis

[a]Number of Pharmachild patients ever treated with biologic therapy is greater than the number reported on biologic therapy at registration (table 1).

[b]The sum of individual biologic exposure is greater than overall total exposure as it includes the 90 days added exposure window.

DISCUSSION

This analysis is the first and largest to investigate the occurrence of a selection of routinely collected comorbidities in 8066 CYP with JIA from three of the largest JIA registries. At registration into the cohorts, proportions of patients with a history of uveitis (13-19%) and TB (0-1.5%) were similar. However, there were differences in the proportion of systemic-JIA patients with a history of MAS (4-24%). This study also identified differences in the general health systems reporting into these registries, such as the common use of VZV in Germany (56%), and not in the UK (16%) and Pharmachild countries (13%) which could result in difference in the occurrence of related comorbidities. As a result, the proportion of patients in Germany who had a history of varicella infection was much lower (11% versus 32-49%).

The difference in disease activity parameters at registration between Pharmachild and the UK/Germany can be explained by the moment of inclusion into the registries. Patients in the UK and German registers are included following initiation of biologic or methotrexate therapy, which might indicate a worsening of the disease. The moment of inclusion into Pharmachild is at random and not necessarily after starting a particular therapy.

The increased prevalence of TB at registration and incidence rates within Pharmachild as compared with the other registers is likely due to the countries involved. Countries known to have relatively high rates of TB that contribute patients to Pharmachild include Russia, South Africa and Brazil[9]. The observed rate of TB on biologic therapy in the UK was higher than the 2018 overall rate of TB in children below the age of 15 born in the UK[16]. JIA patients under biologic therapy are at an increased risk for developing TB and other serious infectious diseases[17]. Given the potential severity of TB infection, it is recommended that CYP with immune-mediated diseases such as JIA should be screened for latent-TB infection before commencing immunosuppressive drugs[18–20] although this would not prevent symptomatic de novo infection.

Prevalence rates of uveitis at most recent follow-up in this study (15–19%) were in concordance with the existing literature[6]. The UK had higher incidence rates of uveitis compared with BiKeR/JuMBO and Pharmachild, most likely due to shorter disease duration at registration (1 versus 3 years). In addition, within the UK and Pharmachild, CYP on methotrexate had higher incidence rates of uveitis compared with those on biologics. It is known that uveitis is more likely to happen within the first two years following JIA diagnosis[21], and therefore more common among CYP on methotrexate therapy (first choice therapy). In contrast, Germany observed higher rates of uveitis on biologic versus methotrexate therapy. Perhaps explained as uveitis occurs most frequently in oligoarthritis patients and these on methotrexate were not enrolled in BiKeR[21].

In Germany, VZV has been part of the routine childhood vaccination programme, in the first two years of life, since 2004[22]. The proportion of the population coverage in 2010, the most appropriate comparison for the age of this cohort, was roughly 50%, consistent with the 56% of the patients vaccinated in the German registers. In contrast, the UK does not offer VZV as part of their routine childhood vaccination programme resulting in minimal national coverage. However, UK patients with JIA without varicella immunity are considered for vaccination[23]. Whilst 16% of patients were vaccinated, due to the late introduction of this question into the registers (with data available since 2016), this percentage could be as low as 3% (assuming patients with missing data were unvaccinated). In addition, Pharmachild covers 31 countries, the majority of which do not routinely vaccinate against varicella[24]. These differences in vaccination coverage between register are likely to explain the lower rate of varicella and herpes zoster infection in Germany. In addition, the higher incidence rate of varicella in the UK compared with Pharmachild could be explained by the average younger age of patients in the UK register. This could also explain why more patients in Pharmachild had had varicella at registration versus the UK register. As to be expected, higher rates of herpes zoster were observed in the adult JuMBO cohort compared with the juvenile BiKeR cohort, whilst the opposite was true for varicella on biologic therapy[25]. Although little is known about this subject, a meta-analysis showed that the most frequent serious infections on biologics in JIA were varicella next to bronchopulmonary infections[26]. Taking into account the potential seriousness of this diagnosis in immunocompromised children, the results of our analysis provide rationale for routine VZV in JIA. It must be noted that although VZV in JIA appears to be safe, it does not always protect against varicella infection[27]. Nevertheless, the most recent EULAR recommendations for vaccination in adult patients with rheumatic diseases already indicate that VZV may be considered in high-risk patients[28].

There was no difference in the proportion of varicella or herpes zoster infections that resulted in hospitalization between events on methotrexate and biologic therapy within the registers, although the UK reported much higher proportions than Pharmachild and BiKeR/JuMBO. These proportions were also much higher than previously reported numbers of complications per varicella case in Europe, ranging from 0 to 6%[29,30]. Possible reasons for the discrepancy in proportions between the UK and other registers are sociodemographic differences such as reduced access to healthcare in low- and middle-income countries that contribute to Pharmachild and cultural/treatment protocol differences in hospitalising patients on immunosuppressive therapy that experience varicella/herpes zoster[31]. For example, if a varicella infection in an immunocompromised patient is generally assessed as life-threatening, it might be decided to administer acyclovir or another antiviral therapy intravenously instead of oral, which requires hospitalization but is more effective[32].

Proportions of systemic-JIA patients who had experienced MAS at most-recent follow-up in this study were in line with the existing literature[2,7]. MAS was less common in systemic-JIA patients from BiKeR/JuMBO registers (6%), compared with the UK and Pharmachild registers (15-17%) at most recent follow-up. The lower proportion of MAS in systemic-JIA patients in BiKeR/JuMBO may be explained by enrolling patients with start of treatment with etanercept most notably in the early years of BiKeR. We hypothesize that those patients had less severe systemic-features and the joint involvement was the primary reason for treatment start with etanercept. Pharmachild and the UK observed a higher rate of MAS in systemic-JIA patients on methotrexate therapy compared with biologic therapy. This might be explained by existing evidence suggesting that the commonly prescribed IL-1-inhibiting agent anakinra is effective in the treatment of MAS in systemic-JIA[33–35].

These analyses are not without limitations. All of these registries are observational cohort studies and rely on data input from clinicians/research nurses. It is possible that events are not reported to the clinic team, and thus research studies, and therefore these rates may be underestimated. Nevertheless, similar results across the registries are likely more reliable and therefore will lower the risk of underestimation. There may also be variations in reporting between countries. However, the analysed events are considered important in paediatric rheumatology internationally and therefore the impact is likely minimal. It is also possible that drug (methotrexate/biologic) start and stop dates are missing, although most data should be up-to-date as patients were censored at their final follow-up date. This analysis did not report the comorbidities for the entire BiKeR cohort, just the subpopulation that reached 18 years on the cut-off date and were followed into adulthood. These patients tended to be more severely affected by JIA versus those not observed in JuMBO. However, the combined BiKeR/JuMBO cohort provided data for onset of comorbidities in CYP and young adulthood. Considering the variations across the populations, analysis with pooled data might be preferable. Differences in patients within each register may account for variations in results observed: oligoarthritis patients receiving methotrexate were not enrolled in BiKeR, and shorter disease duration and younger age at registration into the UK register, thus influencing rates of uveitis and varicella. It is also important not to directly compare the rates of comorbidities between methotrexate and biologic treated patients as there may be some confounding by indication.

In conclusion, this study looks at a selection of key comorbidities and the roles of anti-rheumatic drugs in over eight-thousand CYP with JIA across three large registers. It highlights relatively similar rates of comorbidities, as well as the impact of VZV in populations on the comparability of varicella infections. This study shows the ability for

JIA registers to work together, running synchronized analyses, and is the first step towards more harmonised collaborations.

ACKNOWLEDGEMENTS

The authors would like to express their acknowledgements to the European Reference Network for Immunodeficiency, Autoinflammatory, Autoimmune and Paediatric Rheumatic diseases (ERN-RITA).

FUNDING

This work was supported by a research grant from FOREUM Foundation for Research in Rheumatology.

The UK JIA Biologic Registers – including the Biologics for Children with Rheumatic Diseases (BCRD) study and the BSPAR Etanercept Cohort (BSPAR-ETN) study – are jointly funded by the British Society for Rheumatology (BSR) and Versus Arthritis (UK grant number 20747) via a research grant to the University of Manchester. The research team at The University of Manchester are additionally supported by the Centre for Epidemiology Versus Arthritis (UK grant number 21755). This report includes independent research supported by the NIHR Manchester Biomedical Research Centre (KLH).

The BIKER registry was supported by an unconditional grant from Pfizer, Abbvie, Merck Sharp & Dohme (MSD), Novartis and Roche. The JuMBO registry was supported by a joint unconditional grant from Pfizer, Abbvie, Roche, BMS and Biogen. The companies had no influence on study design or on the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication.

Pharmachild has been supported by EU grant (2011-2014):"Long-term PHARMacovigilance for Adverse effects in Childhood arthritis focusing on Immune modulatory drugs" (project number 260353) and IRCCS Istituto G. Gaslini in Genoa, Italy.

COMPETING INTERESTS

KLH reports honoraria from Abbvie and Grants from Pfizer and BMS. All other authors report no disclosures.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Comparison of the cohorts.

	UK Paediatric Biologics Registers	BiKeR	JuMBO	Pharmachild register
Year of study initiation	2010	2001	2007	2011
Population	JIA patients aged <16 years old starting either methotrexate or biologic DMARDs	JIA patients aged <16 years old starting either methotrexate or biologic DMARDs	JIA patients aged ≥18 years old (or graduating from paediatric care) transferred from BiKeR	JIA patients of any age receiving NSAIDs, intraarticular or systemic steroids, conventional or biologic DMARDs
Country / countries	United Kingdom	Germany, Austria	Germany, Austria	Argentina, Austria, Brazil, Bulgaria, Croatia, Czech Republic, Denmark, Ecuador, France, Greece, Hungary, India, Israel, Italy, Latvia, Libya, Lithuania, Mexico, Netherlands, Norway, Oman, Poland, Romania, Russian Federation, Saudi Arabia, Serbia, Singapore, Slovakia, Spain, Switzerland and Turkey
Patient recruitment	Patients are recruited from centres all over the country.	Patients are recruited from centres all over the country.	Patients are recruited from centres all over the country.	Patients are recruited from PRINTO member centres from 31 countries.
Baseline data collected	Demographic, clinical, laboratory data. Drug exposure and comorbidities.	Demographic, clinical, laboratory data. Drug exposure and comorbidities.	Demographic, clinical, laboratory data. Drug exposure and comorbidities.	Demographic, clinical, laboratory data. Drug exposure, safety events and comorbidities.
Baseline comorbidities collected	Tick boxes (including date and free text for further information):	Tick boxes (including date and free text for further information):	Tick boxes (including date and free text for further information):	Tick boxes (yes / no / unknown):
	Allergies	Allergies	Allergic diseases	
		Alcohol, medication or drugs abuse	Alcohol, medication or drugs abuse	
	Cancer / Neoplasia	Cancer / Neoplasia	Neoplasms	
	Cardiovascular	Cardiovascular	Cardiovascular diseases	
	Endocrinology / Metabolism	Endocrinology / Metabolism	Endocrinology / Metabolism	
	Eye disease (except uveitis)	Eye disease (except uveitis)	Eye diseases not related to rheumatic disease	
	Gastrointestinal	Gastrointestinal	Gastrointestinal diseases	

Supplementary Table 1. Continued.

	UK Paediatric Biologics Registers	BiKeR	JuMBO	Pharmachild register
Baseline comorbidities collected	Gynaecological / Obstetrics		Gynaecological diseases	
	Haematological	Haematological	Hematologic diseases	
	Kindey / Renal	Kindey / Renal	Kidney diseases/ diseases of the urinary tract	
	Liver Disease	Liver Disease	Liver / bile diseases	
	MAS			MAS
		Measles		
	Mental illness / depression	Mental illness / depression	Psychiatric disorders / depression	
			Metabolic disorders	
	Neurological	Neurological	Neurological diseases	
	Respiratory	Respiratory	Pulmonary diseases	
	Skin Disease	Skin Disease	Skin Disease	
	Tuberculosis	Tuberculosis	Tuberculosis	Tuberculosis (previous/ latent/exposure)
	Uveitis	Uveitis	Uveitis	Uveitis (acute anterior uveitis/chronic iridocyclitis)
	Varicella	Varicella		Varicella
			Chronic virus infections	
	Other (free text)	Other (free text)	Other diseases	History of other comorbidities are reported in open text fields.
Follow-up data collected	At 6 months, 12 months then annually: clinical and laboratory data, drug exposure, AEs, disease activity, and HRQoL	3 and 6 months after enrolment, and 6 monthly thereafter: clinical and laboratory data, drug exposure, patient-reported outcomes, AEs, disease activity, and HRQoL	6 monthly: clinical and laboratory data, drug exposure, patient-reported outcomes, AEs, disease activity, and HRQoL	6 monthly: clinical and laboratory data, drug exposure, patient-reported outcomes, AEs, disease activity, HRQoL, growth and joint damage

Supplementary Table 1. Continued.

	UK Paediatric Biologics Registers	BiKeR	JuMBO	Pharmachild register
AE data collection	All AEs (serious and non-serious) on follow-up forms (free text). Additional information are requested on each serious AE and ESI sent if necessary.			Moderate/severe/serious AEs are reported on follow-up forms (check boxes and free-text) using classic CIOMS form and MedDRA coding system. Additional information on ESIs are reported on separate dedicated case report forms.
AEs classified as Events of Special Interest (ESI)	Serious infection	Serious infection (including opportunistic infection)		Serious/targeted infections (Epstein-Barr virus, cytomegalovirus, papilloma virus, herpes zoster primary and reactivation and opportunistic infections)
	Tuberculosis	Tuberculosis		Tuberculosis
	Congestive heart failure	Cardiovascular events (e.g., myocardial infarction, stroke)		Congestive heart failure
	Aplastic anaemia / pancytopenia / neutropenia	Serious/medically significant cytopenia		Aplastic anaemia Neutropenia Pancytopenia
	Demyelination optic neuritis	New-onset of demyelinating disease		Demyelination, optic neuritis
	Gastro-intestinal ulcer / bleed / perforation	Gastro-intestinal perforation Serious / medically significant bleeding events		Gastro-intestinal ulcer/bleed/perforation
	Inflammatory bowel disease	New-onset of inflammatory bowel disease		Inflammatory bowel disease
	Immunologic reaction (significant, includes anaphylaxis)	Anaphylaxis/hypersensitivity reactions		Infusion/injection related reactions
	Lymphoproliferative malignancy Non-haematological malignancy	Malignancy		Lymphomas, leukaemia's, (haematopoietic) neoplasms
	Lupus / lupus like reaction	New-onset of systemic lupus erythematosus		Lupus erythematosus systemic/lupus-like syndrome
	Uveitis	New-onset of uveitis		
		New-onset of other immune-mediated inflammatory disease		
				Other autoimmune diseases
	Pregnancy	Pregnancy		Pregnancy
		Serious / medically significant hepatic events		
		MAS		MAS
				Multiple sclerosis

AE: adverse event; DMARD: disease-modifying antirheumatic drug; HRQoL: health-related quality of life; JIA: juvenile idiopathic arthritis; MAS: macrophage activation syndrome; NSAID: non-steroidal anti-inflammatory drug; PRINTO: Paediatric Rheumatology International Trials Organisation

Supplementary Table 2. Varicella vaccination coverage per country at registration into Pharmachild for patients with available data on vaccination (n = 2934).

Country	Varicella vaccination coverage
Turkey	8/8 (100.0%)
Greece	87/166 (52.4%)
Brazil	18/59 (30.5%)
Spain	99/343 (28.9%)
Norway	42/175 (24.0%)
Saudi Arabia	10/45 (22.2%)
Israel	5/28 (17.9%)
Hungary	12/72 (16.7%)
Latvia	2/14 (14.3%)
Italy	68/810 (8.4%)
France	15/239 (6.3%)
Mexico	5/108 (4.6%)
Ecuador	1/25 (4.0%)
Czech Republic	2/115 (1.7%)
Romania	1/84 (1.2%)
Lithuania	1/140 (0.7%)
Austria	0/2 (0.0%)
Croatia	0/22 (0.0%)
Denmark	0/3 (0.0%)
India	0/93 (0.0%)
Libya	0/10 (0.0%)
Netherlands	0/301 (0.0%)
Poland	0/25 (0.0%)
Russian Federation	0/25 (0.0%)
Slovakia	0/21 (0.0%)
Switzerland	0/1 (0.0%)

CHAPTER 5

5

A clinical prediction model for estimating the risk of developing uveitis in patients with juvenile idiopathic arthritis

Joeri W. van Straalen[1], Gabriella Giancane[2,3], Yasmine Amazrhar[1], Nikolay Tzaribachev[4], Calin Lazar[5], Yosef Uziel[6], Albena Telcharova - Mihaylovska[7], Claudio A. Len[8], Angela Miniaci[9], Alina L. Boteanu[10], Giovanni Filocamo[11], Mariel V. Mastri[12], Thaschawee Arkachaisri[13], Maria G. Magnolia[14], Esther Hoppenreijs[15], Sytze de Roock[1], Nico M. Wulffraat[1], Nicolino Ruperto[2]* and Joost F. Swart[1]* for the Paediatric Rheumatology International Trials Organisation (PRINTO)

[1]Department of Paediatric Immunology and Rheumatology, Wilhelmina Children's Hospital, Utrecht, Netherlands
[2]IRCCS Istituto Giannina Gaslini, Clinica Pediatrica e Reumatologia, Genoa, Italy
[3]Università degli Studi di Genova, Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili (DiNOGMI), Genoa, Italy
[4]Pediatric Rheumatology Research Institute, Bad Bramstedt, Germany
[5]Spitalul Clinic de Urgenta pentru Copii, Paediatrics, Cluj-Napoca, Romania
[6]Meir Medical Centre, Paediatric Rheumatology Unit, Department of Paediatrics, Kfar Saba, Israel and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
[7]University Children Hospital, Department of Paediatric Rheumatology, Sofia, Bulgaria
[8]Universidade Federal de São Paulo, Paediatrics Department, Sao Paulo, Brazil
[9]Azienda Ospedaliero-Universitaria S.Orsola-Malpighi, Salute della Donna, del Bambino e dell'Adolescente-Padiglione 16 Ambulatorio di reumatologia, Bologna, Italy
[10]University Hospital Ramón y Cajal, Paediatric Rheumatology Unit, Madrid, Spain.
[11]Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Paediatric Rheumatology, Milan, Italy
[12]Hospital Sor Maria Ludovica, Unidad de Reumatologia, La Plata, Argentina
[13]KK Women's and Children's Hospital, Rheumatology and Immunology Service Department of Paediatric Subspecialties, Singapore, and Duke-NUS Medical School, Singapore
[14]Santa Maria della Stella Hospital, Paediatrics, Ciconia - Orvieto (TR), Italy
[15]Radboud University Medical Centre/Sint Maartenskliniek, Paediatric Rheumatology, Nijmegen, Netherlands

**Joost F. Swart and Nicolino Ruperto contributed equally*

Rheumatology (Oxford). 2021;60(6):2896-2905.

ABSTRACT

Objectives

To build a prediction model for uveitis in children with juvenile idiopathic arthritis (JIA) for use in current clinical practice.

Methods

Data from the international observational Pharmachild registry were used. Adjusted risk factors as well as predictors for JIA-associated uveitis (JIA-U) were determined using multivariable logistic regression models. The prediction model was selected based on Akaike information criterion. Bootstrap resampling was used to adjust the final prediction model for optimism.

Results

JIA-U occurred in 1,102 of 5,529 JIA patients (19.9%). The majority of patients that developed JIA-U were female (74.1%), ANA positive (66.0%) and had oligoarthritis (59.9%). JIA-U was rarely seen in patients with systemic arthritis (0.5%) and RF positive polyarthritis (0.2%). Independent risk factors for JIA-U were ANA positivity (OR: 1.88, 1.54 – 2.30) and HLA-B27 positivity (OR: 1.48, 1.12 – 1.95) while older age at JIA onset was an independent protective factor (OR: 0.84, 0.81 – 0.87). On multivariable analysis, the combination of age at JIA onset (OR: 0.84, 0.82 – 0.86), JIA category and ANA positivity (OR: 2.02, 1.73 – 2.36) had the highest discriminative power among the prediction models considered (optimism-adjusted AUC = 0.75).

Conclusion

We developed an easy to read model for individual patients with JIA to inform patients/parents on the probability of developing uveitis.

Key words: uveitis, juvenile idiopathic arthritis, prediction model, risk factors, confounders

Key messages:

- We provide for the first time a model for predicting uveitis in juvenile idiopathic arthritis.
- Individual risk estimates for uveitis might guide physicians in determining ophthalmological screening frequencies.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a group of diseases characterized by arthritis of unknown origin persisting for >6 weeks before the age of 16[1,2]. It is the commonest rheumatic disease in children with a prevalence varying between 3.8-400 per 100,000[3–5]. JIA patients are at an increased risk of developing uveitis, which is an inflammatory condition of the uvea, including the iris, ciliary body and choroid[6]. A systematic review reported a cumulative incidence of JIA-associated uveitis (JIA-U) of 11.4%[7]. Frequency of JIA-U varies geographically and is highest in patients with oligoarthritis while low in patients with systemic and rheumatoid factor (RF) positive arthritis[8,9]. JIA-U occurs more often in girls and known risk factors are younger age at JIA onset and having antinuclear antibodies (ANA) positivity[6,10–18]. The estimated prevalence of JIA-U varies up to 30%[6], but the risk of acquiring uveitis for an individual JIA patient is unknown. Chronic anterior uveitis or silent uveitis is the most common form of JIA-U and is usually asymptomatic. On the contrary, acute anterior uveitis presents with apparent symptoms such as eye pain, redness of eyes and headaches[6,19]. If left un- or undertreated, (silent) uveitis may result in sight-threatening complications including synechiae, cataracts and glaucoma in 25-50% and vision loss in 10-20% of paediatric uveitis cases[20].

Therefore, early detection and subsequent intensive treatment is the key. Several guidelines exist for the routine screening of JIA patients by ophthalmologists. These include the 1993 American Academy of Pediatrics guidelines, the 2006 British Society for Paediatric and Adolescent Rheumatology (BSPAR) guidelines and the 2019 American College of Rheumatology (ACR) guidelines, as well as screening recommendations by Heiligenhaus *et al.* following a 2007 nation-wide study in Germany[6,11,20–22]. These guidelines are all based on the risk factors: age at JIA onset, ANA status, JIA category and disease duration. Nevertheless, they use different cut-off values for the age at JIA onset, include different JIA categories and recommend different screening frequencies. It can be concluded that while screening for JIA-U is of utmost importance, there is neither global consensus on the screening frequency, nor on the criteria to identify high-risk patients for uveitis[23]. In fact, the treating physician does not have tools to estimate the real risk of acquiring uveitis for the individual patient.

The objective of this study is to develop a prediction model for JIA-U for use in everyday clinical practice for individual JIA patients rather than arbitrary groups. Individual risk predictions could provide quantitative risk estimates for uveitis to individual patients and guide clinicians in determining screening frequencies.

METHODS

Patients

We used data from the international observational Pharmachild registry, an ongoing project that started in 2011 with the primary aim of collecting adverse events in JIA patients undergoing treatment with biologic agents. The scope was later broadened by also including patients on nonsteroidal anti-inflammatory drugs (NSAIDs), steroids and synthetic disease-modifying antirheumatic drugs (DMARDs). Pharmachild contains information of JIA patients treated in 86 medical centres from 32 countries in Europe, Asia, Africa and South America that belong to the Paediatric Rheumatology International Trials Organisation (PRINTO)[24]. Full details of the Pharmachild registry have been published elsewhere[25].

Data were locked on May 3, 2019. For inclusion into the study, patients had to provide informed consent and meet the International League of Associations for Rheumatology (ILAR) criteria for JIA. Exclusion criteria were an age at JIA onset of ≥16 years, development of uveitis prior to JIA, an observation period of <4 years and a diagnosis of systemic JIA with a history of acute anterior uveitis. An observation period of at least four years was chosen such that every patient had had enough time to develop uveitis.

For every patient, information was gathered about the age at JIA onset, observation period, ANA, RF and human leukocyte antigen (HLA-)B27 status, use of medication, occurrence of uveitis and JIA ILAR category[2]. A patient was classified as RF positive if two positive RF determinations, at least 3 months apart were documented. For ANA positivity, one positive determination was required. The additive value of requiring two positive ANA determinations was also studied. Occurrence of uveitis was determined from three sources: free-text fields and checkmarks indicating a history of uveitis at registration into Pharmachild and adverse events reported during follow-up after registration. All prospective and a number of retrospective uveitis cases were reported using the MedDRA coding system, including a date of onset. Of these, we included the following preferred terms: uveitis, iridocyclitis, autoimmune uveitis and iritis. Since the date of onset was not available for all uveitis cases, ever use of drugs of interest was collected. This was defined as having ever taken the drug during the disease course. Drugs included were NSAIDs, intraarticular steroids, systemic steroids, methotrexate, cyclosporine, anti-TNF, anti-IL1, anti-IL6 and other biologicals.

Statistical analysis

Chi square and Mann-Whitney U tests at a significance level of 5% were performed to examine differences in characteristics between patients who developed JIA-U and those who did not. Based on the existing literature and consensus of the authors, the following

variables were chosen as potential risk factors and confounding variables for JIA-U: age at JIA onset, gender, JIA category, ANA status, RF status and HLA-B27 status. Crude and adjusted odds ratios for the (independent) relationship between these variables and JIA-U were established using logistic regression in a complete-case analysis. A 95% confidence interval for the main effect that did not contain 1 was considered statistically significant. Subsequently, all independent statistically significant risk factors were considered for inclusion into a multivariable logistic regression model, to predict the probability of developing JIA-U. The main effects of this prediction model were selected using a backward procedure based on Akaike information criterion. For all analyses, oligoarticular JIA was chosen as the reference JIA category. Linearity between continuous predictors and the logit outcome was tested using the Box-Tidwell test. Model performance was assessed based on the area under the receiver operating characteristic curve (AUC) in the training data and ten-fold cross validation. It was also assessed if adding interaction terms for the main effects to the prediction model resulted in improved model performance. The reduced model was internally validated and adjusted for overfitting by bootstrap resampling. A description of the bootstrapping procedure is provided in the supplementary material (Supplementary Data 1). Internal calibration of the final prediction model was assessed by a plot of observed frequencies of JIA-U within deciles of the predicted probabilities versus the mean predicted probabilities. Lastly, a formula for predicting the individual risk of developing uveitis was determined based on the coefficients of the prediction model. All analyses were performed with the stats, car, caret, pROC and rms packages for R version 3.6.3[26].

RESULTS

Characteristics of study population

A total of 5,529/8,942 (62%) patients were included in the analysis (Figure 1). The majority of excluded patients had a follow-up of <4 years (3,303/8,838; 37%). Characteristics of patients included and excluded were similar (Supplementary Table 1).

Of the patients analysed, 1,102 (19.9%) had ever developed JIA-U (Table 1). 18/91 (20%) cases of uveitis in enthesitis-related arthritis (ERA) patients with available specification were of chronic uveitis type. Children who developed JIA-U, had a longer observation period, younger age at JIA onset and were more often female and HLA-B27 positive compared to patients who did not. The majority of JIA-U patients had oligoarthritis and was ANA positive. RF negative polyarthritis was the second most common JIA category in patients that developed JIA-U. Moreover, RF positivity, systemic arthritis and the ever use of anti IL-1 and anti IL-6 were lower in the JIA-U group. On the contrary, the ever use of

anti-TNF was more frequent in patients with JIA-U than in those without. We did not find differences among patients receiving systemic steroids.

Time between onset of JIA and JIA-U

Of all patients who developed JIA-U, 138 patients had a known date of uveitis onset. We observed that 93/138 patients (67.4%) developed JIA-U within the first four years after JIA onset (Figure 2). Two patients (1.4%) developed JIA-U after 15 years, namely in the 18th and 19th year after JIA onset. Furthermore, the median time interval between JIA onset and onset of JIA-U was 2.4 years.

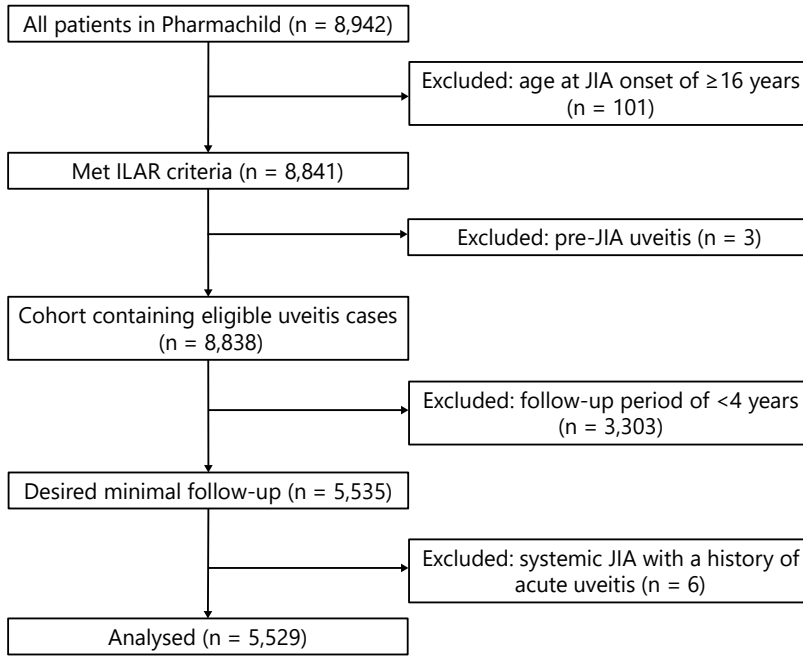

Figure 1. Flowchart of study population.

Table 1. Characteristics of Pharmachild cohort used for analysis.

	Total cohort (N = 5,529)	**No uveitis (N = 4,427)**	**Uveitis (N = 1,102)**	***P*-value**
Female gender	3,881 (70.2%)	3,064 (69.2%)	8,17 (74.1%)	<0.01[a]
Age at JIA onset (years)	4.36 (2.14 – 8.60)	5.16 (2.39 – 9.23)	2.60 (1.69 – 4.70)	<0.01[a]
Observation time (years)	7.91 (5.78 – 11.02)	7.64 (5.60 – 10.58)	9.14 (6.56 – 12.79)	<0.01[a]
JIA category				
Oligoarthritis	2,182 (39.5%)	1,522 (34.4%)	660 (59.9%)	<0.01[a]
Persistent oligoarthritis	1,272 (23.0%)	872 (19.7%)	400 (36.3%)	<0.01[a]
Extended oligoarthritis	910 (16.5%)	650 (14.7%)	260 (23.6%)	<0.01[a]
Polyarthritis (RF-)	1,504 (27.2%)	1,285 (29.0%)	219 (19.9%)	<0.01[a]
Polyarthritis (RF+)	184 (3.3%)	182 (4.1%)	2 (0.2%)	<0.01[a]
Psoriatic arthritis	197 (3.6%)	160 (3.6%)	37 (3.4%)	0.75
ERA	527 (9.5%)	435 (9.8%)	92 (8.3%)	0.15
Systemic arthritis	569 (10.3%)	564 (12.7%)	5 (0.5%)	<0.01[a]
Undifferentiated arthritis	366 (6.6%)	279 (6.3%)	87 (7.9%)	0.07
Immunologic markers				
1x ANA positive	2,273 (43.7%) N = 5,201	1,571 (38.0%) N = 4,138	702 (66.0%) N = 1,063	<0.01[a]
2x ANA positive	1,372 (34.8%) N = 3,946	891 (28.9%) N = 3,086	481 (55.9%) N = 860	<0.01[a]
RF positive	190 (3.9%) N = 4,877	184 (4.7%) N = 3,943	6 (0.6%) N = 934	<0.01[a]
HLA-B27 positive	714 (21.2%) N = 3,375	555 (20.3%) N = 2,729	159 (24.6%) N = 646	0.02[a]
Anti-inflammatory treatment ever				
NSAIDs	4,635 (83.8%)	3,747 (84.6%)	888 (80.6%)	<0.01[a]
Intraarticular steroids	3,118 (56.4%)	2,389 (54.0%)	729 (66.2%)	<0.01[a]
Systemic steroids	2,322 (42.0%)	1,838 (41.5%)	484 (43.9%)	0.16
Synthetic DMARDs	5,068 (91.7%)	4,012 (90.6%)	1,056 (95.8%)	<0.01[a]
Methotrexate	4,925 (89.1%)	3,883 (87.7%)	1,042 (94.6%)	<0.01[a]
Cyclosporine	441 (8.0%)	308 (7.0%)	133 (12.1%)	<0.01[a]
Biologic DMARDs	4,157 (75.2%)	3,263 (73.7%)	894 (81.1%)	<0.01[a]
Anti-TNF	3,801 (68.7%)	2,917 (65.9%)	884 (80.2%)	<0.01[a]
Anti-IL1	248 (4.5%)	243 (5.5%)	5 (0.5%)	<0.01[a]
Anti-IL6	491 (8.9%)	446 (10.1%)	45 (4.1%)	<0.01[a]
Other biologicals	530 (9.6%)	425 (9.6%)	105 (9.5%)	0.99

Data are presented as median with interquartile range for numerical measures and frequency with percentage of column total for categorical measures.

ANA: antinuclear antibodies; DMARD: disease-modifying antirheumatic drug; ERA: enthesitis-related arthritis; JIA: juvenile idiopathic arthritis; NSAID: non-steroidal anti-inflammatory drug; RF: rheumatoid factor

[a]statistically significant difference at α = 0.05

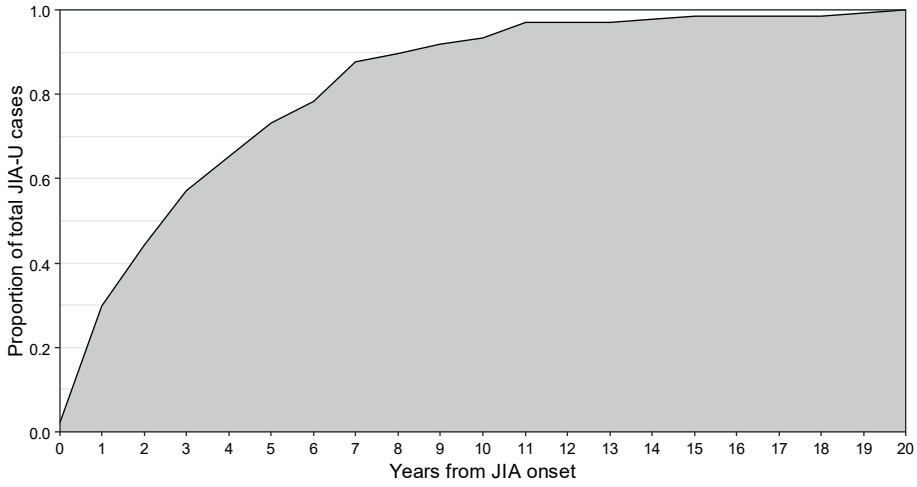

Figure 2: Cumulative juvenile idiopathic arthritis-associated uveitis (JIA-U) onset rate (n = 138).

Adjusted risk factors

Crude odds ratios for JIA-U corresponding to the data presented in Table 1 are presented in Table 2. After correcting for confounding variables, ANA positivity and HLA-B27 turned out to be statistically significant risk factors for JIA-U. Older age at JIA onset (numerical variable), polyarthritis and systemic arthritis were associated with significantly decreased odds for JIA-U (compared to oligoarthritis). While female gender was a risk factor for JIA-U on univariable analysis, this did not hold true after adjusting for confounders. Also, the statistically significant protective effect of psoriatic arthritis, ERA and undifferentiated arthritis for JIA-U compared to oligoarthritis disappeared after confounder adjustment. Patients with a twice positive ANA determination had higher odds for JIA-U than patients with only one positive ANA determination.

Table 2. Odds ratios for the development of JIA-U per risk factor.

Risk factor	Crude OR (95% CI)	Adjusted OR (95% CI)
Female gender	1.28 (1.10 – 1.48)[a]	0.90 (0.72 – 1.12)
Age at JIA onset	0.83 (0.81 – 0.85)[a]	0.84 (0.81 – 0.87)[a]
Oligoarthritis	1	1
Polyarthritis (RF-)	0.39 (0.33 – 0.47)[a]	0.60 (0.47 – 0.76)[a]
Polyarthritis (RF+)	0.03 (0.00 – 0.08)[a]	0.06 (0.00 -0.48)[a]
Psoriatic arthritis	0.53 (0.36 – 0.76)[a]	0.89 (0.55 – 1.41)
ERA	0.49 (0.38 – 0.62)[a]	1.15 (0.77 – 1.69
Systemic arthritis	0.02 (0.01 – 0.04)[a]	0.07 (0.03 – 0.16)[a]
Undifferentiated arthritis	0.72 (0.55 – 0.93)[a]	1.30 (0.87 – 1.91)
1x ANA positive	3.18 (2.76 – 3.66)[a]	1.88 (1.54 – 2.30)[a]
2x ANA positive	3.13 (2.68– 3.65)[a]	2.27 (1.82 – 2.85)[a]
RF positive	0.13 (0.05 – 0.27 [a]	0.98 (0.22 – 3.43)
HLA-B27 positive	1.28 (1.04 – 1.56)[a]	1.48 (1.12 – 1.95)[a]

ANA: antinuclear antibodies; CI: confidence interval; ERA: enthesitis-related arthritis; HLA: human leucocyte antigen; JIA-U: juvenile idiopathic arthritis-associated uveitis; OR: odds ratio; RF: rheumatoid factor
[a]statistically significant

Prediction model

Our best prediction model for estimating the probability of developing JIA-U included the following predictors: age at JIA onset, ANA positivity and JIA category (Table 3). According to this model, the individual risk of developing JIA-U can be calculated using the following formula:

$$P(\text{uveitis}) = {}^{1}/_{1 + e^{-(-0.65 - 0.17 \times \text{age at JIA onset} + \text{JIA category coefficient} + 0.67 \times \text{ANA status})}}$$

For this estimation, the age at JIA onset in years, ANA status (1 = positive, 0 = negative) and a JIA category coefficient from Table 3 are needed.

Table 3. Coefficients table of prediction model for juvenile idiopathic arthritis-associated uveitis (n = 5,201). Optimism-adjusted AUC = 0.75.

Predictor	OR (95% CI)	β	Optimism-adjusted β
(Intercept)	0.53 (0.44 – 0.63)[a]	-0.63	-0.65
ANA positive	2.02 (1.73 – 2.36)[a]	0.70	0.67
Age at JIA onset	0.84 (0.82 – 0.86)[a]	-0.17	-0.17
Oligoarthritis	1	0	0
Undifferentiated arthritis	1.11 (0.84 – 1.46)	0.10	0.10
Polyarthritis (RF-)	0.55 (0.46 – 0.66)[a]	-0.60	-0.58
Polyarthritis (RF+)	0.06 (0.01 – 0.20)[a]	-2.78	-2.69
Psoriatic arthritis	0.85 (0.56 – 1.24)	-0.17	-0.16
ERA	1.53 (1.13 – 2.05)[a]	0.42	0.41
Systemic arthritis	0.04 (0.01 – 0.08)[a]	-3.32	-3.21

ANA: antinuclear antibodies; AUC: area under the curve; CI: confidence interval; ERA: enthesitis-related arthritis; JIA: juvenile idiopathic arthritis; OR: odds ratio; RF: rheumatoid factor

[a]statistically significant

Oligoarticular JIA was chosen as the reference category because this was the largest category and therefore would provide stable odds ratios for the other JIA categories. The analysis eliminated 328/5,529 (5.9%) of all patients due to missing ANA determinations, resulting in 5,201 patients with 1,063 outcome events (Supplementary Table 2). ANA positivity and a younger age at JIA onset were associated with significantly higher odds for developing uveitis, while systemic arthritis and polyarthritis were associated with significantly decreased odds when compared with oligoarthritis. The prediction model had good discriminative power in the training data (AUC = 0.76, 95% CI: 074 – 0.77). Ten-fold cross validation revealed similar model performance: the average AUC was 0.75 with a standard deviation of 0.02 (Supplementary Figure 1). Internal validation by bootstrap resampling revealed little overfitting, optimism of the AUC estimate was small (0.004) and the shrinkage factor of the model coefficients was close to 1 (0.97). According to the calibration plot of observed versus predicted probabilities of JIA-U (Supplementary Figure 2), the optimism-adjusted model fitted the data well. For clinical practice, a diagram is provided from which the predicted individual uveitis risk as a function of the predicting variables can be read (Figure 3). Individual risks can also be obtained from a risk calculator (Supplementary Data 2; available on the *Rheumatology* website at https://academic.oup.com/rheumatology/article/60/6/2896/6020103).

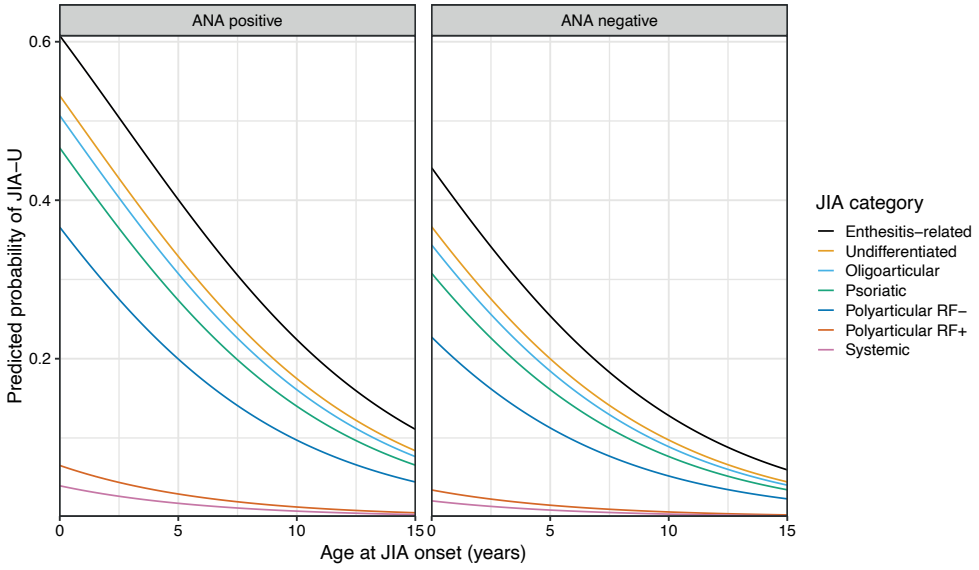

Figure 3. Diagram of optimism-adjusted clinical prediction model for juvenile idiopathic arthritis-associated uveitis (JIA-U). First, distinguish between ANA positive and negative patients (left or right diagram). Then, pick a line corresponding to the JIA category (see legend) and finally, read off the predicted probability for JIA-U (y-axis) as a function of the age at JIA onset (x-axis).

DISCUSSION

In this study, we developed a clinical prediction model for estimating JIA-U in order to be able to inform patients/parents on the probability that they/their child will develop uveitis. For the first time, quantitative risk estimates can easily be obtained for an individual newly diagnosed JIA patient and these estimates could also aid clinicians in determining screening frequencies. As a result, screening frequencies can be tailored towards the individual rather than followed for arbitrary groups. Attributing a percent risk for developing JIA-U is a step forward from only being able to inform patients and parents of a "high", "low" or "moderate" risk as used in existing screening guidelines[20,21], since these terms are highly subjective and identify an unidentified risk range. In addition, higher risk estimates following our model might encourage clinicians to earlier escalate drug therapy to methotrexate or adalimumab, which is superior to etanercept in the treatment of silent uveitis[6].

The combination of age at JIA onset, ANA status and JIA category had the highest predictive power among the models we considered. HLA-B27 appeared to be statistically significant in predicting JIA-U when added to our model ($p < 0.01$). However, this addition

also decreased the discriminative power of our model (AUC = 0.74). Because there were many missing observations for HLA-B27 and since this is an expensive test that cannot be measured as a point-of-care, we decided not to include HLA-B27 in our model. Including HLA-B27 as a predictor variable in our model could have introduced selection bias and would cause our model to be useless in clinical settings without resources for this determination. Nonetheless, by not including HLA-B27 as a predictor variable, the model might predict acute anterior uveitis slightly worse[6]. We also decided not to incorporate a twice positive ANA determination in the model for similar reasons: a substantial number of patients did not have two ANA determinations while adding this variable to the model did not result in an increase of discriminative power. We furthermore considered adding interaction terms for the main effects to the model to account for possible differences in risk prediction between categories of predictors. Other studies have reported that the age at JIA onset and ANA-associated risk of JIA-U differs between boys and girls[10,15,27]. Nonetheless, including interaction terms next to the main effects did not improve the discriminative power of our model. Lastly, we adjusted our model by distinguishing between persistent and extended oligoarthritis within the group of oligoarthritis patients. This was based on a study by Sim *et al.* which reported that patients with extended oligoarthritis are at higher risk for developing JIA-U and develop JIA-U earlier than patients with persistent oligoarthritis[28]. The adjustment, however, resulted in worse model fit as determined by the calibration plot. We therefore decided to stick with the oligoarthritis group as a whole. Moreover, we wanted our prediction model to make baseline risks for JIA patients and this is not possible when having to distinguish between persistent and extended oligoarthritis, which might take years to become obvious.

The variables included in our model are identical to the parameters used in current screening guidelines, let alone the disease duration. In addition, several studies found that on multivariable analysis, young age at JIA onset, ANA positivity and JIA category were indeed the best predictors based on statistical significance[13,14,29,30]. However, when building prediction models including the JIA categories and cut-off values for age at JIA onset that are used in these guidelines, this resulted in less discriminative power than our individualized model ($AUC_{BSPAR} = 0.66$ and $AUC_{Heiligenhaus/ACR} = 0.71$).

Our analyses revealed that the relationship between several factors and JIA-U is confounded by extraneous variables. For the ERA patients in our cohort, the relationship with JIA-U can be explained due to the predominance of HLA-B27 positivity (data not shown), which is associated with acute anterior uveitis[20]. Similar to ERA, undifferentiated arthritis was no more associated with decreased odds for JIA-U compared to oligoarthritis after adjusting for confounders. This could be explained by the fact that a large percentage of patients with undifferentiated arthritis in our cohort were ANA and HLA-B27 positive and that a reasonable number of acute anterior uveitis cases were present in this group (data not shown). In addition, male gender, another risk factor for acute anterior uveitis[6,31],

was relatively common in undifferentiated arthritis patients that developed JIA-U in comparison to all other JIA-U patients (data not shown). Although the vast majority of patients that developed JIA-U in our cohort were female, female gender itself was not an independent risk factor for JIA-U after confounder adjustment. Several studies have also reported this bias, explained by the fact that female JIA patients on average have a lower age at JIA onset and are more often ANA positive than male JIA patients[7,32–34]. In addition, we observed that RF negative polyarthritis was associated with decreased odds for JIA-U compared to oligoarthritis, regardless of adjusting for confounding. In fact, this was the JIA category with the third lowest percentage of JIA-U. This implies that even though it is known that uveitis occurs most frequently in patients with oligoarthritis and RF negative polyarthritis[6,9], RF negative polyarthritis on its own is not associated with a high risk of developing uveitis. The large cohort study by Heiligenhaus *et al.* also observed relatively low rates of JIA-U in patients with RF negative polyarthritis[11].

Our study supports well-established epidemiologic features of JIA-U. The prevalence of JIA-U in our cohort used for analysis was 20.0%, which is in line with a review by Clarke *et al*[6]. The (independent) association with a younger age at JIA onset, ANA positivity and oligoarthritis is also frequently described[13,14,29,35,36]. Furthermore, we observed that JIA-U is extremely rare in systemic arthritis and RF positive polyarthritis patients, which is in concordance with other studies[8,11–13,29,35]. Occurrence of uveitis in systemic JIA patients might therefore be a good moment for reconsidering the initial diagnosis. Nevertheless, because of diagnosis uncertainty and overlapping symptoms, the guidelines indicate screening in this group of patients and thus recognize a small risk of uveitis in patients initially labelled as systemic JIA[6,37,38].

We excluded patients with an observation period of <4 years since the risk of developing uveitis after four years of JIA is markedly reduced[21,39] and we only wanted to analyse patients who had had enough time to develop uveitis. Extending this period would lead to a decreased sample size for analyses. We observed that 67% of JIA-U cases occurred within the first four years since JIA onset and other studies have reported numbers between 63% and 91%[11,12,15,33,40]. The cut-off value of four years has also been used in other studies on JIA-U on the basis of the aforementioned reasons[7,29,41].

The study has some limitations given it lacks an association with relevant medication prior to uveitis onset as well as the disease duration. Because of the latter, our prediction model should not directly replace current screening guidelines. Nevertheless, we believe it is very useful for clinicians, parents and patients to estimate an individual "starting risk" of developing uveitis. A great strength of our model is its large sample size with data of patients from 32 countries around the world, making its risk predictions well generalizable. However, it should be mentioned that our cohort is subject to a certain amount of referral

bias since in the Pharmachild registry many of the contributing centres are academic hospitals, which might lead to an underrepresentation of JIA patients with low disease activity and not in need of DMARDs. Therefore, our prediction model might perform worse and might need to be recalibrated especially for non-academic centres with a higher proportion of JIA patients that do well on NSAIDs and intra-articular injections only.

For the future, a dynamic model for predicting JIA-U that incorporates medication and disease duration would certainly be ideal. A further step in modelling JIA-U would be to include additional information on relevant biomarkers, including HLA-B27. Studies have already indicated HLA type DRB1*11, anti-histone antibodies, an elevated erythrocyte sedimentation rate and calcium-binding protein S100A12 as predictive factors for JIA-U[14,15,27,40–44]. Furthermore, some studies have identified particular T cell subsets and monocyte phenotypes as potential biomarkers for JIA-U[45,46].

In conclusion, here, we provide a clinical tool for predicting JIA-U based on data from the largest registry of JIA patients. For every individual with JIA, this model informs patients/parents on the probability of developing uveitis. Known risk factors of JIA-U have been confirmed. In our model, ANA-positive patients with early-onset JIA are at highest risk for JIA-U contrary to systemic and RF positive polyarticular JIA patients.

ACKNOWLEDGEMENTS

We thank all participating PRINTO centres for the data collection. We also thank all patients and their families for their consent to this study.

FUNDING

This work was supported by a research grant from FOREUM Foundation for Research in Rheumatology. Pharmachild has been supported by a grant from the European Union (grant 260353) and by funding from the Italian public hospital IRCCS Istituto Giannina Gaslini.

COMPETING INTERESTS

JS received grants from Swedish Orphan Biovitrum, outside the submitted work. CL received EULAR 2019 taxes from ABBVIE, outside the submitted work.
All other authors declare no conflict of interest.

ETHICS APPROVAL

Pharmachild and all participating centres obtained approval from their respective ethics committees and were conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent/assent based on existing national regulations.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Characteristics of included and excluded patients.

	Included patients (N = 5,529)	Excluded patients (N = 3,413)
Female gender	3,881 (70.2%)	2,191 (64.2%)
Age at JIA onset (years)	4.36 (2.14 – 8.60)	7.54 (3.04 – 11.94)
Observation time (years)	7.91 (5.78 – 11.02)	2.18 (1.26 – 3.10)
JIA category		
Oligoarthritis	2,182 (39.5%)	1,200 (35.2%)
Persistent oligoarthritis	1,272 (23.0%)	978 (28.7%)
Extended oligoarthritis	910 (16.5%)	222 (6.5%)
Polyarthritis (RF-)	1,504 (27.2%)	860 (25.2%)
Polyarthritis (RF+)	184 (3.3%)	173 (5.1%)
Psoriatic arthritis	197 (3.6%)	104 (3.0%)
ERA	527 (9.5%)	450 (13.2%)
Systemic arthritis	569 (10.3%)	387 (11.3%)
Undifferentiated arthritis	366 (6.6%)	239 (7.0%)
Immunologic markers		
1x ANA positive	2,273 (43.7%) N = 5,201	1,218 (38.4%) N = 3,174
2x ANA positive	1,372 (34.8%) N = 3,946	527 (28.4%) N = 1,854
RF positive	190 (3.9%) N = 4,877	153 (5.1%) N = 3,029
HLA-B27 positive	714 (21.2%) N = 3,375	427 (21.1%) N = 2,027
Anti-inflammatory treatment ever		
NSAIDs	4,635 (83.8%)	2,774 (81.3%)
Intraarticular steroids	3,118 (56.4%)	1,449 (42.5%)
Systemic steroids	2,322 (42.0%)	1,245 (36.5%)
Synthetic DMARDs	5,068 (91.7%)	2,720 (79.7%)
Methotrexate	4,925 (89.1%)	2,587 (75.8%)
Cyclosporine	441 (8.0%)	86 (2.5%)
Biologic DMARDs	4,157 (75.2%)	1,722 (50.5%)
Anti-TNF	3,801 (68.7%)	1,404 (41.1%)
Anti-IL1	248 (4.5%)	177 (5.2%)
Anti-IL6	491 (8.9%)	209 (6.1%)
Other biologicals	530 (9.6%)	92 (2.7%)

Data are presented as median with interquartile range for numerical measures and frequency with percentage of column total for categorical measures.

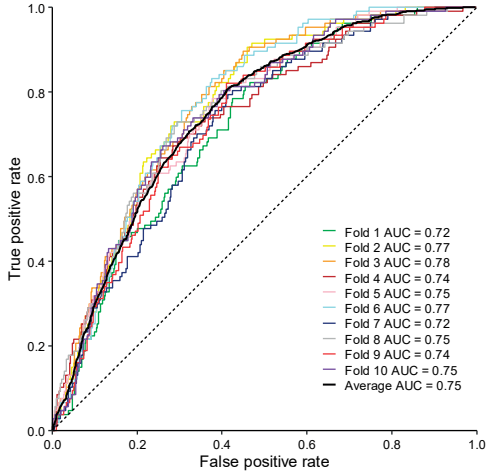
ANA: antinuclear antibodies; DMARD: disease-modifying antirheumatic drug; ERA: enthesitis-related arthritis; JIA: juvenile idiopathic arthritis; NSAID: non-steroidal anti-inflammatory drug; RF: rheumatoid factor

Supplementary Table 2. Characteristics of included patients with and without known ANA status.

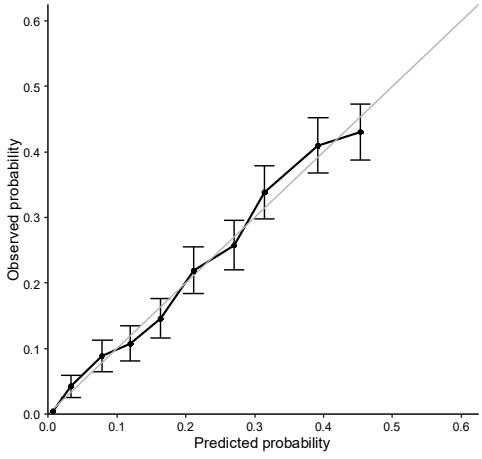
	ANA status known (N = 5,201)	ANA status unknown (N = 328)
Female gender	3,687 (70.9%)	194 (59.1%)
Age at JIA onset (years)	4.30 (2.11 – 8.50)	5.89 (2.84 – 9.67)
Observation time (years)	7.91 (5.79 – 11.03)	7.86 (5.64 – 10.63)
JIA category		
Oligoarthritis	2,105 (40.5%)	77 (23.5%)
Persistent oligoarthritis	1,227 (23.6%)	45 (13.7%)
Extended oligoarthritis	878 (16.9%)	32 (9.8%)
Polyarthritis (RF-)	1,431 (27.5%)	73 (22.3%)
Polyarthritis (RF+)	176 (3.4%)	8 (2.4%)
Psoriatic arthritis	183 (3.5%)	14 (4.3%)
ERA	458 (8.8%)	69 (21.0%)
Systemic arthritis	520 (10.0%)	55 (16.8%)
Undifferentiated arthritis	334 (6.4%)	32 (9.8%)
Immunologic markers		
RF positive	182 (3.9%) N = 4,666	8 (3.8%) N = 211
HLA-B27 positive	645 (19.9%) N = 3,241	69 (51.5%) N = 134
Anti-inflammatory treatment ever		
NSAIDs	4,357 (83.8%)	278 (84.8%)
Intraarticular steroids	2,989 (57.5%)	129 (39.3%)
Systemic steroids	2,170 (41.7%)	152 (46.3%)
Synthetic DMARDs	4,789 (92.1%)	279 (85.1%)
Methotrexate	4,664 (89.7%)	261 (79.6%)
Cyclosporine	434 (8.3%)	7 (2.1%)
Biologic DMARDs	3,902 (75.0%)	255 (77.7%)
Anti-TNF	3,601 (69.2%)	200 (61.0%)
Anti-IL1	217 (4.2%)	31 (9.5%)
Anti-IL6	466 (9.0%)	25 (7.6%)
Other biologicals	483 (9.3%)	47 (14.3%)

Data are presented as median with interquartile range for numerical measures and frequency with percentage of column total for categorical measures.

ANA: antinuclear antibodies; DMARD: disease-modifying antirheumatic drug; ERA: enthesitis-related arthritis; JIA: juvenile idiopathic arthritis; NSAID: non-steroidal anti-inflammatory drug; RF: rheumatoid factor



Supplementary Figure 1. Receiver operating characteristic curves for ten-fold cross-validation. Dashed diagonal line indicates random chance.
AUC: area under the curve



Supplementary Figure 2. Internal calibration plot of prediction model for juvenile idiopathic arthritis-associated uveitis (JIA-U). Observed probabilities are the frequency of JIA-U within deciles of the predicted probabilities with 95% confidence intervals. Grey diagonal line indicates perfect calibration.

Supplementary Data 1. Internal validation and optimism adjustment of prediction model for juvenile idiopathic arthritis-associated uveitis.

For internally validating the prediction model, we drew 200 samples with replacement from the original sample of equal size. In each of these bootstrap resamples, the entire model building process, including variable selection, was repeated and the resulting bootstrap models were tested on the original sample. Model overfitting or optimism was assessed by the average difference between AUC and model coefficients of these 200 bootstrap and test models. An optimism-corrected AUC estimate was obtained by subtracting the AUC optimism from the AUC estimate of the original reduced model. Optimism-corrected model coefficients were obtained by multiplying all coefficients of the original reduced model by a uniform shrinkage factor that corrects for the observed optimism in model coefficients. Finally, the optimism-adjusted intercept was re-estimated from a model with the linear predictor of the optimism-adjusted coefficients as an offset variable.

CHAPTER 6

6

Development and external validation of a model for predicting new-onset chronic uveitis at different disease durations in juvenile idiopathic arthritis

Joeri W. van Straalen[1,2], Lianne Kearsley-Fleet[3], Jens Klotsche[4], Sytze de Roock[1,2], Kirsten Minden[4,5], Arnd Heiligenhaus[6,7], Kimme L. Hyrich[3,8], Joke H. de Boer[9], Lovro Lamot[10,11], Alma N. Olivieri[12], Romina Gallizzi[13], Elzbieta Smolewska[14], Enrique Faugier[15], Serena Pastore[16], Philip J. Hashkes[17,18], Cristina N. Herrera[19], Wolfgang Emminger[20], Rita Consolini[21], Nico M. Wulffraat[1,2], Nicolino Ruperto[22] and Joost F. Swart[1,2] for the Paediatric Rheumatology International Trials Organisation (PRINTO), UK CAPS study and German ICON study

[1]Department of Paediatric Immunology and Rheumatology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, Netherlands
[2]Faculty of Medicine, Utrecht University, Utrecht, Netherlands
[3]Centre for Epidemiology Versus Arthritis, The University of Manchester, Manchester, UK
[4]Epidemiology unit, German Rheumatism Research Centre Berlin, Berlin, Germany
[5]Department of Paediatric Respiratory Medicine, Immunology and Critical Care Medicine, Charité Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt- Universität zu Berlin, Berlin, Germany
[6]Department of Ophthalmology, St. Franziskus Hospital, Münster, Germany
[7]University of Duisburg-Essen, Essen, Germany
[8]NIHR Manchester BRC, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK
[9]Department of Ophthalmology, University Medical Centre Utrecht, Utrecht, Netherlands
[10]Sestre Milosrdnice University Hospital Centre Zagreb, Zagreb, Croatia
[11]University of Zagreb School of Medicine, Zagreb, Croatia
[12]Dipartimento della Donna del Bambino e di Chirurgia Generale e Specialistica, Università degli Studi della Campania L.Vanvitelli, Naples, Italy
[13]Department of Medical of Health Sciences, Magna Graecia University, Catanzaro, Italy
[14]Paediatric Cardiology and Rheumatology, Medical University of Lodz, Lodz, Poland
[15]Medicina Interna y Reumatologia, Hospital Infantil de México Federico Gómez, Mexico City, Mexico
[16]Institute for Maternal and Child Health, IRCCS Burlo Garofolo, Trieste, Italy
[17]Pediatric Rheumatology Unit, Shaare Zedek Medical Centre, Jerusalem, Israel
[18]Hebrew University Hadassah School of Medicine, Jerusalem, Israel
[19]Servicio de Reumatología, Hospital de Niños Roberto Gilbert Elizalde, Guayaquil, Ecuador
[20]Department of Paediatrics, University Children's Hospital, Medical University of Vienna, Vienna, Austria
[21]Division of Paediatrics, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
[22]Clinica Pediatrica e Reumatologia, IRCCS Istituto Giannina Gaslini, Genoa, Italy

Arthritis Rheumatol. 2022;10.1002/art.42329.art.42329.

ABSTRACT

Objective

To develop and externally validate a prediction model for chronic uveitis in children with juvenile idiopathic arthritis (JIA) for clinical application.

Methods

Data from the international Pharmachild register were used to develop a multivariable Cox proportional hazards model. Predictors were selected by backward selection and missing values were handled by multiple imputation. The model was subsequently validated and recalibrated in two inception cohorts: the UK CAPS study and German ICON study. Model performance was evaluated by calibration plots and C-statistics for the 2, 4 and 7-year risk of uveitis. A diagram and digital risk calculator were created for use in clinical practice.

Results

5393 patients were included for model development and predictor variables were age at JIA onset (HR: 0.83, 95% CI: 0.77 – 0.89), ANA positivity (HR: 1.59, 95% CI: 1.06 – 2.38) and ILAR category (HR for oligoarticular, psoriatic and undifferentiated arthritis versus RF-polyarthritis: 1.40, 95% CI: 0.91 – 2.16). Performance of the recalibrated prediction model in the validation cohorts was acceptable: calibration plots indicated good calibration and C statistics for the 7-year risk of uveitis were 0.75 (95% CI: 0.72 – 0.79) for ICON and 0.70 (95% CI: 0.64 – 0.76) for CAPS.

Conclusion

We present for the first time a validated prognostic tool for easily obtaining individual chronic uveitis risks for JIA patients using common clinical parameters. This model could be used by clinicians to inform patients/parents and provide guidance in choice of uveitis screening frequency and arthritis drug therapy.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is defined as arthritis of unknown cause lasting for >6 weeks in a child younger than 16 years[1]. JIA is the most common form of chronic rheumatic illness in childhood worldwide with an incidence estimated to be between 1.6 – 23 cases per 100,000 children[2]. On average, 13% of JIA patients develop uveitis[3], an intraocular inflammation which can lead to serious complications including loss of vision if not treated in a timely manner[4,5]. Chronic uveitis with insidious onset of flare is the most common form of JIA-related uveitis and usually does not present with apparent symptoms until ocular complications arise[6,7]. For this reason, JIA patients should be screened by an ophthalmologist and several guidelines for the frequency and duration of this screening exist[7–11].

Current screening guidelines differentiate patients at a roughly high, moderate or low risk of developing uveitis, which are subjective terms that could be interpreted differently by each individual. To date, paediatric rheumatologists do not have a comprehensive and validated tool for obtaining absolute risk estimates for chronic uveitis based on characteristics of individual JIA patients.

The objective of this study is to (1) develop a prediction model for new-onset chronic uveitis in JIA that could be of assistance in clinical practice and (2) validate this model in two external cohorts.

PATIENTS AND METHODS

Patients

Data from the international Pharmachild registry were used for developing the prediction model. Pharmachild is an ongoing pharmacovigilance project that started in 2011 with the objective of monitoring adverse events in JIA patients under drug therapy[12]. Inclusion criteria are children with JIA according to International League of Associations for Rheumatology (ILAR) criteria under treatment or previously treated with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, conventional synthetic or biological disease-modifying antirheumatic drugs (DMARDs). Patients are included from 85 Paediatric Rheumatology International Trials Organisation (PRINTO) centres from 31 countries[13].

Data were locked on May 3, 2019. Only patients with ≥2 registered visits were included in the current study. Exclusion criteria were enthesitis-related arthritis (ERA), systemic arthritis, rheumatoid factor (RF) positive polyarthritis, uveitis prior to JIA onset, a diagnosis of acute uveitis and an unknown date of uveitis diagnosis. ERA patients were excluded

because of probable acute uveitis onset[4]. Systemic and RF+ polyarthritis patients were excluded because of their known low risk for uveitis development[9]. RF+ patients from other ILAR categories were not excluded.

Outcome and predictors

The outcome predicted in this study was the 2, 4 and 7-year risk of new-onset chronic uveitis after onset of JIA. These time-points are thresholds for disease duration in current screening guidelines[9]. For all patients, a first diagnosis of chronic uveitis was determined from three sources: free-text fields and tick boxes filled in at registration into Pharmachild and adverse events reported using the Medical Dictionary for Regulatory Activities (MedDRA) coding system (version 22) during follow-up. Dates of therapy switches due to uveitis were not used as uveitis diagnosis dates. All uveitis event descriptions were reviewed by three researchers (JS, SdR and JvS) to ensure acute and posterior cases were excluded.

Potential predictors of uveitis were identified by consensus of the researchers and the existing literature. For each patient, if available, the following information was collected: sex, age at JIA onset, ILAR category of JIA, antinuclear antibodies (ANA) status, human leukocyte antigen (HLA) B27 status, RF status, family history of autoimmune disease in first and second degree relatives (yes/no) and geographic region. Patients were grouped into the following geographic regions based on the country of the centre in which they were treated: Western Europe, Central and Eastern Europe, Scandinavia, Southern Europe and other region[14]. The latter category included patients from Latin America, Africa and Asia and had to be analysed as a whole due to few events of uveitis. An overview of included countries and corresponding regions is provided in Supplementary Table 1. Onset date of JIA was defined on the Pharmachild case report forms as the "date of occurrence of the first clinical manifestation consistent with the disease". Age at JIA onset was treated as a continuous variable.

Methotrexate (MTX) and adalimumab (ADA) therapy are effective in the treatment of uveitis in JIA[4,8]. Therefore, we also collected data on MTX and ADA use and discontinuation prior to uveitis onset to study a possible protective effect. These variables were not considered for inclusion into the prediction model since it is not possible to determine whether a newly diagnosed JIA patient will receive ADA or MTX and we wanted our prediction model to make uveitis predictions early in the disease course.

Model development

Variables collected were first analysed in univariable Cox proportional hazards regression analysis. Variables were considered statistically significant if the 95% CI of the hazard ratio (HR) did not contain 1. Missing values were handled by multiple imputation using

chained equations[15]. Estimates for 20 imputed datasets were pooled using Rubin's rules. Subsequently, all variables were entered into a multivariable Cox prediction model and removed by stepwise backward selection in the multiple imputed datasets with a threshold of $P = 0.15$. In order to avoid overfitting and poor performance of the prediction model during the external validation, we decided a priori to create risk groups of ILAR categories with similar risks of developing uveitis. Based on two large-scale studies, we grouped together RF- polyarthritis versus psoriatic, undifferentiated and oligoarticular arthritis[9,16]. The proportional hazards assumption was checked in the 20th imputed dataset by testing for independence of the Schoenfeld residuals over time and linearity of continuous variables was checked by plotting these against the Martingale residuals.

External validation

For external validation and subsequent model recalibration, data from two JIA inception cohorts were used and the same exclusion criteria were applied.

CAPS cohort

The Childhood Arthritis Prospective Study (CAPS) is a United Kingdom (UK) prospective inception cohort study of children with new onset idiopathic inflammatory arthritis in childhood[17]. It was established in 2001 and children are recruited within six months of first presentation to paediatric rheumatology from one of seven tertiary care UK rheumatology centres if they are aged <16 years with new onset arthritis in one or more joints lasting for ≥2 weeks. Baseline data are collected from clinical records and include demographic information, disease duration, ILAR category, clinical markers of disease, current medication, JIA core outcome variables, and information on uveitis diagnosis and treatment. Patients are followed annually for five years, with additional data collected at seven and ten years. Follow up information includes disease activity, ILAR category, changes in medication, and information on uveitis.

ICON cohort

The Inception Cohort of Newly diagnosed patients with juvenile idiopathic arthritis (ICON) is a multicentre-controlled cohort study[18]. Patients were enrolled within 12 months after a diagnosis of JIA according to ILAR criteria at 11 of the largest paediatric rheumatology centres in Germany from 2010 to 2014 and have been followed since then. At first presentation in ICON, demographic information, disease duration, ILAR category, clinical markers of disease, current medication, history of uveitis and JIA core outcome variables are reported. Follow-up information on clinical markers of disease, current medication, diagnosis of uveitis and JIA core outcome variables were collected every three months during the first year and then every six months.

Model validation and recalibration

For external validation, coefficients of the prediction model and the mean linear predictor in the imputed Pharmachild datasets were transferred to the analysts for CAPS (LKF) and ICON (JK). Using these, linear predictors were calculated for all patients in the validation datasets[19]. The prediction model was recalibrated in two ways, (1) by determining the 2, 4 and 7-year baseline survival probabilities in the validation cohorts after fitting a Cox regression with the linear predictors as the only parameter (i.e. recalibration in the large) and (2) by also using the coefficient of this model as a shrinkage factor for the linear predictors (i.e. logistic recalibration)[20,21]. Performance of the recalibrated prediction models in the validation cohorts was assessed for the 2, 4 and 7-year risk of chronic uveitis by means of the corresponding C statistic and calibration plots. The C statistic ranges from 0.5 – 1 and indicates how well a model can distinguish patients that will develop the predicted outcome from patients that will not[22]. For the calibration plots, observed probabilities or Kaplan-Meier estimates of chronic uveitis within quintiles of the validation data were plotted against the mean predicted probabilities. The recalibrated model that demonstrated best calibration in both validation cohorts was presented as our final prediction model. In order to compare discriminative ability of our model with current uveitis screening guidelines, we also determined the C statistics for a model based on parameters from the 2007 Heiligenhaus modifications of the American Section of Rheumatology and Ophthalmology screening guidelines[9]. All analyses were performed with R version 4.0.0 [23] and the stats, rms, survival, psfmi, and Hmisc packages. We adhered to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines[24].

The methodology of this article was selected for the February 2023 *Arthritis & Rheumatology* Journal Club feature (Supplementary Data 1).

Ethics statement

Pharmachild, CAPS, ICON and all participating centres obtained approval from their respective ethics committees and were conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent/assent based on existing national regulations.

RESULTS

Cohort characteristics

After excluding 2,756 patients, 2,244 because of ERA, systemic arthritis or RF+ polyarthritis, 6,186 patients remained (Supplementary Figure 1). New-onset uveitis had occurred in 900 cases (14.5%), however another 793 of these patients were excluded from further

analysis because of an unknown date of uveitis diagnosis (see Supplementary Table 2 for the characteristics of all 900 uveitis cases). Eventually, 5,393 Pharmachild patients were included for this study. These included 107 uveitis cases with a median time from JIA onset to uveitis diagnosis of 2.3 years (IQR: 0.7 – 4.5). The majority of all 5,393 included patients were girls (74.3%), were treated in Southern Europe (36.0%) and the commonest ILAR categories were oligoarthritis (47.7%) and RF- polyarthritis (38.4%) (Table 1). Patients who developed uveitis were younger at JIA onset (median 2.2 versus 5.0 years), more often ANA positive (63.6% versus 44.5%), and less likely to have RF- polyarthritis (27.1% versus 38.6%) than patients who did not develop uveitis. Furthermore, patients who developed uveitis had more often used MTX (84.2% versus 65.4%) or ADA (15.3% versus 3.7%).

Characteristics of patients in CAPS and ICON with complete information for the prediction model variables are presented in Table 2. In the CAPS cohort, 88 out of 700 (12.6%) included patients developed uveitis. In the ICON cohort, 119 out of 758 (15.7%) included patients developed uveitis. For both cohorts, the median time from JIA onset to uveitis diagnosis was shorter than observed in Pharmachild: 2.1 years for CAPS (IQR: 1.1 - 4.8) and 1.0 years for ICON (IQR: 0.3 – 2.6). Patients who developed uveitis more often had a positive ANA status (81.1% for CAPS and 87.4% for ICON) and oligoarthritis (61.4% for CAPS and 68.1% for ICON) compared to Pharmachild (63.6% ANA positive and 54.2% oligoarthritis).

Table 1. Patient characteristics of Pharmachild cohort used for model development.

Characteristics	Total cohort (n = 5393)	No chronic uveitis (n = 5286)	Chronic uveitis (n = 107[1])	HR (95% CI)
Geographic region, n (%)				
Southern Europe	1943 (36.0%)	1912 (36.2%)	31 (29.0%)	Reference group
Scandinavia	540 (10.0%)	535 (10.1%)	5 (4.7%)	0.52 (0.20 – 1.34)
Western Europe	961 (17.8%)	902 (17.1%)	59 (5.5%)	3.74 (2.40 – 5.81)*
Central and Eastern Europe	1432 (26.6%)	1422 (26.9%)	10 (9.3%)	0.47 (0.23 – 0.98)*
Other	517 (9.6%)	515 (9.7%)	2 (1.9%)	0.24 (0.06 – 1.03)
Girls, n (%)	4007 (74.3%)	3925 (74.3%)	82 (76.6%)	1.05 (0.67 – 1.65)
Age at JIA onset (years), median (IQR)	4.9 (2.3 – 9.2)	5.0 (2.3 – 9.3)	2.2 (1.6 – 4.1)	0.81 (0.75 – 0.88)*
ILAR category, n (%)				
Oligoarthritis	2575 (47.7%)	2517 (47.6%)	58 (54.2%)	Reference group
	Persistent: 1707 (66.2%)	Persistent: 1668 (66.3%)	Persistent: 37 (63.8%)	
	Extended: 870 (33.8%)	Extended: 849 (33.7%)	Extended: 21 (36.2%)	
Polyarthritis RF-	2072 (38.4%)	2043 (38.6%)	29 (27.1%)	0.60 (0.38 – 0.95)*
Psoriatic arthritis	259 (4.8%)	251 (4.7%)	8 (7.5%)	1.30 (0.61 – 2.74)

Table 1. Continued

Characteristics	Total cohort (n = 5393)	No chronic uveitis (n = 5286)	Chronic uveitis (n = 107[1])	HR (95% CI)
Undifferentiated arthritis	487 (9.0%)	475 9.0%)	12 (11.2%)	1.10 (0.59 – 2.06)
Laboratory characteristics, n (%)				
ANA positive	2309 (44.9%) n = 5141	2241 (44.5%) n = 5034	68 (63.6%) n = 107	2.09 (1.40 – 3.12)*
RF positive	26 (0.5%) n = 4821	26 (0.5%) n = 4730	0 (0.0%) n = 91	-
HLA-B27 positive	348 (11.0%) n = 3153	339 (11.0%) n = 3092	9 (14.8%) n = 61	1.24 (0.58 – 2.65)
Family history of autoimmune disease[2], n (%)	1468 (28.2%) n = 5198	1434 (28.2%) n = 5091	34 (31.8%) n = 107	1.24 (0.82 – 1.88)
Family history of uveitis[2], n (%)	9 (0.2%) n = 5198	9 (0.2%) n = 5091	0 (0.0%) n = 107	-
Drug therapy				
MTX prior to uveitis or last follow-up, n (%)	4521 (83.8%)	4451 (84.2%)	70 (65.4%)	0.28 (0.19 – 0.42)*
Duration from last MTX stop to uveitis diagnosis in years, median (IQR)	-	-	0.9 (0.4 – 2.2) n = 34	
ADA prior to uveitis or last follow-up, n (%)	811 (15.0%)	807 (15.3%)	4 (3.7%)	0.18 (0.06 – 0.49)*
Duration from last ADA stop to uveitis diagnosis in years, median (IQR)	-	-	2.7 (1.6 – 3.8) n = 2	

HR = hazard ratio, IQR = interquartile range, n = number

[1]this only includes cases with available diagnosis date

[2]taking into account first and second degree relatives

*statistically significant

Missing values were imputed via multiple imputation

Table 2. Patient characteristics of CAPS and ICON cohorts used for external validation.

Characteristics	CAPS cohort			ICON cohort		
	Total cohort (n = 700)	**No chronic uveitis (n = 612)**	**Chronic uveitis (n = 88)**	**Total cohort (n =758)**	**No chronic uveitis (n = 639)**	**Chronic uveitis (n =119)**
Girls, n (%)	475 (67.9%)	410 (67.0%)	65 (73.9%)	547 (72.2%)	456 (71.4%)	91 (76.5%)
Age at JIA onset (years), median (IQR)	6.2 (2.5, 10.5)	6.8 (2.9, 10.8)	2.4 (1.6, 5.3)	5.4 (2.5 – 10.3)	6.5 (2.9 – 11.0)	2.5 (1.7 – 3.7)
ILAR category, n (%)						
Oligoarthritis	426 (60.9%)	372 (60.8%)	54 (61.4%)	412 (54.4%)	331 (51.8%)	81 (68.1%)
Persistent oligoarthritis	378 (54%)	332 (54%)	46 (52%)	339 (44.7%)	271 (42.4%)	68 (57.1%)
Extended oligoarthritis	48 (7%)	40 (7%)	8 (9%)	73 (9.7%)	60 (9.4%)	13 (10.9%)
Polyarthritis RF-	182 (26.0%)	160 (26.1%)	22 (25.0%)	239 (31.5%)	208 (32.5%)	31 (26.1%)
Undifferentiated arthritis	37 (5.3%)	34 (5.6%)	3 (3.4%)	62 (8.2%)	57 (8.9%)	5 (4.2%)
Laboratory characteristics, n (%)						
ANA positive	386 (55.1%)	314 (51.3%)	72 (81.8%)	450 (59.4%)	346 (54.2%)	104 (87.4%)
RF positive	28 (5.0%) N=562	24 (4.9%) N=491	4 (5.6%) N=71	23 (3.0%) N = 758	19 (2.9%) N = 639	4 (3.4%) N = 119
HLA-B27 positive	32 (15.8%) N=203	28 (15.5%) N=181	4 (18.2%) N=22	70 (9.2%) N = 758	68 (10.6%) N = 639	5 (4.2%) N = 119
Family history of autoimmune disease[1], n (%)	371 (53.0%)	320 (52.3%)	51 (58.0%)	-	-	-
Family history of uveitis[1], n (%)	3 (0.4%)	3 (0.5%)	0 (0.0%)	-	-	-
Drug therapy						
MTX prior to uveitis or last follow-up, n (%)	373 (53.3%)	323 (52.8%)	50 (56.8%)	509 (67.2%)	451 (70.6%)	57 (47.9%)
Duration from last MTX stop to uveitis diagnosis in years, median (IQR)	-	-	2.1 (1.1 - 5.0) n = 9	-	-	1.0 (1.0 - 1.0) n = 1
ADA prior to uveitis or last follow-up, n (%)	42 (6.0%)	37 (6.0%)	5 (5.7%)	88 (11.6%)	88 (13.8%)	0 (0.0%)
Duration from last ADA stop to uveitis diagnosis in years, median (IQR)	-	-	5.3 (5.3 - 5.3) n = 1	-	-	- n = 0

ADA = adalimumab, ANA = antinuclear antibodies, CAPS = Childhood Arthritis Prospective Study, HLA = human leucocyte, ICON = Inception Cohort of Newly diagnosed patients with juvenile idiopathic arthritis, ILAR = International League of Associations for Rheumatology, IQR = interquartile range, n = number, MTX = methotrexate, RF = rheumatoid factor

[1]taking into account first and second degree relatives

ICON does not collect data on familial autoimmune diseases

Development of prediction model

On univariable analysis, ANA status (HR = 2.09, 95% CI: 1.40 – 3.12) and age at JIA onset (HR = 0.81, 95% CI: 0.75 – 0.88) were significantly associated with uveitis. In addition, RF- polyarthritis patients (HR = 0.60, 95% CI: 0.38 – 0.95) had a significantly lower hazard for uveitis compared to oligoarthritis, unlike psoriatic arthritis (HR = 1.30, 95% CI: 0.61 – 2.74) and undifferentiated arthritis patients (HR = 1.10, 95% CI: 0.59 – 2.06). Compared to patients from Southern Europe, Western European patients had a significantly higher hazard for uveitis (HR = 3.74, 95% CI: 2.40 – 5.81) and Central and Eastern European patients had a significantly lower hazard for uveitis (HR = 0.47, 95% CI: 0.23 – 0.98). Ultimately, the best combined predictors for uveitis were age at JIA onset (HR: 0.83, 95% CI: 0.77 – 0.89), ANA status (HR: 1.59, 95% CI: 1.06 – 2.38) and ILAR category risk group (Table 3). Patients with oligoarthritis, psoriatic arthritis or undifferentiated arthritis had a 1.40 times higher hazard for developing uveitis throughout the study compared to patients with RF- polyarthritis (95% CI: 0.91 – 2.16). The mean linear predictor in the Pharmachild dataset for calculating a predicted probability of uveitis was -0.71.

Table 3. Coefficients table of prediction model for chronic uveitis.

Predictor variable	β	HR (95% CI)
Age at JIA onset (years)	-0.19	0.83 (0.77 – 0.89)*
ANA positive	0.46	1.59 (1.06 – 2.38)*
ILAR category risk groups		
Polyarthritis RF-	0	1
Oligoarthritis, psoriatic arthritis, undifferentiated arthritis	0.34	1.40 (0.91 – 2.16)

ANA = antinuclear antibodies, CI = confidence interval, HR = hazard ratio, ILAR = International League of Associations for Rheumatology, JIA = juvenile idiopathic arthritis, RF = rheumatoid factor
*statistically significant
2-year baseline survival probability = 0.94
4-year baseline survival probability = 0.91
7-year baseline survival probability = 0.90
Mean linear predictor = -0.71

External validation and recalibration of prediction model

The C statistics of the prediction model for the 2, 4 and 7-year risk of uveitis in the CAPS and ICON cohorts ranged from 0.67 (95% CI: 0.59 – 0.74) to 0.75 (95% CI: 0.72 – 0.79). These were slightly higher than the C statistics of a model with parameters used in the Heiligenhaus screening recommendations (Table 4). Based on calibration plots, the overall best performing model was obtained by incorporating the 2, 4 and 7-year baseline survival probabilities from the ICON cohort into the model (Figure 1). These were 0.94,

0.91 and 0.90, respectively. The formula of this calibrated model for calculating a predicted probability of developing uveitis in an individual JIA patient is as follows:

$$P(\text{chronic uveitis}) = 1 - S_0(t)^{\exp(0.46 \times \text{ANA status} - 0.19 \times \text{age at JIA onset} + 0.34 \times \text{ILAR category} + 0.71)}$$

Variables used in this formula are the baseline survival probability (S_0), ANA status (1 = positive, 0 = negative), age at JIA onset in years and ILAR category (1 = oligoarthritis, psoriatic arthritis or undifferentiated arthritis, 0 = RF- polyarthritis). Different baseline survival probabilities are used for different predictions, i.e. for obtaining the 2-year risk of uveitis, the 2-year baseline survival probability should be inserted in the formula.

Table 4. C statistics (95% CI) of prediction model and Heiligenhaus screening recommendations in validation cohorts.

Model	Cohort	2-year uveitis risk	4-year uveitis risk	7-year uveitis risk
Prediction model	CAPS	0.67 (0.59 – 0.74)	0.69 (0.63 – 0.76)	0.70 (0.64 – 0.76)
	ICON	0.74 (0.69 – 0.78)	0.75 (0.71 – 0.78)	0.75 (0.72 -0.79)
Heiligenhaus screening recommendations	CAPS	0.65 (0.58 – 0.75)	0.69 (0.63 – 0.75)	0.70 (0.64 – 0.75)
	ICON	0.70 (0.65 – 0.74)	0.71 (0.67 – 0.74)	0.71 (0.68 – 0.75)

CAPS = Childhood Arthritis Prospective Study, ICON = Inception Cohort of Newly diagnosed patients with juvenile idiopathic arthritis

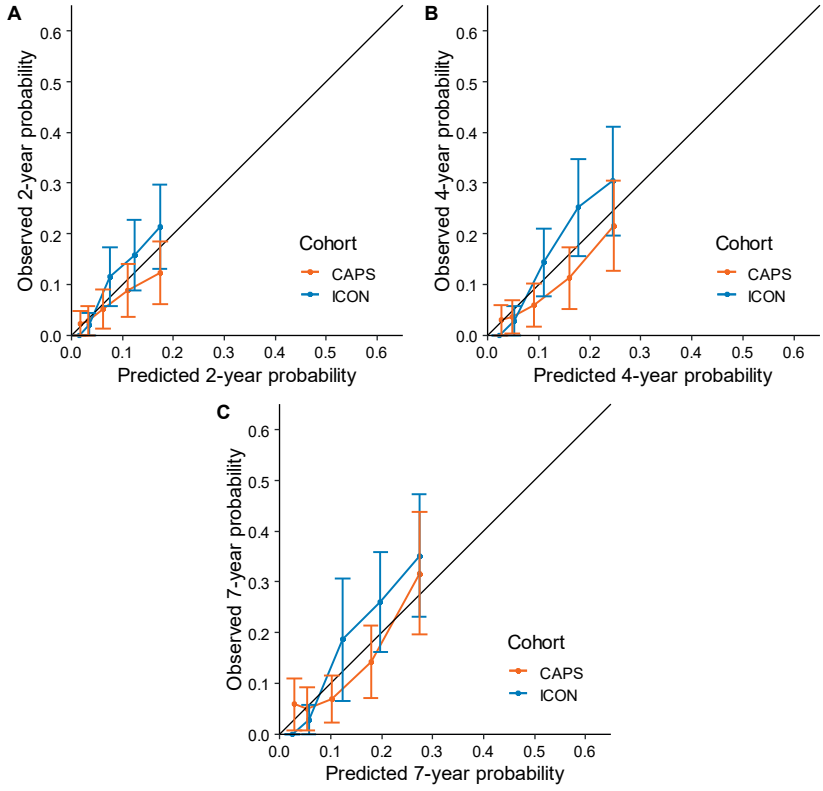


Figure 1. Calibration plots of calibrated prediction model for chronic uveitis. The plots represent the observed 2 (A), 4 (B) and 7-year (C) probabilities/Kaplan-Meier estimates of chronic uveitis versus the mean predicted probabilities within quintiles of the validation cohorts.

For clinical practice, a diagram is provided from which the cumulative 2, 4 and 7-year risk of new-onset chronic uveitis can be determined as a function of the predictor variables (Figure 2). Predictions can also be obtained from a digital risk calculator (Supplementary Table 3; available on the *Arthritis & Rheumatology* website at https://onlinelibrary.wiley.com/doi/10.1002/art.42329).

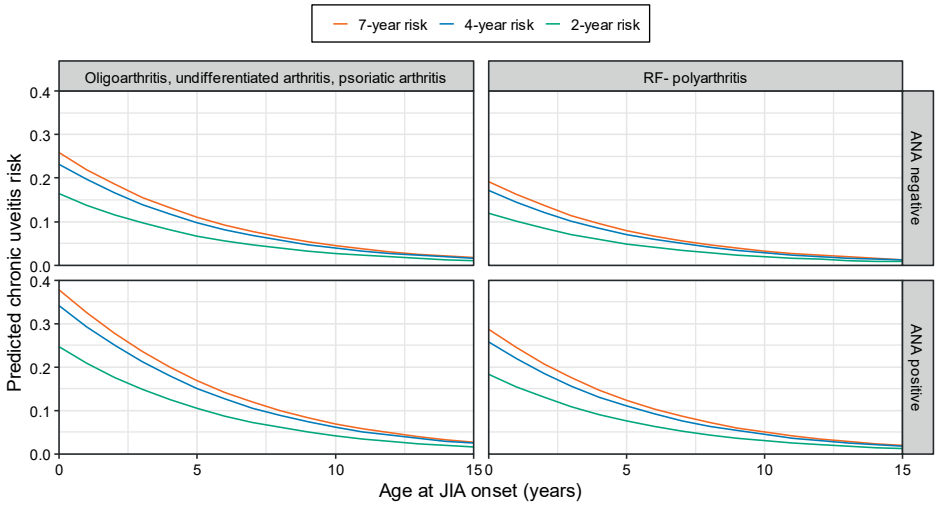


Figure 2. Diagram of cumulative predicted probabilities from calibrated prediction model for chronic uveitis. First, pick the panel of interest based on the ILAR category (on top) and ANA status (on the right). Then, read of the predicted probability on the y-axis as a function of the age at JIA onset on the x-axis. The 2, 4 or 7-year risk denotes the risk of developing uveitis in the first 2, 4 or 7 years after onset of JIA.
ANA = antinuclear antibodies, JIA = juvenile idiopathic arthritis, RF = rheumatoid factor

DISCUSSION

In this study, we developed and externally validated a prediction model for new-onset chronic uveitis in JIA patients. Using this model, individual risk estimates for chronic uveitis can easily be obtained from a diagram or risk calculator. Predictions following this model could be used by paediatric rheumatologists to more accurately inform patients and parents and might provide rationale for therapy with adalimumab or infliximab instead of etanercept for arthritis. In addition, these predictions have the potential to guide clinicians in determining screening frequencies.

The variables in the prediction model are common clinical parameters in the management of JIA, making our model well-applicable for clinical practice worldwide. Several studies have shown that ANA status and age at JIA onset are associated with the risk of developing uveitis in JIA[5,25–27] and current ophthalmological screening guidelines also incorporate these factors[4,7,9–11]. Previous studies have suggested sex differences in risk factors for uveitis in JIA[28], but in the current study the same model predictors were selected when restricting analyses to only boys or girls. The decision to group together psoriatic, undifferentiated and oligoarticular arthritis was based on two large studies which found that RF- polyarthritis patients run a lower risk of developing uveitis compared to this group of patients[9,16]. Since we want our model to be able to provide risk estimates for

uveitis early in the disease course of JIA, we decided not to distinguish between persistent and extended oligoarthritis, given that the latter diagnosis might take years to become obvious. For the same reason, we did not consider drug therapy for inclusion in the prediction model. Nevertheless, for both Pharmachild and ICON we observed that JIA patients who did not develop uveitis more often used MTX and ADA than patients who did, suggesting a protective effect. This effect might be further supported by the short duration from last MTX stop to uveitis onset that was observed in the Pharmachild cohort (median <1 year). Several other studies have reported evidence for a protective effect of MTX and/or ADA on the development of uveitis in JIA [25,29–32]. Geographical residence was significantly associated with uveitis in Pharmachild, with Western European residence being a significant risk factor which is consistent with the literature[14]. However, addition of this variable to the prediction model resulted in C statistics of 0.37 and 0.39 in ICON and CAPS. This can probably be attributed to unstable coefficient estimates due to the high heterogeneity in the "other region" group and the fact that there were no patients from Germany and the UK in Pharmachild.

This study provides the first validated tool for predicting chronic uveitis at different disease durations in an individual JIA patient. One previous study provided a prediction model for uveitis in JIA patients, but this model did not discriminate between acute and chronic uveitis, did not incorporate disease duration and was not externally validated[16]. Another study reported a model for chronic uveitis, but this model also did not incorporate disease duration, lacked external validation and only included RF- polyarthritis and oligoarthritis patients[33].

Calibration and discrimination of our model in the validation cohorts was satisfactory. This demonstrates that the model is well capable of predicting the risk of uveitis in JIA patients from other settings than Pharmachild. For instance, patients from the current validation cohorts were more often ANA positive than patients from Pharmachild. This could be partly caused by different methodologies for ANA testing worldwide, but is most probably the result of a difference in oligoarthritis prevalence, which is known to be higher in Western European countries compared to the rest of the world[1]. The calibration plots revealed that the majority of model predictions for uveitis in the CAPS cohort were slight overestimations, whereas predictions in the ICON cohort were slight underestimations. This is probably caused by the larger uveitis prevalence in ICON (15.7%) compared to CAPS (12.6%). Nonetheless, the prevalence of uveitis in both validation cohorts corresponds to the range of prevalence rates reported in the literature[3]. It was furthermore observed that our model had higher discriminative power in the ICON cohort compared to the CAPS cohort, likely due to differences in ILAR categories of patients that developed uveitis. Whereas 17% of patients with psoriatic, undifferentiated or oligoarticular arthritis in ICON developed uveitis, this percentage was notably lower for CAPS (13%).

The cumulative 2, 4 and 7-year predicted risks for uveitis following our recalibrated model reflect that the instantaneous risk of developing uveitis decreases with increasing disease duration. For example, the 7-year predicted risk is only slightly larger than the 4-year predicted risk. This is in line with earlier evidence on the relationship between JIA disease duration and risk of uveitis[9,34–37]. Nevertheless, since the number of censored patients for deriving a 7-year risk is higher than the number of censored patients for deriving a 2-year risk, it is not straightforward or recommended to use our model to obtain a "remaining risk" for uveitis as a function of the disease duration of a patient and is most valid when applied at first presentation with JIA. Also, as can be seen from the different C statistics and calibration plots, our model performs better in predicting long-term risks than short-term risks.

The prediction model had higher discriminative power in both validation cohorts than a model based on parameters from the commonly used Heiligenhaus screening recommendations[9]. This screening guideline uses a cut-off value of 6 for age at JIA onset and does not distinguish between psoriatic, oligoarticular, undifferentiated and RF- polyarticular JIA. Nevertheless, it can be concluded that the performance of the Heiligenhaus parameters in both validation cohorts was acceptable, with C statistics of 0.70 and 0.71 for the 7-year predicted uveitis risk. We therefore conclude that these guidelines remain suitable for ophthalmological screening of JIA patients and need not to be replaced by a prediction model. However, one advantage of a prediction model over a screening guideline is the ability to obtain/provide absolute risk estimates instead of subjective "high", "low" or "moderate" risk categories.

Based on the prediction model, the authors propose a set of points to consider for improving the current standard of care in JIA patients with regard to uveitis development. First of all, given the high predicted uveitis risk for ANA positive patients with oligoarthritis, psoriatic arthritis or undifferentiated arthritis and age at JIA onset ≤6 years, one can think of 2-monthly screening for uveitis during the first year after JIA onset, 3-monthly screening during the second year and 4-monthly screening during the third and fourth year. It has long been suggested to increase uveitis screening frequency to every two months in the highest risk group of JIA patients[38]. Also, 4-monthly screening during the first two years and 6-monthly screening during the next two years could be considered for ANA positive patients with oligoarthritis, psoriatic arthritis or undifferentiated arthritis and age at JIA onset >6 years. ANA negative patients with oligoarthritis, psoriatic arthritis or undifferentiated arthritis and age at JIA onset ≤6 years might be screened 4-monthly during the first four years. Given our model, it could furthermore be considered to differentiate between RF- polyarthritis and oligoarthritis, psoriatic arthritis or undifferentiated arthritis when determining screening frequencies, which is not reflected in the Heiligenhaus screening recommendations. These suggestions will be discussed in the Multinational

Interdisciplinary Working Group for Uveitis in Childhood (MIWGUC), with the aim of tailoring uveitis screening in JIA using evidence-based medicine. Apart from modifying screening frequencies, low predictions for uveitis according to our model could also be used to comfort patients and parents. For example, a paediatric rheumatologist could tell parents that out of 100 patients similar to their child, only a certain number will develop uveitis. Lastly, it could be considered to start MTX or even ADA therapy instead of intra-articular injections in JIA patients with high predicted risks for uveitis, which we define as ≥15 %.

This study has limitations. First, for a large number of uveitis cases within Pharmachild no diagnosis date was available. Therefore, these cases had to be excluded and the resulting prediction model had to be recalibrated to one of the validation cohorts. We observed that uveitis cases without diagnosis date had more often oligoarthritis and a positive ANA status. Yet, the recalibrated prediction model performed well in the validation cohorts. Also, multivariable logistic regression analysis in the Pharmachild cohort including uveitis cases without diagnosis date yielded the same predictor variables. Furthermore, the majority of included patients were treated in tertiary care centres. Therefore, it is uncertain how our model performs in JIA patients not seen in centres with ample experience in JIA and uveitis who have low disease activity and do not receive DMARDs, for which additional recalibration might be needed.

A great strength of the present study is the large sample size of the model development data with patients from multiple countries and the use of inception cohorts from further geographical settings for validation. The latter is ideal for studying early-onset uveitis in JIA.

For the future, further practical recommendations for health care providers and patients based on the model should be jointly formulated by doctors and patients and endorsed by organizations such as the European Reference Network on immunodeficiency, auto-inflammatory and autoimmune diseases (ERN-RITA). In addition, it should be evaluated if use of the model in clinical practice impacts management and outcomes of JIA patients. Unfortunately, this model impact research is rarely performed[39]. In addition, the current model could be extended with relevant biomarker data. Studies have highlighted an elevated erythrocyte sedimentation rate, calcium-binding protein S100A12 and HLA DRB1*11 in girls as potential predictive factors[25,28,37,40].

To conclude, we provide for the first time a validated prediction model for new-onset chronic uveitis at different disease durations in an individual JIA patient. Model predictions can easily be obtained from common clinical parameters.

ACKNOWLEDGEMENTS

The authors thank all PRINTO centres for their contribution to the data collection and PRINTO research assistants (Chiara Pallotti, Silvia Scala, Simona Angioloni and Luca Villa). The authors would also like to express their acknowledgements to ERN-RITA.

We also thank all principal investigators of CAPS, clinical staff and research coordinators who have made this research possible, as well as members of the research team at the University of Manchester, UK. These include: G Cleary, E Baildam (Alder Hey Children's Hospital, UK), L Wedderburn (Great Ormond Street Hospital, UK), J Davidson (Royal Hospital for Sick Children, Edinburgh and Royal Hospital for Children, Glasgow, UK), A Chieng (Royal Manchester Children's Hospital, UK), F McErlane, H Foster (Royal Victoria Infirmary, UK), C Ciurtin, Y Ioannou (University College London Hospital, UK) and W Thomson, K Hyrich (University of Manchester).

We would like to acknowledge the contributions of the following ICON JIA Study Group collaborators: Tilmann Kallinich (Universitätsmedizin Charité Berlin), Frank Dressler (Medizinische Hochschule Hannover), Jasmin Kümmerle Deschner (Universität Tübingen), Frank Weller-Heinemann (Prof. Hess Kinderklinik Bremen), Gerd Horneff (Asklepios Kinderklinik Sankt Augustin), Anton Hospach (Olgahospital Stuttgart), Kirsten Mönkemöller (Kinderkrankenhaus der Stadt Köln), Johannes Peter Haas (Deutsches Zentrum für Kinder- und Jugendrheumatologie Garmisch Partenkirchen), Daniel Windschall (St. Joseph Stift Sendenhorst), Ivan Foeldvari (Kinderrheumatologische Praxis am AK Eilbek Hamburg), Dirk Foell (Klinik für Pädiatrische Rheumatologie und Immunologie, Universitätsklinikum Münster).

FUNDING

This work was supported by a research grant from FOREUM Foundation for Research in Rheumatology. Pharmachild has been supported by a grant from the European Union (260353) and by funding from the Italian public hospital IRCCS Istituto Giannina Gaslini.

CAPS was funded by Versus Arthritis (UK grant number 20542). The research team at The University of Manchester are additionally supported by the Centre for Epidemiology Versus Arthritis (UK grant number 21755), the Centre for Genetics and Genomics Versus Arthritis (UK grant number 21754) and the NIHR Manchester Biomedical Research Centre.

The ICON study is funded by the German Federal Ministry of Education and Research (BMBF, FKZ 01ER0812, 01ER0813, 01ER0828, and FKZ 01ER1504A, 01ER1504B, 01ER1504C).

COMPETING INTERESTS

AH reports grants from BMBF and DFG, payments from AbbVie, Santen, Allergan and UCB Pharma, travel support from Allergan, MSD Sharp and Dohme and UCB Pharma and participation on an advisory board for AbbVie and Novartis. CH reports a speaker fee and research grant from Roche. KH reports institution grants from Pfizer and BMS and institution payments from AbbVie. KM reports payments from AbbVie, Roche, Pfizer, Novartis and Medac and participation on an advisory board for Sanofi, Pfizer and Novartis. NR reports honoraria for consultancies or speaker bureaus from 2 Bridge, Amgen, AstraZeneca, Aurinia, Bayer, Brystol Myers and Squibb, Celgene, inMed, Cambridge Healthcare Research, Domain Therapeutic, EMD Serono, Glaxo Smith Kline, Idorsia, Janssen, Eli Lilly, Novartis, Pfizer, Sobi, UCB.

All other authors declare no competing interests.

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SUPPLEMENTARY MATERIAL

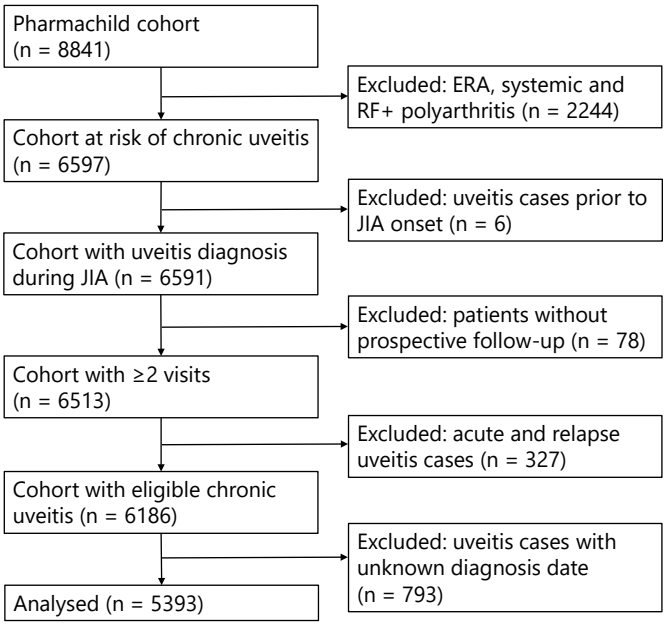
Supplementary Table 1. Overview of countries of included patients and corresponding geographical regions.

Geographical region	Countries
Southern Europe	Greece, Italy, Spain
Central and Eastern Europe	Bulgaria, Croatia, Czech Republic, Hungary, Latvia, Lithuania, Poland, Romania, Serbia, Slovakia, Russia, Slovenia
Western Europe	Austria, France, Netherlands, Switzerland
Scandinavia	Denmark, Norway
Other	Israel, Libya, Oman, Saudi Arabia, Turkey, Argentina, Brazil, Peru, Ecuador, Mexico, India, Singapore

Supplementary Table 2. Characteristics of chronic uveitis cases with and without available diagnosis date in the Pharmachild cohort.

Characteristics	Chronic uveitis with diagnosis date (n = 107)	Chronic uveitis without diagnosis date (n = 793)
Girls, n (%)	82 (76.6%)	632 (79.7%)
Age at JIA onset (years), median (IQR)	2.2 (1.6 – 4.1)	2.6 (1.7 – 4.4)
ILAR category, n (%)		
Oligoarthritis	58 (54.2%)	531 (67.0%)
Polyarthritis RF -	29 (27.1%)	173 (21.8%)
Psoriatic arthritis	8 (7.5%)	27 (3.4%)
Undifferentiated arthritis	12 (11.2%)	62 (7.8%)
Laboratory characteristics, n (%)		
ANA positive	68 (63.6%) n = 107	560 (72.2%) n = 776
RF positive	0 (0.0%) n = 91	2 (2.9%) n = 692
HLA-B27 positive	9 (14.8%) n = 61	52 (12.1%) n = 430 12.1%)

ANA: antinuclear antibodies; HLA: human leucocyte antigen; ILAR: International League of Associations for Rheumatology; RF: rheumatoid factor



Supplementary Figure 1. Selection of participants in Pharmachild.
ERA: enthesitis-related arthritis; JIA: juvenile idiopathic arthritis; RF: rheumatoid factor

Supplementary Data 1. Journal club feature.

Journal Club

A monthly feature designed to facilitate discussion on research methods in rheumatology.

Development and External Validation of a Model Predicting New-Onset Chronic Uveitis at Different Disease Durations in JIA

van Straalen et al, *Arthritis Rheumatol.* 2023;75:318–327

Chronic uveitis is a common comorbidity in juvenile idiopathic arthritis (JIA), affecting ~1 in every 6 patients. If not treated in a timely manner, uveitis can cause significant visual disability, including cataracts, synechiae, and glaucoma. Therefore, ophthalmologic screening guidelines for JIA-associated uveitis exist, and are based on known risk factors, such as antinuclear antibody (ANA) status, JIA category, age at JIA onset, and disease duration. Nonetheless, prediction models based on such risk factors have the potential to produce more accurate, personalized, and objective probabilities of uveitis development. van Straalen et al developed a model predicting new-onset chronic uveitis at different disease durations in JIA using data from the international PharmaChild registry (n = 5,393) and subsequently validated this model in 2 independent inception cohorts: the UK Childhood Arthritis Prospective Study (CAPS) (n = 700) and the German Inception Cohort of Newly diagnosed patients with JIA (ICON) (n = 758).

The model was developed using a multivariable Cox proportional hazards regression, predicting the 2-, 4-, and 7-year risk of new-onset chronic uveitis. The researchers used multiple imputation of missing values using chained equations to avoid a loss of statistical power and possible selection bias as a result of restricting the data to complete cases. Model variables were selected by stepwise backward selection in 20 imputed data sets. ANA status, JIA category, and age at JIA onset were selected as predictor variables, and coefficient estimates in the imputed data sets were pooled using Rubin's rules. The resulting prediction model was subsequently recalibrated to adjust for possible overfitting. This was done in 2 ways: by using the baseline survival probability in the validation cohorts (the "recalibration in the large" method) and by adjusting the model coefficients with a shrinkage factor as determined from the validation cohorts (the "logistic recalibration" method). Performance of the recalibrated models in the validation cohorts was assessed by the C statistic for discrimination and calibration plots of mean predicted probabilities versus observed probabilities within quintiles of the data. The recalibrated model that performed best in both validation cohorts was presented as the final prediction model for clinical application using a diagram or digital risk calculator.

Questions

1. **Which JIA patients are known to be at an increased risk of developing chronic uveitis?**
2. **What is the advantage of multiple imputation using chained equations in dealing with missing data over other imputation techniques?**
3. **What other methods exist for adjusting prediction models for overfitting?**
4. **How might the choice of development and validation cohorts have influenced the prediction model?**

A10

CHAPTER 7

7

Juvenile idiopathic arthritis patients with positive family history of autoimmune thyroid disease might benefit from serological screening: analysis of the international Pharmachild registry

Joeri W. van Straalen[1,2], Laurie Baas[1,2], Gabriella Giancane[3,4], Lyudmila Grebenkina[5], Jurgen Brunner[6,7], Gabriel Vega-Cornejo[8], Vyacheslav G. Chasnyk[9], Liora Harel[10,11], Simone Appenzeller[12], Elisabeth Gervais[13], Sytze de Roock[1,2], Nico M. Wulffraat[1,2], Nicolino Ruperto[14] and Joost F. Swart[1,2], for the Paediatric Rheumatology International Trials Organisation (PRINTO)

[1]Department of Paediatric Immunology and Rheumatology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, The Netherlands
[2]Faculty of Medicine, Utrecht University, Utrecht, The Netherlands
[3]Clinica Pediatrica e Reumatologia, IRCCS Istituto Giannina Gaslini, Genoa, Italy
[4]Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili (DiNOGMI), Università degli Studi di Genova, Genoa, Italy
[5]Paediatric Department, Togliatti City Clinical Hospital №5, Togliatti, Russia
[6]Paediatric Rheumatology, Department of Paediatrics, Medical University Innsbruck, Innsbruck, Austria
[7]Danube Private University, Krems, Austria
[8]Clínica Pediátrica de Reumatología y Enfermedades Autoinmunes (CREA), Hospital México Americano, Guadalajara, México
[9]Department of Hospital Paediatrics, Saint Petersburg State Paediatric Medical University, Saint Petersburg, Russia
[10]Pediatric Rheumatology Unit, Schneider Children's Medical Centre, Petach-Tikvah, Israel
[11]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
[12]Department of Orthopaedics, Rheumatology and Traumatology, School of Medical Science, University of Campinas, Campinas, Brazil
[13]Rheumatology, Centre Hospitalier Universitaire (CHU) de Poitiers, Poitiers, France
[14]UOSID Centro trial, IRCCS Istituto Giannina Gaslini, Genoa, Italy

ABSTRACT

Background

Little is known about the association between juvenile idiopathic arthritis (JIA) and autoimmune thyroid disease (AITD) and therefore there are no indications for AITD screening in this population, which is possible using standard blood tests. The objective of this study is to determine the prevalence and predictors of symptomatic AITD in JIA patients from the international Pharmachild registry.

Methods

Occurrence of AITD was determined from adverse event forms and comorbidity reports. Associated factors and independent predictors for AITD were determined using univariable and multivariable logistic regression analyses.

Results

The prevalence of AITD after a median observation period of 5.5 years was 1.1% (96/8965 patients). Patients who developed AITD were more often female (83.3% vs. 68.0%), RF positive (10.0% vs. 4.3%) and ANA positive (55.7% vs. 41.5%) than patients who did not. AITD patients were furthermore older at JIA onset (median 7.8 years vs. 5.3 years) and had more often polyarthritis (40.6% vs. 30.4%) and a family history of AITD (27.5% vs. 4.8%) compared to non-AITD patients. A family history of AITD (OR = 6.8, 95% CI: 4.1 – 11.1), female sex (OR = 2.2, 95% CI: 1.3 – 4.3), ANA positivity (OR = 2.0, 95% CI: 1.3 – 3.2) and older age at JIA onset (OR = 1.1, 95% CI: 1.1 – 1.2) were independent predictors of AITD on multivariable analysis. Based on our data, 16 female ANA positive JIA patients with a family history of AITD would have to be screened during ±5.5 years using standard blood tests to detect one case of AITD.

Conclusions

This is the first study to report independent predictor variables for symptomatic AITD in JIA. Female ANA positive JIA patients with positive family history are at increased risk of developing AITD and thus might benefit from yearly serological screening.

Keywords: juvenile idiopathic arthritis, autoimmune thyroid disease, Hashimoto's disease, Graves' disease, screening, risk factors, epidemiology, registry

BACKGROUND

Juvenile idiopathic arthritis (JIA) is a diagnosis of exclusion that includes all forms of chronic arthritis of unknown origin with onset below the age of 16 years[1]. It is the most common childhood rheumatic disease with an estimated global incidence of 1.6 – 23 cases per 100,000 children[2] and often persists into adulthood[3]. The International League of Associations for Rheumatology (ILAR) distinguishes seven JIA categories with different clinical and laboratory measures[4], although another classification system is under development[5].

There is some evidence that children with JIA suffer more often from autoimmune thyroid disease (AITD) than the general paediatric population[6–8]. AITD comprises Hashimoto's thyroiditis which causes hypothyroidism and Graves' disease which causes hyperthyroidism. If undiagnosed and thus left untreated, hyper- and hypothyroidism may lead to a variety of complaints, such as constipation or diarrhoea, irritability, fatigue, hair loss but ultimately also growth retardation and depression[9].

Currently, little is known about the association between JIA and AITD and therefore there are no indications for AITD screening in this population, which is possible using standard blood tests. Previous studies reported a prevalence of (subclinical) AITD in JIA varying from 1– 44%[7,8,10–16]. One study of 81 JIA patients reported a significant association between a family history of thyroid disease and AITD[17]. Nevertheless, studies that primarily focus on AITD in JIA are scarce and most include not only symptomatic but also subclinical AITD. Furthermore, no study has yet established independent predictor variables for AITD in JIA.

The purpose of this study is to determine the prevalence of symptomatic AITD in JIA and moreover to identify independent predictors for AITD using data from the international observational Pharmachild registry.

METHODS

Pharmachild

Pharmachild was set up in 2011 with the primary aim of studying safety and effectiveness of drug therapies in JIA. Pharmachild collects demographic, clinical and laboratory data of JIA patients from 85 Paediatric Rheumatology International Trials Organisation (PRINTO) medical centres from 31 countries across the globe[18]. Inclusion criteria are JIA classified according to ILAR criteria while under treatment or previously treated with nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroids, systemic corticosteroids, and/or conventional synthetic (cs-) or biological (b-) disease-modifying antirheumatic

drugs (DMARD) as per physician decision. The registry consists of two cohorts. The first is a cohort of all included patients with retrospective information about drug exposure and adverse events (AEs) from disease onset until registration into Pharmachild. The second is a cohort of patients with additional prospective information about disease activity and patient-reported outcomes for hospital visits after registration into Pharmachild. More information about the Pharmachild registry is published elsewhere[19]. Data lock occurred on 18 December, 2019 and all patients at that time were included in the present study.

Outcome and determinants

The outcome of interest in this study was the ever occurrence of symptomatic AITD (Hashimoto's thyroiditis, Graves' disease and non-specified AITD). This outcome (yes/no) was evaluated for all patients from two sources: free-text fields for comorbidity reporting at registration into Pharmachild and AE forms. AEs in Pharmachild are reported using the Medical Dictionary of Regulatory Activities (MedDRA) coding system (version 22) with a three-level monitoring check for consistency by the treating physician, medical monitor (JS) and PRINTO certified MedDRA coders[20]. The following MedDRA preferred terms were considered as AITD: "hypothyroidism", "autoimmune thyroiditis", "thyroiditis", "hyperthyroidism" and "Basedow's disease". Goiter and congenital thyroid disorder were not considered as AITD. Laboratory results were not considered for determining AITD, since these were likely to involve subclinical cases. All mentions of possible AITD cases were retrieved and reviewed by one researcher (LB) and event descriptions were subsequently independently evaluated by two other researchers (JS and JvS). In order to explore the coexistence of endocrinopathies, mentions of growth retardation/short stature, diabetes mellitus and celiac disease were retrieved from both free-text comorbidity reports and AE forms. For this assessment, the following mentions were included: "growth retardation", "growth retarded", "short stature", "stature short", "coeliac disease", "celiac disease", "type 1 diabetes mellitus", "diabetes", "type I diabetes mellitus" and "diabetes mellitus insulin-dependent". In addition, the following patient characteristics were collected for all patients: sex, ethnicity, age at JIA onset, ILAR category, anti-nuclear antibodies (ANA) status, rheumatoid factor (RF) status, human leukocyte antigen (HLA)-B27 status, family history of autoimmune disease and AITD (in first, second and/or third-degree relatives), observation period (time from JIA onset until last Pharmachild visit), the number of active joints at JIA diagnosis (max. 12 months later) and drug history at last visit. Ethnicity was reported by the treating physician from a fixed set of categories. For ANA positivity, only one positive ANA test was required. A positive RF status was defined as two positive RF determinations at least three months apart. Drugs included were NSAIDs, intraarticular corticosteroids, systemic corticosteroids, cs- and b-DMARDs.

Statistical analysis

The retrospective and prospective Pharmachild cohorts were analysed together. Patient characteristics were compared between patients with and without AITD using univariable logistic regression analyses. When the 95% confidence interval (CI) of the odds ratio (OR) did not contain 1, this was considered a statistically significant effect. All variables that differed statistically significant between AITD and non-AITD patients were considered for inclusion into a complete case multivariable logistic regression model in order to identify independent predictors of AITD. Predictors were selected using a stepwise backward procedure based on the Akaike's Information Criterion (AIC). This measure is used to select a model that best predicts the observed data while adding a penalty for the number of variables in the model[21]. Because onset dates of AITD were not available for all cases, the observation period and drug history were not considered for inclusion into the multivariable model. The active joint count was also not considered since this measure was only available for (part of the) patients from the prospective Pharmachild cohort. Numerical variables were tested for a linear relationship with the logit outcome using the Box-Tidwell test. The performance of the multivariable model in distinguishing between AITD and non-AITD patients was evaluated by the area under the receiver operating characteristic curve (AUC). Based on the prevalence of AITD in patients at increased risk for developing AITD following our prediction model, we calculated a number needed to screen (NNS) (1 divided by the absolute risk reduction). IBM SPSS statistics (version 25.0.0.2) and R (version 4.0.3) were used for the statistical analyses.

RESULTS

Patient characteristics

A total of 8,965 patients were included from the Pharmachild registry for analysis with a total observation period of 57,053 years (median 5.5 years, IQR: 2.8–9.0). Within these patients, 96 cases of clinical AITD (1.1%) were identified (Figure 1). Hashimoto's thyroiditis occurred in 58/96 (60.4%) cases and Graves' disease in 4/96 (4.2%) of cases. The remaining 34/96 (35.4%) of AITD cases were unspecified. Patients who developed AITD were more often female, RF positive and ANA positive than patients who did not develop AITD (Table 1). Furthermore, AITD patients were older at JIA onset and had more often polyarthritis and a family history of autoimmune disease and AITD compared to non-AITD patients. Celiac disease and diabetes mellitus were reported significantly more often in AITD patients compared to patients without AITD: 4.2% vs. 0.6% ($P < 0.01$) and 2.1% vs. 0.3% ($P = 0.04$), respectively. No significant difference was found for growth retardation/short stature: 0.0% for AITD patients and 0.3% for non-AITD patients ($P = 1.0$). AITD patients had less often systemic arthritis than non-AITD patients. The observation period, HLA-B27 status, active joint count at JIA diagnosis, ethnicity and drug history at last visit did not

differ significantly between the two groups. A distribution of different AITD cases per ILAR category is provided in Table 2.

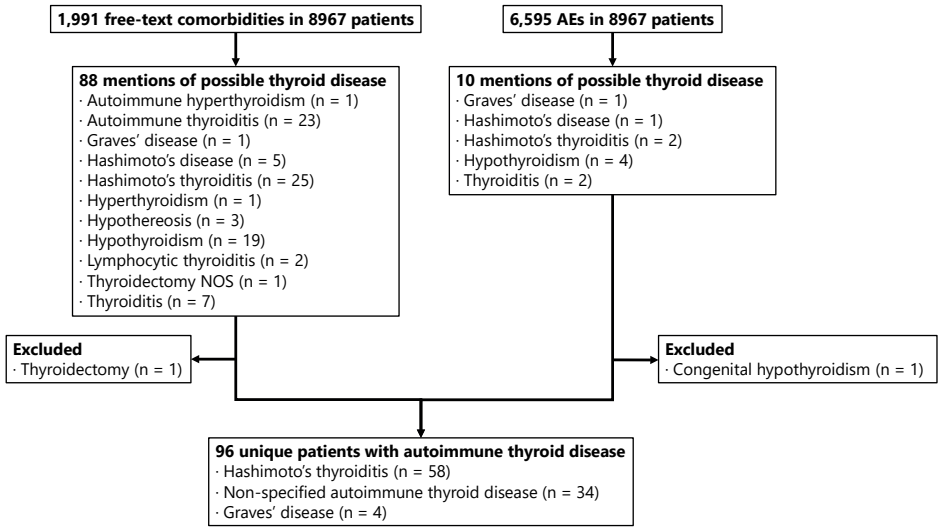


Figure 1. Flowchart of selected AITD cases.

Table 1. Characteristics of patients in Pharmachild with and without AITD.

	Total (n = 8965)	**No AITD (n = 8869)**	**AITD (n = 96)**
Observation period in years, median (IQR)	5.5 (2.8 – 9.0)	5.5 (2.8 – 9.0)	4.9 (3.0 – 9.5)
Female sex, n (%)	6107 (68.1%)	6027 (68.0%)	80 (83.3%)
Ethnicity, n (%)			
European	6940 (86.9%)	6853 (86.9%)	87 (90.6%)
Hispanic	249 (3.1%)	248 (3.1%)	1 (1.0%)
Indian	145 (1.8%)	144 (1.8%)	1 (1.0%)
Middle Eastern	196 (2.5%)	193 (2.4%)	3 (3.1%)
Multiethnic	110 (1.4%)	109 (1.4%)	1 (1.0%)
North African	154 (1.9%)	152 (1.9%)	2 (2.1%)
Southeast Asian	64 (0.8%)	64 (0.8%)	0 (0.0%)
Sub-Saharan African	78 (1.0%)	78 (1.0%)	0 (0.0%)
Other	48 (0.6%) n = 7986	47 (0.6%) n = 7888	1 (1.0%) n = 96

Table 1. Continued

	Total (n = 8965)	**No AITD (n = 8869)**	**AITD (n = 96)**
Family history of autoimmune disease, n (%)	2632 (30.4%) n = 8669	2584 (30.1%) n = 8578	48 (52.7%) n = 91
Family history of AITD, n (%)	441 (5.1%) n = 8669	416 (4.8%) n = 8578	25 (27.5%) n = 91
Age at JIA onset in years, median (IQR)	5.3 (2.4 – 9.9)	5.3 (2.4 – 9.9)	7.8 (3.1 – 12.7)
ILAR category, n (%)			
Enthesitis-related arthritis	969 (10.8%)	961 (10.8%)	8 (8.3%)
Oligoarthritis	3370 (37.6%)	3338 (37.6%)	32 (33.3%)
Polyarthritis (RF-)	2371 (26.4%)	2341 (26.4%)	30 (31.3%)
Polyarthritis (RF+)	367 (4.1%)	358 (4.0%)	9 (9.4%)
Psoriatic arthritis	298 (3.3%)	292 (3.3%)	6 (6.2%)
Systemic arthritis	968 (10.8%)	966 (10.9%)	2 (2.1%)
Undifferentiated arthritis	622 (6.9%)	613 (6.9%)	9 (9.4%)
Active joint count at JIA diagnosis, median (IQR)	3.0 (1.0 – 6.0) n = 70	3.0 (0.8 – 6.0) n = 68	4.0 (4.0 – 4.0) n = 2
ANA positive, n (%)	3486 (41.7%) n = 8365	3437 (41.5%) n = 8277	49 (55.7%) n = 88
RF positive, n (%)	342 (4.3%) n = 7876	333 (4.3%) n = 7786	9 (10.0%) n = 90
HLA-B27 positive, n (%)	1122 (20.7%) n = 5414	1114 (20.8%) n = 5363	8 (15.7%) n = 51
Drug history at last visit, n (%)			
NSAIDs	7375 (82.3%)	7298 (82.3%)	77 (80.2%)
Intraarticular corticosteroids	4545 (50.7%)	4496 (50.7%)	49 (51.0%)
Systemic corticosteroids	3582 (40.0%)	3551 (40.0%)	31 (32.3%)
cs-DMARDs	7795 (86.9%)	7712 (87.0%)	83 (86.5%)
Methotrexate	7524 (83.9%)	7446 (84.0%)	78 (81.2%)
b-DMARDs	5946 (66.3%)	5878 (66.3%)	68 (70.8%)
Anti-TNF	5248 (58.5%)	5183 (58.4%)	65 (67.7%)

AITD: autoimmune thyroid disease, ANA: anti-nuclear antibodies, b: biological, cs: conventional synthetic, DMARDs: disease-modifying antirheumatic drugs, HLA: human leukocyte antigen, ILAR: International League of Associations for Rheumatology, JIA: juvenile idiopathic arthritis, NSAIDs: nonsteroidal anti-inflammatory drugs, RF: rheumatoid factor, TNF: tumour necrosis factor.

Table 2. Distribution of different AITD cases per ILAR category.

ILAR category	Total AITD (n = 96)	Hashimoto's disease (n = 58)	Graves' disease (= 4)	Unspecified AITD (n = 34)
Enthesitis-related arthritis	8 (8.3%)	6 (10.3%)	0 (0.0%)	2 (5.9%)
Oligoarthritis	32 (33.3%)	17 (29.3%)	3 (75.0%)	12 (35.3%)
Polyarthritis (RF-)	30 (31.3%)	21 (36.2%)	0 (0.0%)	9 (26.5%)
Polyarthritis (RF+)	9 (9.4%)	4 (6.9%)	0 (0.0%)	5 (14.7%)
Psoriatic arthritis	6 (6.2%)	3 (5.2%)	1 (25.0%)	2 (5.9%)
Systemic arthritis	2 (2.1%)	1 (1.7%)	0 (0.0%)	1 (2.9%)
Undifferentiated arthritis	9 (9.4%)	6 (10.3%)	0 (0.0%)	3 (8.8%)

AITD: autoimmune thyroid disease, ILAR: International League of Associations for Rheumatology, RF: rheumatoid factor

Predictors for AITD

On multivariable analysis, a family history of AITD, female sex, ANA positivity and older age at JIA onset were independent predictors of AITD (Table 3). This model included 7,345 patients and 82 AITD events due to 1,620 patients with missing data. The model had good discriminatory power (AUC = 0.71, 95% CI: 0.65 – 0.78). Based on the data in Pharmachild, the number of female ANA positive JIA patients with a family history of AITD needed to screen to detect one case of AITD is 16. This number decreases with increasing age at JIA onset (Table 4).

Table 3. Risk factors and independent predictors for AITD on univariable and multivariable analysis.

	Univariable analysis		Multivariable analysis	
Variable	**OR**	**95% CI**	**OR**	**95% CI**
Family history of AITD	7.43	4.56 – 11.74*	6.84	4.07 – 11.14*
Female sex	2.36	1.42 – 4.19*	2.22	1.25 – 4.25*
ANA positive	1.77	1.16 – 2.71*	1.99	1.25 – 3.18*
Age at JIA onset in years	1.10	1.05 – 1.15*	1.12	1.07 – 1.18*
Observation period in years[1]	1.02	0.98 – 1.07		
Ethnicity				
European	1.00	Reference		
African	-	-		
Hispanic	0.32	0.02 – 1.44		
Indian	0.55	0.03 – 2.48		
Middle Eastern	1.22	0.30 – 3.30		

Table 3. Continued.

	Univariable analysis		Multivariable analysis	
Variable	**OR**	**95% CI**	**OR**	**95% CI**
North African	1.04	0.17 – 3.32		
Southeast Asian	-	-		
Other	1.68	0.09 – 7.80		
Family history of autoimmune disease	2.59	1.71 – 3.93*		
ILAR category				
Oligoarthritis	1.00	Reference		
Enthesitis-related arthritis	0.87	0.37 – 1.80		
Polyarthritis (RF-)	1.34	0.81 – 2.21		
Polyarthritis (RF+)	2.62	1.17 – 5.31*		
Psoriatic arthritis	2.14	0.80 – 4.81		
Systemic arthritis	0.22	0.03 – 0.71*		
Undifferentiated arthritis	1.53	0.68 – 3.09		
RF positive	2.49	1.15 – 4.73*		
HLA-B27 positive	0.71	0.31 – 1.43		
Drug history at last visit[1]				
NSAIDs	0.87	0.54 – 1.49		
Intraarticular corticosteroids	1.01	0.68 – 1.52		
Systemic corticosteroids	0.71	0.46 – 1.09		
cs-DMARDs	0.96	0.55 – 1.81		
Methotrexate	0.83	0.51 – 1.43		
b-DMARDs	1.24	0.80 – 1.95		
Anti-TNF	1.49	0.98 – 2.32		

AITD: autoimmune thyroid disease, ANA: anti-nuclear antibodies, b: biological, CI: confidence interval, cs: conventional synthetic, DMARD: disease-modifying antirheumatic drug, HLA: human leukocyte antigen, ILAR: International League of Associations for Rheumatology, JIA: juvenile idiopathic arthritis, NSAIDs: nonsteroidal anti-inflammatory drugs, OR: odds ratio, RF: rheumatoid factor, TNF: tumor necrosis factor.

[1]Not considered for multivariable analysis due to missing AITD onset dates.

[2]Only available for patients from the prospective cohort and therefore not considered for multivariable analysis.

*statistically significant effect.

Table 4. Number of high-risk JIA patients needed to screen (NNS) to detect a case of AITD. The table summarizes the number of ANA positive girls with a family history of AITD who would have to be screened to detect one case of AITD as a function of the age at JIA onset.

Age at JIA onset (years)	AITD prevalence	NNS
≥0	14/196 (7.1%)	16
≥4	10/85 (11.8%)	9
≥8	5/34 (14.7%)	7
≥12	4/18 (22.2%)	5

AITD: autoimmune thyroid disease, ANA: anti-nuclear antibodies, JIA: juvenile idiopathic arthritis, NNS: number needed to screen

DISCUSSION

The prevalence of AITD observed in the current study (1.1%) was lower compared to prevalence rates reported in the majority of previous studies about AITD in JIA (5.0% – 44.4%)[7,8,10,11,14–17]. These studies, however, also included cases of subclinical AITD based on active screening for serum levels of thyroid hormones (T_3 and T_4), thyroid-stimulating hormone (TSH) and anti-thyroid antibodies (TgA: thyroglobulin antibodies and/or TPOA: thyroid peroxidase antibodies). Two previous studies focused on clinical AITD in JIA and found similar prevalence rates as the current study (0.8% and 1.3%) [12,13]. AITD has a varying prevalence in the general paediatric population (0.1 – 9.6%) according to the criteria used for diagnosis[22–26]. A population-based study from Scotland focused on clinical hypothyroidism in young people aged <22 years and found a prevalence of 0.14%[27], which is over four times as low as the prevalence of clinical hypothyroidism in JIA found in the current study. In addition, several studies reported increased serum levels of anti-thyroid antibodies in children with JIA compared to healthy controls[7,8,15,17].

Our study highlighted as independent predictors of AITD in JIA a family history of AITD, female sex, a positive ANA status and older age at JIA onset. In fact, previous studies about AITD in JIA also report a female predominance in the AITD group[7,8,10,11,17]. This can be explained by the predominance of girls in most JIA categories[28] and autoimmunity in general[29]. Previous studies have suggested that oligoarthritis might be associated with AITD in JIA[7,8,11,15], but with the current study we conclude that this effect is likely explained by ANA positivity and female sex, which is highly frequent in oligoarthritis[28]. Similarly, the association between AITD and RF positivity and RF+ polyarthritis that we observed in univariable analyses is probably explained by older age and female sex[28].

This is the first study to report an (adjusted) association between AITD and a positive ANA status in JIA, likely due to limited sample size of previous studies. An association between thyroid disorders and ANA positivity has previously been reported in adult RA[30] and a

raised prevalence of ANA in AITD patients has also been previously reported, although the mechanism behind this phenomenon is not known[31–33]. More interestingly, we found a significant association between AITD in JIA patients and a family history of AITD, as described before in another study[17]. Previous studies on AITD patients have also reported high frequencies of familial AITD[34–36] or familial autoimmune disease in general[37]. The association between older age at JIA onset and AITD has not been previously reported. We hypothesize that this effect is caused by merely age rather than age at JIA onset, since older patients in general have an increased cumulative risk of developing any disease including AITD. In fact, it is known that the prevalence of paediatric AITD peaks during adolescence[25,26,38]. Systemic arthritis was observed considerably less in AITD patients than non-AITD patients in the current study, which might be explained by the fact that this JIA category resembles more an auto-inflammatory rather than an autoimmune disease and does not predominantly affect girls[39].

After a median observation period of 5.5 years, we observed a considerable increase in AITD prevalence for JIA patients at increased risk for developing AITD according to our analyses, providing rationale for yearly AITD screening in this high-risk group. Based on the Pharmachild data, only five ANA positive girls with a family history of AITD and an age at JIA onset of ≥12 years would have to be screened during 5.5 years to detect one case of clinical AITD. According to the coefficients in our prediction model, it is safe to conclude that a family history of AITD is the most important predictor of AITD in JIA, with an even larger OR for AITD than a 10-year increase in age at JIA onset. Hence, this would be the most important factor for clinicians to determine in JIA patients when estimating the risk of developing AITD. Screening for thyroid disease is based on abnormal levels of free thyroxine (T_4) and thyroid stimulating hormone (TSH), which are standard blood tests. AITD is diagnosed when these abnormal levels are found in the presence of anti-thyroid antibodies. Interestingly, it has previously been mentioned that female sex, older age and a family history of autoimmune should raise suspicion for anti-thyroid antibodies screening in children with positive ANA of unknown cause[32].

This study has strengths and limitations. First of all, due to missing onset dates for AITD cases, no association between drug therapy, disease activity, disease duration, other endocrinopathies and AITD onset could be investigated. In the current study, we observed that AITD patients had more often received TNF inhibitors than non-AITD patients. However, although a decrease in thyroid dysfunction has been reported in autoimmune disease patients treated with TNF inhibitors[40–42], we cannot draw conclusions from our study since it is unknown whether TNF inhibitor therapy was received before or after AITD onset. Another limitation of our study is that baseline comorbidities and subsequent adverse events in Pharmachild are gathered using spontaneous reporting (i.e. these have to be reported by treating physicians), which might have led to an underestimation of the

actual AITD prevalence. Furthermore, it is possible that the median observation period of 5.5 years was too short for patients with young age at JIA onset to develop AITD. The exact NNS reported in this study might therefore be applicable for a follow-up period of ±5.5 years after onset of JIA only, but higher or lower afterwards. Also, the results of our study might not be generalizable to all JIA patients, since the Pharmachild registry has a selection bias towards JIA patients with a more severe disease course requiring DMARD treatment, Nevertheless, this is the first study to report independent predictors of AITD in JIA. Contrary to most of the few previous studies on AITD in JIA, we report only symptomatic AITD cases and have included patients from multiple centres around the world.

Given the AUC of our prediction model, there is room for improvement in identifying other relevant predictive factors for AITD in JIA. Further research should therefore focus on incorporating drug therapy and disease duration. As suggested previously[10], the incidence of AITD increases with time from diagnosis of JIA and therefore disease duration might be a better predictor than age at JIA onset. Another relevant predictor might be iodine intake, since it is well-described that AITD is more common in iodine-replete areas around the world[22,26,43,44].

CONCLUSIONS

To conclude, this is the first study to report independent predictors for AITD in JIA. These results provide evidence for the added value of yearly serological screening for AITD in ANA positive girls with positive family history, in order to guide a practical approach to the paediatric patient with JIA at risk of developing AITD.

ACKNOWLEDGEMENTS

The authors would like to acknowledge all PRINTO centres for contributing to the acquisition of data, PRINTO personnel for data quality control, and the European Reference Network for Immunodeficiency, Autoinflammatory, Autoimmune and Paediatric Rheumatic diseases (ERN-RITA). We also thank all patients and their parents/caregivers for their participation in Pharmachild.

FUNDING

This work was supported by a research grant from FOREUM Foundation for Research in Rheumatology. Pharmachild has been supported by funding from the Italian public hospital IRCCS Istituto Giannina Gaslini and a grant from the European Union (grant 260353).

COMPETING INTERESTS

NR has received honoraria for consultancies or speaker bureaus from the following pharmaceutical companies in the past 3 years: 2 Bridge, Amgen, AstraZeneca, Aurinia, Bayer, Brystol Myers and Squibb, Celgene, inMed, Cambridge Healthcare Research, Domain Therapeutic, EMD Serono, Glaxo Smith Kline, Idorsia, Janssen, Eli Lilly, Novartis, Pfizer, Sobi, UCB. The IRCCS Istituto Giannina Gaslini (IGG), where NR works as full-time public employee has received contributions from the following industries in the last 3 years: Bristol Myers and Squibb, Eli-Lilly, F Hoffmann-La Roche, Novartis, Pfizer, Sobi. This funding has been reinvested for the research activities of the hospital in a fully independent manner, without any commitment with third parties.

All other authors declare no conflicts of interest.

ETHICS APPROVAL

Pharmachild and all participating centres obtained approval from their respective ethics committees and were conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent/assent based on existing national regulations.

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CHAPTER 8

Increased incidence of inflammatory bowel disease on etanercept in juvenile idiopathic arthritis regardless of concomitant methotrexate use

Joeri W. van Straalen[1], Roline M. Krol[1], Gabriella Giancane[2, 3], Violeta Panaviene[4, 5], Laura Marinela Ailioaie[6], Pavla Doležalová[7], Marco Cattalini[8], Gordana Susic[9], Flavio Sztajnbok[10], Despoina Maritsi[11], Tamas Constantin[12], Sujata Sawhney[13], Marite Rygg[14, 15], Sheila Knupp Oliveira[16], Ellen Berit Nordal[17, 18], Claudia Saad-Magalhaes[19], Nadina Rubio-Perez[20], Marija Jelusic[21], Sytze de Roock[1], Nico M. Wulffraat[1], Nicolino Ruperto[2]* and Joost F. Swart[1]* for the Paediatric Rheumatology International Trials Organisation (PRINTO)

[1]Department of Paediatric Immunology and Rheumatology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, The Netherlands
[2]Clinica Pediatrica e Reumatologia, IRCCS Istituto Giannina Gaslini, Genoa, Italy
[3]Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili (DiNOGMI), Università degli Studi di Genova, Genoa, Italy
[4]Children's Hospital, Affiliate of Vilnius University Hospital Santaros Clinic, Vilnius, Lithuania
[5]Clinic of Children's Diseases, Vilnius University, Vilnius, Lithuania
[6]Alexandru Ioan Cuza University of Iasi, Iasi, Romania
[7]Department of Paediatrics and Inherited Metabolic Disorders, 1st Faculty of Medicine and General University Hospital, Charles University in Prague, Prague, Czech Republic
[8]Unita' di Immunologia e Reumatologia Pediatrica, Clinica Pediatrica dell'Universita' di Brescia, Spedali Civili, Brescia, Italy
[9]Paediatric Rheumatology, Institute of Rheumatology of Belgrade, Belgrade, Serbia
[10]Hospital Universitario Pedro Ernesto, Nucleo de Estudos da Saúde do Adolescente, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil
[11]2nd Department of Paediatrics Athens Medical School, National and Kapodistrian University of Athens (NKUA), Athens, Greece
[12]Unit of Paediatric Rheumatology-Immunology, Second Department of Paediatrics, Semmelweis University, Budapest, Hungary
[13]Centre for Child Health, Sir Ganga Ram Hospital, New Delhi, India
[14]Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, NTNU - Norwegian University of Science and Technology, Trondheim, Norway
[15]Paediatrics, St. Olavs University Hospital of Trondheim, Trondheim, Norway
[16]Instituto de Puericultura e Pediatria Martagao Gesteira (IPPMG), Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil
[17]Department of Paediatrics, University Hospital of North Norway, Tromso, Norway
[18]Department of Clinical Medicine, UiT the Arctic University of Norway, Tromso, Norway
[19]São Paulo State University (UNESP), Botucatu, Brasil
[20]Departamento de Pediatria, Facultad de Medicina, Hospital Universitario "Dr. J. E. González", Universidad Autónoma de Nuevo León, Monterrey NL, Mexico
[21]Department of Paediatrics, University of Zagreb School of Medicine, Zagreb, Croatia

Joost F. Swart and Nicolino Ruperto contributed equally

Rheumatology (Oxford). 2022;61(5):2104-2112.

ABSTRACT

Objectives

To describe risk factors for inflammatory bowel disease (IBD) development in a cohort of children with juvenile idiopathic arthritis (JIA).

Methods

JIA patients who developed IBD were identified from the international Pharmachild register. Characteristics were compared between IBD and non-IBD patients and predictors of IBD were determined using multivariable logistic regression analysis. Incidence rates of IBD events on different disease-modifying anti-rheumatic drugs (DMARDs) were calculated, differences between therapies were expressed as relative risks (RR).

Results

Out of 8,942 patients, 48 (0.05%) developed IBD. These were more often male (47.9% versus 32.0%) and HLA-B27 positive (38.2% versus 21.0%) and older at JIA onset (median 8.94 versus 5.33 years) than patients without IBD development. They also had more often a family history of autoimmune disease (42.6% versus 24.4%) and enthesitis-related arthritis (ERA) (39.6% versus 10.8%). The strongest predictors of IBD on multivariable analysis were ERA (OR: 3.68, 95% CI: 1.41 – 9.40) and a family history of autoimmune disease (OR: 2.27, 95% CI: 1.12 – 4.54). Compared to methotrexate monotherapy, the incidence of IBD on etanercept monotherapy (RR: 7.69, 95% CI: 1.99 – 29.74), etanercept with methotrexate (RR: 5.70, 95% CI: 1.42 – 22.77) and infliximab (RR: 7.61, 95% CI: 1.27 – 45.57) therapy was significantly higher. Incidence on adalimumab was not significantly different (RR: 1.45, 95% CI: 0.15 – 13.89).

Conclusion

IBD in JIA was associated with ERA and a family history of autoimmune disease. An increased IBD incidence was observed for etanercept therapy regardless of concomitant methotrexate use.

Keywords: inflammatory bowel disease, juvenile idiopathic arthritis, etanercept, enthesitis-related arthritis

Key messages:

- Inflammatory bowel disease (IBD) significantly impairs quality of life in juvenile idiopathic arthritis (JIA).
- IBD in JIA was associated with enthesitis-related arthritis and a family history of autoimmune disease.
- Incidence of IBD was raised on etanercept therapy, regardless if combined with methotrexate.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most frequent chronic rheumatic disease in childhood with a reported prevalence varying from 16-150 per 100,000 children[1]. As per International League of Associations for Rheumatology (ILAR) criteria, seven mutually exclusive categories of JIA with distinct clinical features can be identified[2]. Treatment of JIA is mainly targeted towards reducing disease activity and commonly used drugs are nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, conventional synthetic disease-modifying anti-rheumatic drugs (cs-DMARDs) and biologic (b-)DMARDs whose administration is now subject to several recommendations and guidelines[3].

A rare comorbidity in JIA is represented by inflammatory bowel disease (IBD), a chronic inflammatory condition of the gastrointestinal tract which comprises ulcerative colitis, Crohn's disease and indeterminate colitis[4]. Entheropathic arthritis may also present as an extra-intestinal manifestation prior to gastrointestinal symptoms in IBD[5,6]. A previous study reported an incidence of 1.31/1000 patient-years for IBD in a registry of 3071 JIA patients treated with and without b-DMARDs[7]. This figure is much higher than the reported incidence of paediatric-onset IBD in the general population, which varies globally up to 0.23/1000 person-years[8]. Reported prevalence of IBD in Western countries varies up to 200 per 100.000 children[9–12]. It is known that IBD has a significant negative impact on quality of life besides complicating the therapeutic approach to JIA[13].

Due to sparse data, there is currently limited knowledge about the characteristics of JIA patients who develop IBD and risk factors for its development. Furthermore, based on limited numbers of IBD cases, several studies suggest an association with IBD and etanercept (ETN) therapy[14] and it has also been proposed that methotrexate (MTX) is effective in preventing or treating IBD in JIA[7,15].

The aim of this study is to describe characteristics of JIA patients who develop IBD in comparison to those who did not, determine predictors for the development of IBD and establish a possible association between drug therapy and IBD in the largest existing pharmacovigilance cohort of JIA patients worldwide. We wanted to explore a possible protective effect of MTX and hypothesized based on literature that IBD is associated with enthesitis-related arthritis (ERA) and ETN therapy[7,16].

METHODS

Patients

Pharmachild is an ongoing international observational registry that started in 2011 and contains both retrospective and prospective clinical, laboratory and demographic data from JIA patients treated in 85 member centres of the Paediatric Rheumatology International Trials Organisation (PRINTO) from 31 countries worldwide[17]. Key objectives of Pharmachild are to capture adverse events (AEs) in JIA patients developing under cs- or b-DMARDs and to determine efficacy of these therapies. Inclusion criteria are children with JIA as defined by ILAR criteria who receive NSAIDs, steroids, cs- or b-DMARDs prescribed by their treating physician. Further details of the Pharmachild registry are available elsewhere[18,19]. All patients from the Pharmachild database were included in the present study. Data lock occurred on May 3, 2019.

For every patient, the ever occurrence of IBD (yes/no) was determined from different sources in Pharmachild. AEs in Pharmachild are reported using version 22 of the Medical Dictionary of Regulator Activities (MedDRA) hierarchy[20]. Furthermore, IBD was one of the 23 events of specific interest (ESI) for which extra specific information such as performed tests and medical history were reported in case IBD was diagnosed. All preferred terms (PTs) of AEs, with a three level monitoring check for consistency[19] (treating physician, medical monitor (JS) and PRINTO certified MedDRA coders), were screened. Definite IBD cases (Crohn's disease, ulcerative colitis or IBD), possible IBD cases (e.g. proctitis) and tests or procedures possibly related to IBD were selected (e.g. colonoscopy). Of the latter two, free-text AE descriptions were screened for further information on IBD diagnosis. IBD after JIA onset could also be mentioned as a free-text comorbidity when the IBD was already established at the moment of inclusion into the registry. Cases were retrieved by two authors (JS, RK) and then checked for correctness by a third reader (JvS).

Characteristics collected for all patients were demographics, a history of autoimmune disease(s) in first and second degree relatives, ILAR category and anti-nuclear antibodies (ANA), human leukocyte antigen (HLA-)B27 and rheumatoid factor (RF) status. For ANA positivity only one positive test was required. For a positive RF status, two positive tests at least three months apart were required as per ILAR classification criteria.

Statistical analysis

Patient characteristics

Descriptive statistics of patient characteristics at last visit were summarized for patients who developed IBD (both with and without available onset date) and patients who did not. Categorical variables were compared between these patients by Chi square tests or Fisher's exact test if appropriate. Continuous variables were compared by Mann-Whitney

U tests. All tests were performed two-sided and results were considered statistically significant in case of a *P*-value of <0.05. Subsequently, all statistically significant variables were entered as independent variables in a multivariable logistic regression based on complete case analysis in order to develop a prediction model for the outcome variable IBD, defined as the ever occurrence of IBD. ILAR categories were treated as separate dichotomous variables in order to avoid fitting an overfit model. Odds ratios with 95% confidence intervals (CI) of predictor variables in the model were reported and their joint ability of predicting IBD was assessed by the area under the receiver operating characteristic curve (AUC). Linearity of continuous variables with the logit outcome was assessed using the Box-Tidwell test.

Drug therapy

In order to establish a possible association between IBD and medication, incidence rates of IBD were determined for MTX, ETN, sulfasalazine, leflunomide, adalimumab (ADA) and infliximab (IFX) therapy. For these analyses, only IBD events with available onset date were included. Incidence rates for ETN were calculated for monotherapy (ETN without MTX) and combination therapy with MTX. Incidence rates for MTX were calculated for monotherapy only (MTX without any biological). An event of IBD was assigned to a particular drug therapy if this therapy was received within the last three months prior to IBD onset[15], also if the therapy was started or stopped within this interval. Incidences were also calculated for an at-risk window of six and 12 months. As a sub-analysis, we repeated all analyses for only ERA patients. Drug therapy received after onset of IBD was censored in all analyses. For all drug therapies, relative risks (i.e. incidence rate ratios) compared to MTX monotherapy were calculated. If the 95% confidence interval of the relative risk did not contain 1, this was considered statistically significant.

All analyses were performed with IBM SPSS version 25 and the stats, pROC and epitools packages for R version 3.6.3[21].

RESULTS

Patient characteristics

8,942 patients were included in this study. Out of 6,506 AEs and 1,994 free-text comorbidities, 48 (0,54%) unique cases of IBD were identified (Figure 1). These included 13 cases (27%) of ulcerative colitis, 22 cases (46%) of Crohn's disease and 13 cases (27%) of indeterminate colitis. Date of onset could not be retrieved for 21/48 (44%) IBD cases (Supplementary Table 1). Characteristics of patients who developed IBD and those who did not are presented in Table 1. The total observation time from JIA onset to last visit of all included patients was 56,138 years with a median of 5.4 years (IQR: 2.7 – 8.9). It was

observed that patients who developed IBD were significantly more often male (47.9%), HLA-B27 positive (38.2%) and older at JIA onset than patients who did not develop IBD. Furthermore, they had significantly more often a family history of autoimmune disease(s) (42.6%) and ERA (39.6%). The most commonly reported autoimmune diseases in first and second degree relatives were psoriasis (25%), rheumatoid arthritis (18%) and Hashimoto's thyroiditis (10%). Other ILAR categories, ANA status and RF status did not differ significantly between IBD and non-IBD patients. No RF positive patients developed IBD. For cases of IBD with available onset date, the median time from JIA onset to IBD onset was 4.2 years (IQR: 2.3 – 7.7) and the median age at IBD onset was 13.7 years (IQR: 11.7 – 15.9).

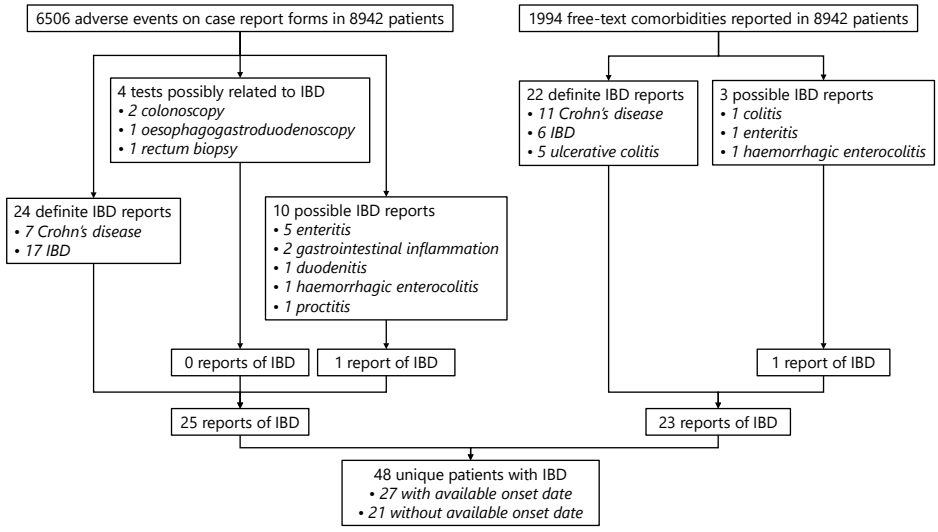

Figure 1: Flowchart of identified IBD cases.
IBD: inflammatory bowel disease; JIA: juvenile idiopathic arthritis

Table 1. Demographic and clinical characteristics of Pharmachild patients included for analysis.

	Total cohort (n = 8942)	No IBD (n = 8894)	IBD (n = 48)	*P*-value
Demographics, % (n)				
Female	67.9% (6072)	68.0% (6047)	52.1% (25)	0.03*
Family history of autoimmune disease(s)[1]	24.5% (2117) n = 8648	24.4% (2097) n = 8601	42.6% (20) n = 47	<0.01*
Clinical characteristics				
Age at JIA onset (years), median (IQR)	5.34 (2.38 - 9.96)	5.33 (2.38 - 9.95)	8.94 (5.95 - 11.53)	<0.01*
ILAR category, % (n)				
Persistent oligoarthritis	25.2% (2250)	25.2% (2245)	10.4% (5)	0.49
Extended oligoarthritis	12.7% (1132)	12.7% (1128)	8.3% (4)	0.49
Systemic JIA	10.7% (956)	10.7% (953)	6.3% (3)	0.48
RF- polyarticular JIA	26.4% (2364)	26.5% (2354)	20.8% (10)	0.47
RF+ polyarticular JIA	4.0% (357)	4.0% (357)	0.0% (0)	0.26
Psoriatic JIA	3.4% (301)	3.4% (300)	2.1% (1)	1
Enthesitis-related JIA	10.9% (977)	10.8% (958)	39.6% (19)	<0.01*
Undifferentiated JIA	6.8% (605)	6.7% (599)	12.5% (6)	0.14
Laboratory characteristics, % (n)				
ANA positive	41.7% (3491) n = 8375	41.7% (3471) n = 8329	43.5% (20) n = 46	0.92
RF positive	4.3% (343) n = 7906	4.4% (343) n = 7868	0.0% (0) n = 38	0.41
HLA-B27 positive	21.1% (1141) n = 5402	21.0% (1128) n = 5368	38.2% (13) n = 34	0.02*

Percentages listed are column percentages.

ANA: antinuclear antibodies; HLA: human leucocyte antigen; IBD: inflammatory bowel disease; ILAR: International League of Associations for Rheumatology; IQR: interquartile range; JIA: juvenile idiopathic arthritis; RF: rheumatoid factor

*statistically significant

[1]only taking into account first and second-degree relatives

Predictors of IBD

When combining all statistically significant variables into a multivariable prediction model, only ERA (OR: 3.68, 95% CI: 1.41 – 9.40) and a family history of autoimmune disease(s) (OR: 2.27, 95% CI: 1.12 – 4.54) remained significantly associated with IBD at a significance level of 5% (Table 2). This model included 5,272 patients with 33 IBD cases due to missing information for predictor variables. The AUC of the model was 0.74 (95% CI: 0.66 – 0.82). The median predicted probability for IBD in the dataset was 0.4% (range: 0.2% – 4.6%).

Table 2: Risk factors for IBD on multivariable logistic regression analysis (n = 5272).

Variable	OR	95% CI
Female	0.70	0.33 – 1.48
Family history of autoimmune disease(s)[1]	2.27	1.12 – 4.54*
Age at JIA onset	1.05	0.96 – 1.15
Enthesitis-related JIA	3.68	1.41 – 9.40*
HLA-B27 positive	0.81	0.33 – 2.02

Area under the receiver operating characteristic curve (AUC) = 0.74 (95% CI: 0.66 – 0.82).
CI: confidence interval; HLA: human leucocyte antigen; IBD: inflammatory bowel disease; JIA: juvenile idiopathic arthritis; OR: odds ratio
*Statistically significant
[1]only taking into account first and second-degree relatives

Drug therapy

Of the 27 patients with known onset date of IBD, 13 (48.1%) used ETN (with or without MTX) within the last three months prior to IBD onset (Table 3). For these patients, the median duration of ETN use to IBD onset was 382 days (IQR: 275 – 853). This duration was positively correlated with JIA disease duration until IBD onset (r = 0.8, P <0.005). For 6 cases (23%), no DMARD therapy was received within the three months at-risk window. Of these cases, 4 (67%) had previously stopped MTX therapy and 2 (33%) had stopped ETN (58 and 4 months before IBD onset). It was observed that incidence rates of IBD were significantly higher for combination therapy with ETN and MTX (6 events during 5,236 exposure years), ETN monotherapy (7 events during 4,524 exposure years) and IFX (2 events during 1,306 exposure years) compared to MTX monotherapy (3 events during 14,913 exposure years). No significant difference was found for ADA therapy (1 event during 3,440 exposure years). The same effects were observed when taking at-risk windows of 6 and 12 months (Supplementary Tables 2 & 3). Incidence rates of IBD on drug therapy in ERA patients were higher compared to the total cohort. Nevertheless, no significant differences were found between drug therapies in this sub-analysis of ERA patients. Drug therapy details for each IBD case with available onset date are presented in Supplementary Data 1.

Table 3. Incidence rates of IBD events with available onset date on drug therapy.

Drug therapy[1]	ERA patients (n = 967)			All patients (n = 8,921)		
	RR (95% CI)	Incidence rate[2] (95% CI)	% (n) of IBD events (n = 9)[3]	RR (95% CI)	Incidence rate[2] (95% CI)	% (n) of IBD events (n = 27)[4]
Synthetic DMARDs						
MTX mono	Reference	0.22 (0.03 – 0.79)	22.2% (2)	Reference	0.02 (0.00 – 0.06)	11.1% (3)
Sulfasalazine	0.68 (0.06 – 7.51)	0.15 (0.00 – 0.83)	11.1% (1)	3.68 (0.38 – 35.40)	0.07 (0.00 – 0.41)	3.7% (1)
Leflunomide	-	-	0.0% (0)	6.96 (0.72 – 66.87)	0.14 (0.00 - 0.78)	3.7% (1)
Biological DMARDs						
ETN mono	3.07 (0.51 – 18.37)	0.67 (0.14 – 1.97)	33.3% (3)	7.69 (1.99 – 29.74)*	0.15 (0.06 – 0.32)	25.9% (7)
ETN + MTX	1.24 (0.11 – 13.66)	0.27 (0.01 – 1.51)	11.1% (1)	5.70 (1.42 – 22.77)*	0.11 (0.04 – 0.25)	22.2% (6)
Infliximab	2.44 (0.22 – 26.89)	0.53 (0.01 – 2.98)	11.1% (1)	7.61 (1.27 – 45.57)*	0.15 (0.02 – 0.55)	7.4% (2)
Adalimumab	-	-	0.0% (0)	1.45 (0.15 – 13.89)	0.03 (0.00 – 0.16)	3.7% (1)

Percentages listed are column percentages.
DMARD: disease-modifying antirheumatic drug; ERA: enthesitis-related arthritis; ETN: etanercept; MTX: methotrexate; RR: relative risk
[1]drug therapy was received within the last three months prior to IBD onset
[2]number of IBD events per 100 exposure years
[3]for one case, no DMARD therapy was received within the last three months prior to IBD onset
[4]for six cases, no DMARD therapy was received within the last three months prior to IBD onset
*statistically significant

DISCUSSION

In this study, IBD patients were older at JIA onset and more often male and HLA-B27 positive than non-IBD patients. Furthermore, they had more often a family history of autoimmune disease and ERA. On multivariable analysis, ERA and a family history of autoimmune disease were the strongest predictors of IBD in JIA. The incidence of IBD on therapy with both ETN and MTX, ETN monotherapy and IFX was significantly higher compared to MTX monotherapy.

The prevalence of IBD in our cohort was 0.54%. This a priori risk is higher than reported prevalence rates varying up to 0.02% in the paediatric population of Western countries[9–12], in which the burden of IBD is known to be highest worldwide[4,8]. Indeed, IBD and JIA share common genetic features[7] and it has been hypothesized that asymptomatic gut wall inflammation can be present in certain patients with JIA[16]. Following our prediction model, the highest predicted probability of IBD in our cohort was 4.6%. Although this risk may not seem high, the implications are huge and screening for underlying IBD is quite simple, cheap and harmless by performing a faecal calprotectin test[22,23]. Therefore, this screening might be appropriate in relative high-risk patients who according to our analysis would be male ERA patients with older age at JIA onset and a family history of autoimmune disease. We found a median age at IBD onset of 13.7 years which is in line with other studies that reported cases of IBD in JIA[7,16,24].

The strongest predictor of IBD in our cohort was ERA, which largely explains why patients with IBD were on average older and more often male and HLA-B27 positive than patients without IBD in our cohort[1]. Moreover, ERA resembles spondyloarthropathy in adults,[16] a rheumatic disease known to be associated with development of IBD[25]. A previous study by Barthel *et al.* also reported a higher percentage of ERA among JIA patients who developed IBD (2/11; 18.2%) compared to the total cohort (425/3060; 13.8%)[7]. The authors of the same study also hypothesized that JIA patients with psoriatic arthritis and extended oligoarthritis were at an increased risk of IBD, which we cannot confirm with the results of our current study. The other statistically significant predictor of IBD in our multivariable analysis was a family history of one or more autoimmune diseases. This is consistent with existing knowledge on the pathophysiology of IBD, which suggests that both genetic and environmental factors play a role[4]. In addition, familial IBD is more common in children than in adult cases[26]. Corresponding to most studies,[14,27,28] no RF positive polyarthritis patients developed IBD in the present study, although IBD in RF positive polyarticular JIA has been reported[29].

Compared to MTX monotherapy, the incidence of IBD on ETN therapy was significantly higher. Several studies have also reported a potential association between ETN and IBD

in JIA[14,15]. In our study, this association was observed even when taking different at-risk windows. In fact, for cases where ETN was received within the last three months prior to IBD onset, the median duration from the start of ETN to IBD onset was little over a year. Due to this rather long duration, the authors believe there is not much bias in the reported IBD events that were attributed to ETN therapy, which would not be the case if patients had only switched to ETN therapy shortly before IBD onset. Other studies confirm this long duration of ETN therapy until IBD onset[7,27]. The observed positive correlation between ETN therapy duration and duration until IBD onset might provide some evidence for a dose-response relationship, given that IBD events that still occurred after the median duration of JIA until IBD onset also had a longer exposure to ETN. Data from the BiKeR register with 14 included IBD cases has suggested that MTX is protective against IBD in JIA, even when combined with ETN[15]. The rate of incident IBD on ETN and MTX combination therapy in the BiKeR study was higher than the rate on MTX monotherapy (0.1 versus 0.03 events per 100 person years), but this was not a statistically significant difference. In the present study, we found a similar effect, which was statistically significant probably due to the larger number of IBD cases included. In our study, ETN was associated with IBD in JIA, regardless of concomitant use of MTX. It remains questionable however whether or not this is a causal relationship. It has been suggested that in JIA patients under ETN therapy, a pre-existing clinically silent IBD can manifest since ETN is ineffective in the treatment of Crohn's disease[27]. One could even argue that patients with silent IBD and arthropathy, misdiagnosed as JIA patients, will not benefit from ETN therapy for their joints either. Hence these patients will be switched to a more effective treatment such as ADA, thereby preventing the symptomatic occurrence of IBD. Nevertheless, IBD onset after ETN therapy has also been reported in patients with long-lasting definite JIA without previous abdominal complaints[30]. In a systematic literature review of 53 cases of IBD in JIA, Bieber *et al*. describe that most cases that developed under ETN therapy improved after discontinuation of ETN, suggesting a causal link[14]. Several hypotheses about the biological mechanism behind a possible relationship between ETN and IBD development exist[7,14,16,27].

Unlike ETN, IFX and ADA have been proven effective in the treatment of IBD[31–33]. We observed that the incidence of IBD on ADA was not significantly higher than MTX monotherapy, but, surprisingly, incidence on IFX was. For two cases of IBD found in our study, IFX was given within the last three months prior to IBD onset, and for one additional case within the last twelve months. However, two of these three cases had previously also received ETN. Tarkiainen *et al.* also reported a case of IBD following IFX therapy and suggested that IBD can develop in JIA patients at a low IFX dosage, which is associated with the formation of anti-IFX antibodies which is linked to a reduced treatment response in Crohn's disease[24]. It is indeed the case that the IFX dosages recommended for JIA are 3 mg/kg bodyweight, while this is 5mg/kg bodyweight for IBD. A randomized placebo-

controlled trial of IFX in JIA also reported an increased risk for development of antibodies to IFX at a dosage of 3 mg/kg compared to 6 mg/kg[34]. Development of IBD following IFX treatment has also been described in an adult spondyloarthropathy patient[35].
We did not find significant differences in rates of incident IBD between different therapies within the subset of ERA patients due to few events. However, the higher absolute incidence rates for all therapies in this sub-analysis compared to our main analysis indicate that ERA patients run a higher overall risk of developing IBD. This confirms our multivariable analysis results.

This study has strengths and limitations. Due to missing onset dates, drug therapy prior to onset could not be retrieved for all IBD cases. Moreover, because of this, drug therapy could not be studied as an independent variable for IBD in addition to the current variables in our complete case logistic regression model. This would have resulted in exclusion of the majority of IBD cases and an overfit model. Missing onset dates of IBD events have influenced absolute incidence rates reported in this study, but the authors do not believe this has caused significant bias in relative risks between drug therapies given the likely missing completely at random (MCAR) nature of the missing observations. The mentioned limitations are partially covered by the relatively large sample size. Although it might be difficult to draw firm conclusions based on 48 cases of IBD, this is the most comprehensive single international registry of IBD in JIA and its characteristics and risk factors. Also, ERA was excluded as a confounding variable in our incidence analyses by performing a sub-analysis in ERA patients only. In this sub-analysis, similar effects were observed as in the main analysis, however these effects were not statistically significant due to a considerably reduced number of observations.

For the future, it would be ideal if a larger number of IBD cases from different national and international cohorts/registries could be combined, and associations with risk factors including drug therapy could be confirmed using multivariable analysis in a case-control study. Next to clinical and genetic features, also dietary and environmental factors should be considered as predictors for IBD in JIA. A 2013 population based study in Denmark revealed that amongst others high sugar intake and urban residency were risk factors for the development of paediatric-onset IBD[36]. Lastly, more experimental work on the biological mechanism behind a possible causal relationship between ETN and IBD (in the presence of MTX) is required.

To conclude, this study has highlighted several risk factors for IBD in patients with JIA, of which the most important are ERA and a family history of autoimmune disease. Moreover, we found that compared to MTX monotherapy the incidence of IBD was higher on therapy with ETN (regardless of concomitant use of MTX) and IFX. Hence, it might be suggested to

consider ADA as the biologic of choice for treatment of ERA patients with a family history of autoimmune disease.

ACKNOWLEDGEMENTS

The authors would like to thank all PRINTO centres for their contribution to the data collection. The authors would also like to express their acknowledgements to the European Reference Network for Immunodeficiency, Autoinflammatory, Autoimmune and Paediatric Rheumatic diseases (ERN-RITA). Finally, we thank all patients and their parents for consenting to this research.

FUNDING

This work was supported by a research grant from FOREUM Foundation for Research in Rheumatology. Pharmachild has been supported by a grant from the European Union (grant 260353) and by funding from the Italian public hospital IRCCS Istituto Giannina Gaslini.

COMPETING INTERESTS

MC reports personal fees from AbbVie, outside the submitted work. PD reports non-financial support from Pfizer, non-financial support from Roche, personal fees and non-financial support from AbbVie, personal fees and non-financial support from Novartis, personal fees and non-financial support from Sobi, personal fees from Eli Lilly and personal fees and non-financial support from MEDAC, outside the submitted work. NR reports personal fees from AstraZeneca - Medimmune, personal fees from Ablynx, personal fees from Biogen, personal fees from Boehringer, grants and personal fees from Hoffman-La Roche, grants and personal fees from Pfizer, grants and personal fees from Novartis, personal fees from Takeda, grants and personal fees from Eli Lilly, grants and personal fees from GSK, grants and personal fees from Janssen, personal fees from EMD Serono, personal fees from Merck, personal fees from R-Pharma, personal fees from Sanofi, personal fees from Servier, personal fees from Sinergie, grants and personal fees from Sobi, personal fees from Aurinia, personal fees from Centrical Global, personal fees from Domain Therapeutics, personal fees from Idorsia and grants and personal fees from Bristol Myers and Squibb, outside the submitted work.
All other authors have nothing to disclose.

ETHICS APPROVAL

Pharmachild and all participating centres obtained approval from their respective ethics committees and were conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent/assent based on existing national regulations.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Characteristics of IBD patients with available onset date vs. IBD patients without available onset date.

	IBD without onset date (n = 21)	IBD with onset date (n = 27)
Demographics, % (n)		
Female	42.9% (9)	59.3% (16)
Family history of autoimmune disease[1]	42.9% (9)	40.7% (11)
Clinical characteristics		
Age at JIA onset (years), median (IQR)	10.08 (7.27 – 13.17)	8.05 (5.63 – 10.22)
ILAR category, % (n)		
Persistent oligoarthritis	4.8% (1)	14.8% (4)
Extended oligoarthritis	9.5% (2)	7.4% (2)
Systemic JIA	9.5% (2)	3.7% (1)
RF- polyarticular JIA	9.5% (2)	29.6% (8)
RF+ polyarticular JIA	0.0% (0)	0.0% (0)
Psoriatic JIA	4.8% (1)	0.0% (0)
Enthesitis-related JIA	47.6% (10)	33.3% (9)
Undifferentiated JIA	14.3% (3)	11.1% (3)
Laboratory characteristics,% (n)		
ANA positive	31.6% (6) n = 19	51.9% (14) n = 27
RF positive	0.0% (0) n = 16	0.0% (0) n = 22
HLA-B27 positive	50.0% (7) n = 14	30.0% (6) n = 20

Percentages listed are column percentages.

ANA: antinuclear antibodies; HLA: human leucocyte antigen; IBD: inflammatory bowel disease; ILAR: International League of Associations for Rheumatology; IQR: interquartile range; JIA: juvenile idiopathic arthritis; RF: rheumatoid factor

[1]only taking into account first and second degree relatives

Supplementary Table 2. Incidence rates of IBD events with available onset date on drug therapy using a six months at-risk window.

Drug therapy[1]	ERA patients (n = 967)			All patients (n = 8,921)		
	RR (95% CI)	Incidence rate[2] (95% CI)	% (n) of IBD events (n = 9)[3]	RR (95% CI)	Incidence rate[2] (95% CI)	% (n) of IBD events (n = 27)[4]
Synthetic DMARDs						
MTX mono	Reference	0.22 (0.03 – 0.79)	22.2% (2)	Reference	0.02 (0.00 – 0.06)	11.1% (3)
Sulfasalazine	0.68 (0.06 – 7.51)	0.15 (0.00 – 0.83)	11.1% (1)	3.68 (0.38 – 35.40)	0.07 (0.00 – 0.41)	3.7% (1)
Leflunomide	-	-	0.0% (0)	6.96 (0.72 – 66.87)	0.14 (0.00 - 0.78)	3.7% (1)
Biological DMARDs						
ETN mono	2.00 (0.29 – 14.53)	0.45 (0.05 – 1.62)	22.2% (2)	7.69 (1.99 – 29.74)*	0.15 (0.06 – 0.32)	25.9% (7)
ETN + MTX	2.48 (0.35 – 17.59)	0.54 (0.07 – 1.96)	22.2% (2)	6.65 (1.72 – 25.70)*	0.13 (0.05 – 0.28)	25.9% (7)
Infliximab	2.44 (0.22 – 26.89)	0.53 (0.01 – 2.98)	11.1% (1)	7.61 (1.27 – 45.57)*	0.15 (0.02 – 0.55)	7.4% (2)
Adalimumab	-	-	0.0% (0)	1.45 (0.15 – 13.89)	0.03 (0.00 – 0.16)	3.7% (1)

Percentages listed are column percentages.

DMARD: disease-modifying antirheumatic drug; ERA: enthesitis-related arthritis; ETN: etanercept; MTX: methotrexate; RR: relative risk

[1]drug therapy was received within the last six months prior to IBD onset

[2]number of IBD events per 100 exposure years

[3]for one case, no DMARD therapy was received within the last six months prior to IBD onset

[4]for five cases, no DMARD therapy was received within the last six months prior to IBD onset

*statistically significant

Supplementary Table 3. Incidence rates of IBD events with available onset date on drug therapy using a 12 months at-risk window.

Drug therapy[1]	ERA patients (n = 967)			All patients (n = 8,921)		
	RR (95% CI)	Incidence rate[2] (95% CI)	% (n) of IBD events (n = 9)	RR (95% CI)	Incidence rate[2] (95% CI)	% (n) of IBD events (n = 27)[3]
Synthetic DMARDs						
MTX mono	Reference	0.33 (0.07 – 0.96)	33.3% (3)	Reference	0.03 (0.01 – 0.07)	14.8% (4)
Sulfasalazine	0.45 (0.05 – 4.36)	0.15 (0.00 – 0.83)	11.1% (1)	2.76 (0.31 – 24.71)	0.07 (0.00 – 0.41)	3.7% (1)
Leflunomide	9.42 (0.98 – 90.54)	3.10 (0.08 – 17.25)	11.1% (1)	10.43 (1.91 – 56.96)*	0.28 (0.03 - 1.01)	7.4% (2)
Biological DMARDs						
ETN mono	0.68 (0.07 – 6.65)	0.22 (0.01 – 1.25)	11.1% (1)	4.94 (1.40 – 17.52)*	0.13 (0.05 – 0.29)	22.2% (6)
ETN + MTX	2.48 (0.50 – 12.28)	0.81 (0.17 – 2.38)	33.3% (3)	5.70 (1.72 – 18.92)*	0.15 (0.07 – 0.30)	29.6% (8)
Infliximab	1.63 (0.17 – 15.63)	0.53 (0.01 – 2.98)	11.1% (1)	8.57 (1.92 – 38.27)*	0.23 (0.05 – 0.67)	11.1% (3)
Adalimumab	-	-	0.0% (0)	1.08 (0.12 – 9.70)	0.03 (0.00 – 0.16)	3.7% (1)

Percentages listed are column percentages.

DMARD: disease-modifying antirheumatic drug; ERA: enthesitis-related arthritis; ETN: etanercept; MTX: methotrexate; RR: relative risk

[1]drug therapy was received within the last 12 months prior to IBD onset

[2]number of IBD events per 100 exposure years

[3]for four cases, no DMARD therapy was received within the last 12 months prior to IBD onset

*statistically significant

Supplementary Data 1. Drug therapy details of IBD cases with available onset date (n = 27).

Patient	Gender	(Provisional) ILAR category	Age at JIA onset (years)	Age at IBD onset (years)	Years from JIA onset to IBD onset	IBD type	Disease flares (JADAS >3) prior to IBD, n
1	M	RF- polyarthritis	7,1	10,7	3,6	UC	NA
2	M	RF- polyarthritis	5,6	13,7	8,1	CD	NA
3	F	RF- polyarthritis	2,1	12,1	10,0	UC	NA
4	M	Oligoarthritis	10,4	12,6	2,3	CD	NA
5	M	ERA	10,6	13,0	2,4	UC	NA
6	M	ERA	12,4	16,2	3,8	UC	NA
7	M	Oligoarthritis	5,3	5,5	0,2	IC	NA
8	F	Undifferentiated	6,1	8,9	2,9	IC	NA
9	F	RF- polyarthritis	5,7	16,1	10,4	UC	NA
10	M	Undifferentiated	8,9	14,8	5,9	UC	NA
11	F	RF- polyarthritis	8,2	13,5	5,3	UC	NA
12	F	RF- polyarthritis	1,0	2,7	1,7	IC	NA
13	F	ERA	13,1	17,2	4,2	IC	NA
14	F	ERA	8,1	12,5	4,4	CD	NA
15	F	Oligoarthritis	5,7	24,8	19,1	CD	NA
16	F	RF- polyarthritis	6,0	13,1	7,1	IC	NA
17	M	ERA	12,0	15,7	3,7	UC	NA
18	M	Systemic arthritis	4,7	16,7	12,0	CD	NA
19	F	Oligoarthritis	6,6	13,9	7,3	UC	NA
20	M	ERA	9,3	14,9	5,6	CD	NA
21	F	Oligoarthritis	1,4	15,1	13,7	CD	NA
22	F	Oligoarthritis	9,3	11,3	2,0	CD	NA
23	F	Undifferentiated	13,4	13,9	0,5	UC	NA
24	M	ERA	10,1	10,8	0,7	CD	0
25	F	ERA	9,0	9,5	0,5	CD	NA
26	F	RF- polyarthritis	5,0	16,7	11,7	CD	3
27	F	ERA	13,7	16,8	3,1	IC	NA

CD: Crohn's disease; ERA: enthesitis-related arthritis; IBD: inflammatory bowel disease; IC: indeterminate colitis; ILAR: International League of Associations for Rheumatology; JADAS: Juvenile Arthritis Disease Activity Score; JIA: juvenile idiopathic arthritis; NA: not applicable; RF: rheumatoid factor; UC: ulcerative colitis

Supplementary Data 1. Continued.

Patient	Drugs before IBD onset	Drugs at IBD onset or 3 months prior	Duration of ETN therapy until IBD onset (months)	Duration of IFX therapy until IBD onset (months)
1	MTX, ETN	MTX, ETN	13	NA
2	MTX, Prednisone, ETN	MTX, ETN	12	NA
3	MTX	NA	NA	NA
4	MTX, ETN, Prednisone	MTX, ETN, Prednisone	1	NA
5	MTX	MTX	NA	NA
6	MTX, Prednisone, ETN	ETN	12	NA
7	NA	NA	NA	NA
8	Prednisone, MTX, ETN	ETN	22	NA
9	SSZ, MTX, LEF, ETN	ETN	28	NA
10	SSZ, Prednisolone, MTX, ETN, ADA, IFX, Abatacept	MTX, ETN	5	NA
11	MTX, ETN	ETN	43	NA
12	MTX, Prednisone	MTX	NA	NA
13	SSZ, MTX, ETN	MTX, ETN	30	NA
14	MTX, ETN	ETN	9	NA
15	Deflazacort, MTX, SSZ, LEF, ETN, Cyclosporine, Azathioprine, Prednisone, Methylprednisolone	ETN, Methylprednisolone	77	NA
16	Prednisone, MTX, SSZ, ETN	NA	NA	NA
17	SSZ, MTX, Prednisone, IFX	MTX, IFX	NA	18
18	MTX, Prednisolone, Cyclosporine, IFX, ETN, Methylprednisolone	MTX, IFX	NA	134
19	MTX, LEF	LEF	NA	NA
20	MTX, Triamcinolone, LEF	NA	NA	NA
21	Prednisolone, MTX, ADA, Prednisone, IFX, Abatacept, Rituximab, Methylprednisolone	ADA, Prednisone	NA	NA
22	MTX, ETN, Methylprednisolone	ETN, MTX	13	NA
23	NA	NA	NA	NA
24	ETN	ETN	5	NA
25	MTX	MTX	NA	NA
26	MTX, ETN, ADA	NA	NA	NA
27	Betamethasone, SSZ, Prednisone	SSZ, Prednisone	NA	NA

ADA: adalimumab; ETN: etanercept; IBD: inflammatory bowel disease; IFX: infliximab; LEF: leflunomide; MTX: methotrexate; NA: not applicable; SSZ: sulfasalazine

PART IV

Treatment and management

CHAPTER 9

9

Methotrexate therapy associated with a reduced rate of new-onset uveitis in biological-naïve juvenile idiopathic arthritis patients

Joeri W. van Straalen[1,2*], Görkem Akay[1,2*], Carlyn V. Kouwenberg[2,3], Sytze de Roock[1,2], Viera Koopman-Kalinina Ayuso[2,3], Nico M. Wulffraat[1,2], Joke H. de Boer[2,3] and Joost F. Swart[1,2]

[1]Department of Paediatric Immunology and Rheumatology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, the Netherlands
[2]Faculty of Medicine, Utrecht University, Utrecht, the Netherlands
[3]Department of Ophthalmology, University Medical Centre Utrecht, Utrecht, the Netherlands

**Joeri W. van Straalen and Görkem Akay contributed equally*

RMD Open. 2023;9(2):e003010.

ABSTRACT

Objectives

To study the effect of methotrexate (MTX) therapy on new-onset uveitis in biological-naïve juvenile idiopathic arthritis (JIA) patients.

Methods

In this matched case-control study, we compared MTX exposure between cases with JIA-associated chronic uveitis (JIA-U) and JIA patients without JIA-U at the time of matching (controls). Data were collected from electronic health records of the University Medical Centre Utrecht, the Netherlands. JIA-U cases were matched 1:1 to JIA control patients based on JIA diagnosis date, age at JIA diagnosis, JIA subtype, ANA status and disease duration. The effect of MTX on JIA-U onset was analysed using a multivariable time-varying Cox regression analysis.

Results

Ninety-two JIA patients were included and characteristics were similar between JIA-U cases (n = 46) and JIA control patients (n = 46). Both ever-use of MTX and exposure years were lower in JIA-U cases than JIA control patients. JIA-U cases significantly more often discontinued MTX treatment ($P = 0.03$) and out of those who did, 50% afterwards developed uveitis within one year. On adjusted analysis, MTX was associated with a significantly reduced new-onset uveitis rate (HR: 0.35, CI: 0.17 – 0.75). No different effect was observed between a low (<10 mg/m^2/wk) and standard MTX dose (≥10 mg/m^2/wk).

Conclusions

This study demonstrates an independent protective effect of MTX on new-onset uveitis in biological-naïve JIA patients. Clinicians might consider early initiation of MTX in patients at high uveitis risk. We advocate more frequent ophthalmologic screening in the first 6-12 months after MTX discontinuation.

Keywords: arthritis, juvenile; uveitis; methotrexate; rheumatology; ophthalmology; epidemiology

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory rheumatic condition of childhood with a global prevalence ranging from 3.8 to 400 cases per 100,000 population[1]. Uveitis is a common extra-articular manifestation of JIA, with a predicted risk of up to 40% in antinuclear antibodies (ANA) positive JIA patients with early onset of oligoarthritis[2]. The chronic form of uveitis is characterized by asymptomatic inflammation of the uveal layer of the eye. Therefore, tailored ophthalmologic screening of JIA patients is essential to early detect chronic uveitis and commence treatment before the development of vision-disabling complications such as cataracts, glaucoma, band keratopathy and macular oedema[3,4].

Although the conventional synthetic disease-modifying antirheumatic drug (DMARD) methotrexate (MTX) is commonly used in the treatment of JIA-associated chronic uveitis (JIA-U),[5] little is known about its possible preventive effect on developing new-onset JIA-U. Two observational studies reported significantly less uveitis development in JIA patients who had ever received MTX compared to patients who had not received MTX[6,7]. In contrast, no preventive effect of MTX on the number of uveitis events was observed in an additional exploratory analysis of a randomized controlled trial (RCT) in oligoarticular JIA patients treated with intra-articular steroids[8].

The primary aim of this study was to investigate the effect of MTX therapy on the development of new-onset chronic uveitis in children with JIA not treated with biological DMARDs. Secondary aims were to study the influence of different MTX doses and discontinuation of MTX therapy.

METHODS

Patients

Whereas a cohort study is concerned with frequency of disease in exposed and non-exposed individuals, a case-control study is concerned with the frequency and amount of exposure in subjects with a specific disease (cases) and people without the disease (controls)[9]. In this matched case-control study, clinical, demographic, laboratory and drug therapy data were collected from electronic health records of JIA-U patients from a previously reported cohort[10,11] and JIA patients who did not develop uveitis at the time of matching from a distinct registry[12]. All patients were treated at the University Medical Centre Utrecht (UMCU), the Netherlands, a tertiary referral centre. JIA-U patients were treated at the UMCU department of ophthalmology and a diagnosis of JIA-U was made by an ophthalmologist specialized in paediatric uveitis. JIA control patients were treated at

the UMCU department of paediatric immunology and rheumatology, located within the Wilhelmina Children's Hospital. A diagnosis of JIA was made by a paediatric rheumatologist according to International League of Associations for Rheumatology (ILAR) criteria[13]. Exclusion criteria for this study were a JIA diagnosis before the year 2000, enthesitis-related arthritis (ERA), systemic arthritis, rheumatoid factor (RF) positive polyarthritis, a diagnosis of uveitis prior to or simultaneously with JIA onset, no records of regular ophthalmologic screening and the use of biological DMARD therapy. Only patients with a JIA diagnosis from 2000 onwards were included since MTX was not commonly used in the UMCU prior to this year. ERA patients were excluded since these commonly present with acute instead of chronic uveitis[3,4]. Systemic arthritis and RF positive polyarthritis patients were excluded due to their minimal risk of developing JIA-U[2,14]. Data were arrested on 19 November, 2021.

Determinants and outcome

For each patient, the following data were collected: gender, date of JIA diagnosis, JIA subtype, JIA disease duration, the number of joints with active inflammation at JIA diagnosis, ANA status, human leukocyte antigen (HLA)-B27 status, erythrocyte sedimentation rate (ESR) at JIA diagnosis, use of non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroids, systemic corticosteroids, MTX and other conventional synthetic DMARDs, MTX dose (mg/m2/week), MTX start and stop dates and date of uveitis diagnosis. For this study, disease duration was defined as the time from JIA diagnosis to uveitis diagnosis for JIA-U cases, and time from JIA diagnosis to last visit or start of biological therapy for JIA control patients. Later data were censored. For the number of active joints, a maximum time difference of six months from JIA diagnosis was allowed. For ANA positivity, only one positive test at a titre of ≥1:40 was required since in multiple occasions this was the only titration that was recorded. For ESR, a maximum time difference of three months from JIA diagnosis was allowed. Patients were only considered to have used MTX if they had received at least four weeks of consecutive MTX therapy. If body surface area for calculation of MTX doses was not available, average values from the Dutch national growth curves were used[15]. We classified MTX doses <10 mg/m^2/wk as low dose MTX and doses ≥10 mg/m^2/wk as standard dose MTX[16].

Matching

JIA-U cases were matched 1:1 to JIA control patients without replacement based on date of JIA diagnosis (to counteract the influence of treatment strategies changing over time) and the following known risk factors for JIA-U: age at JIA diagnosis, JIA subtype, ANA status and JIA disease duration[3,4]. In order to identify similar patients based on all of the before mentioned variables, matching was based on the nearest Mahalanobis distance[17] and no calliper (i.e. maximal acceptable distance) was used. By doing so, JIA-U cases were matched to distinct JIA control patients from similar time periods with similar clinical characteristics and disease duration, who had not developed JIA-U at the time of matching. In case a JIA-U case was

similar to a JIA control patient with longer disease duration, data from the control patient after a disease duration equal to that of the JIA-U case were disregarded. In this way, a JIA patient who developed JIA-U could act as a control patient as long as he or she developed JIA-U after a disease duration equal to that of a matched JIA-U case. We only included unique patients, which means that a patient could not act as both a case and a control in our study.

Statistical analysis

Characteristics of JIA-U cases and JIA control patients were presented as frequency and valid percentage for categorical variables and median and interquartile range (IQR) for numerical variables. Variables were compared between the two groups using the Mann-Whitney U, χ^2 or Fisher's exact test. A *P*-value of 0.05 was considered statistically significant for all analyses. The adjusted effect of (different doses of) MTX therapy on new-onset uveitis was examined using a multivariable Cox regression analysis for which MTX therapy was entered as a time-varying variable. This type of analysis is commonly used to prevent immortal time bias which occurs if exposure time is misclassified in groups with non-constant exposure over time[18]. In order to remove potential bias due to the matched case-control study design[19], the analysis was adjusted for the matching factors age at JIA diagnosis, JIA subtype and ANA status. Linearity of the numerical age at JIA diagnosis variable was checked by plotting it against the Martingale residuals. Associations were reported as adjusted hazard ratios (HRs) with 95% confidence intervals (CI). Analyses were performed with IBM SPSS Statistics version 26.0.0.1 and the survival and survminer packages for R version 4.0.3[20]. We adhered to the Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) checklist for case-control studies[21].

Patient and public involvement

Patients were not involved in the design, conduct, reporting or dissemination plans of this study. Representatives of two Dutch patient associations for JIA (the Dutch JIA patient and parent organisation (JVN) and Youth-R-Well.com) work together with researchers and clinicians from the Wilhelmina Children's Hospital in setting priorities for JIA research[22].

RESULTS

Patient characteristics

Out of 160 JIA-U cases, 46 were eligible for matched analysis. Most cases were excluded because of a JIA diagnosis before the year 2000 or (a history of) uveitis at JIA diagnosis (Figure 1). The majority of included JIA-U cases and matched JIA control patients were girls with ANA positive oligoarthritis, characteristics did not differ significantly between cases and controls (Table 1). In addition, JIA diagnosis dates of cases (median 2-1-2010, range 1-2-2000 – 14-11-2018) and controls (median 12-4-2011, range 21-2-2002 – 20-11-2018) were from a roughly similar time period.

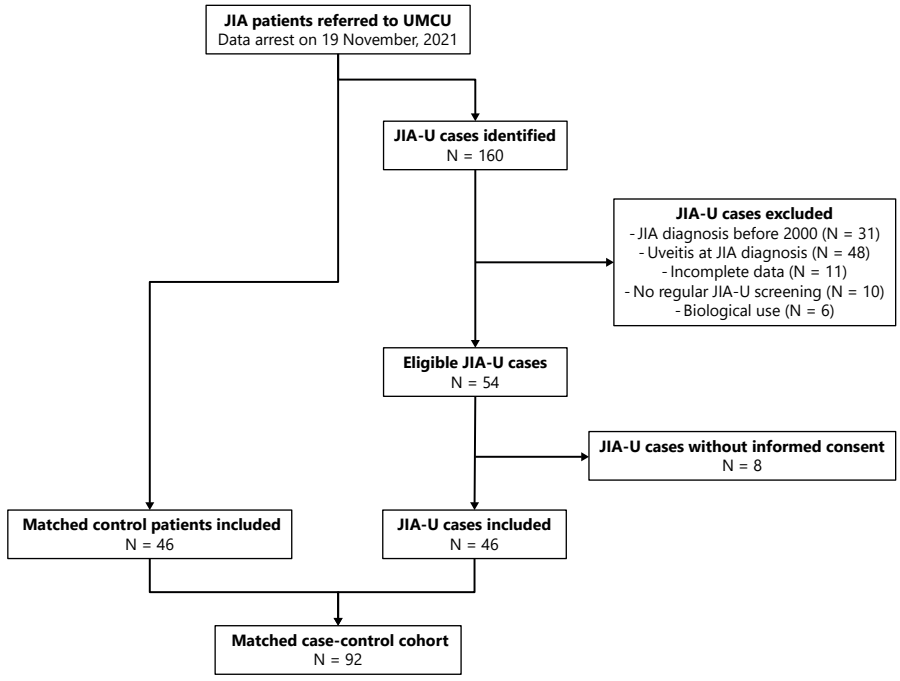

Figure 1. Flowchart of included patients. Patients were matched on date of JIA diagnosis, age at JIA diagnosis, JIA subtype, ANA status and JIA disease duration.
JIA-U: juvenile idiopathic arthritis-associated uveitis, UMCU: University Medical Centre Utrecht.

Table 1. Characteristics of matched JIA-U cases and JIA control patients.

	JIA-U (n = 46)	**JIA (n = 46)**	***P*-value**
Age at JIA diagnosis in years, median (IQR)	2.5 (1.9 – 4.5)	2.6 (2.0 – 5.1)	0.58
Age at uveitis diagnosis in years, median (IQR)	5.1 (4.0 – 6.4)	-	-
Female, n %)	37 (80.4%)	40 (87.0%)	0.57
Disease duration in years, median (IQR)	1.9 (0.6 – 3.0)	1.9 (0.6 – 2.9)	0.92
Active joint count at JIA diagnosis, median (IQR)	3 (1 – 4) n = 22	2 (1 – 3) n = 24	0.70
JIA subtype, n (%)			1
Oligoarthritis	39 (84.8%)	39 (84.8%)	
RF- polyarthritis	7 (15.2%)	7 (15.2%)	
Serum markers			
ANA positive, n (%)	38 (82.6%)	38 (82.6%)	1
HLA-B27 positive, n (%)	2 (20.0%) n = 10	0 (0.0%) n = 8	0.58
ESR (mm/h) at JIA diagnosis, median (IQR)	40 (25 – 50) n = 40	30 (18 – 47) n = 39	0.11

[1]Time from JIA diagnosis to uveitis diagnosis for JIA-U cases, and matched durations for JIA control patients.
ANA: antinuclear antibodies, ESR: erythrocyte sedimentation rate, HLA: human leukocyte antigen, IQR: interquartile range, JIA: juvenile idiopathic arthritis, JIA-U: JIA-associated uveitis, RF: rheumatoid factor

MTX therapy and uveitis onset

Drug history was not significantly different between JIA-U cases and JIA control patients, although ever use of MTX was lower in the cases (50.0% versus 65.2%, respectively) (Table 2). Furthermore the median number of exposure years was also lower in the cases than in the controls (0.1 years versus 0.5 years, respectively).

Table 2. Drug history at censor date of matched JIA-U cases and JIA control patients.

	JIA-U (n = 46)	**JIA (n = 46)**	***P*-value**
NSAIDs, n (%)	44 (95.7%)	45 (97.8%)	1
Intraarticular corticosteroids, n (%)	30 (65.2%)	32 (69.6%)	0.82
Systemic corticosteroids, n (%)	2 (4.3%)	5 (10.9%)	0.43
MTX, n (%)	23 (50.0%)	30 (65.2)	0.21
Days from JIA diagnosis to first MTX start, median (IQR)	31 (13 – 75) n = 23	46 (21 – 220) n = 30	0.11
MTX exposure years, median (IQR)	0.1 (0.0 – 1.5)	0.5 (0.0 – 1.5)	0.36
Frequency of MTX discontinuation, n (%)			0.03*
No discontinuation	7 (30.4%)	18 (60.0%)	
One time	13 (56.5%)	12 (40.0%)	
Two times	3 (13.0%)	0 (0.0%)	
Other cs-DMARDs, n (%)	4 (8.7%)	1 (2.2%)	0.36

cs-DMARDs: conventional synthetic disease-modifying antirheumatic drugs, IQR: interquartile range, JIA: juvenile idiopathic arthritis, JIA-U: JIA-associated uveitis, MTX: methotrexate, NSAIDs: non-steroidal anti-inflammatory drugs

*P-value <0.05

Out of all cases, only 20% (n = 9) developed JIA-U while on MTX therapy. Of these nine patients, seven (78%) had used MTX for less than six months. Also, two (22%) received low-dose MTX therapy. Furthermore, JIA-U cases had significantly more often discontinued MTX therapy than JIA control patients (69.6% vs 40.0%; P = 0.03).

Fifty percent of those JIA-U patients who discontinued MTX therapy and did not restart (n = 14) developed uveitis within one year after discontinuation (Figure 2).

On multivariable analysis, MTX therapy was associated with a significantly reduced new-onset uveitis rate throughout the study (Figure 3). The use of MTX was associated with an almost three times lower adjusted hazard for JIA-U development compared to no MTX use (HR: 0.35, CI: 0.17 – 0.75) (Table 3).

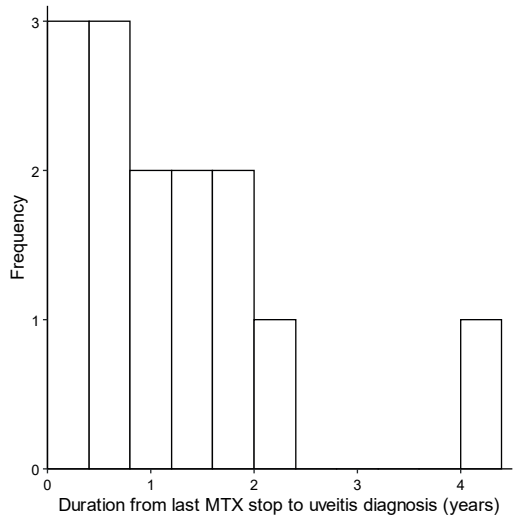

Figure 2. Time from last MTX stop to uveitis diagnosis in juvenile idiopathic arthritis-associated uveitis patients who discontinued MTX and did not restart before uveitis development (n = 14). MTX: methotrexate.

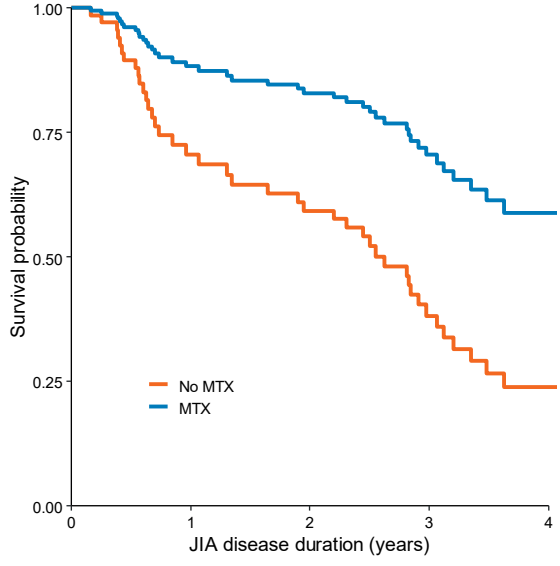

Figure 3. Diagram of average survival curves for new-onset uveitis in current case-control study. The separate curves for subpopulations with and without MTX use are calculated based on the adjusted time-varying Cox model, therefore they follow a similar pattern and do not represent generalisable absolute numbers of patients at risk over time. JIA: juvenile idiopathic arthritis, MTX: methotrexate.

Table 3. Multivariable Cox regression analysis for new-onset chronic uveitis.

Variables	HR	95% CI
Time-varying variable		
MTX	0.35	0.17 – 0.75*
Constant variables		
ANA positive	1.70	0.74 – 3.92
Age at JIA diagnosis (years)	0.88	0.75 – 1.02
RF- polyarthritis	1.00	Reference
Oligoarthritis	1.32	0.57 – 3.09

ANA: antinuclear antibodies, CI: confidence interval, HR: hazard ratio, JIA: juvenile idiopathic arthritis, MTX: methotrexate, RF: rheumatoid factor
*statistically significant

The risk of JIA-U was not significantly different for low dose MTX therapy (<10 mg/m2/wk) compared to standard dose therapy (Table 4, Figure 4), indicating that MTX was protective against JIA-U already at a low dose.

Table 4. Multivariable Cox regression analysis for new-onset chronic uveitis as a function of different MTX therapy doses.

Variables	HR	95% CI
Time-varying variable		
Standard dose MTX	1.00	Reference
Low-dose MTX	0.93	0.19 – 4.61
No MTX	2.79	1.21 – 6.45*
Constant variables		
ANA positive	1.70	0.74 – 3.93
Age at JIA diagnosis (years)	0.88	0.75 – 1.02
RF- polyarthritis	1.00	Reference
Oligoarthritis	1.33	0.57 – 3.10

ANA: antinuclear antibodies, CI: confidence interval, HR: hazard ratio, JIA: juvenile idiopathic arthritis, MTX: methotrexate, RF: rheumatoid factor
*statistically significant

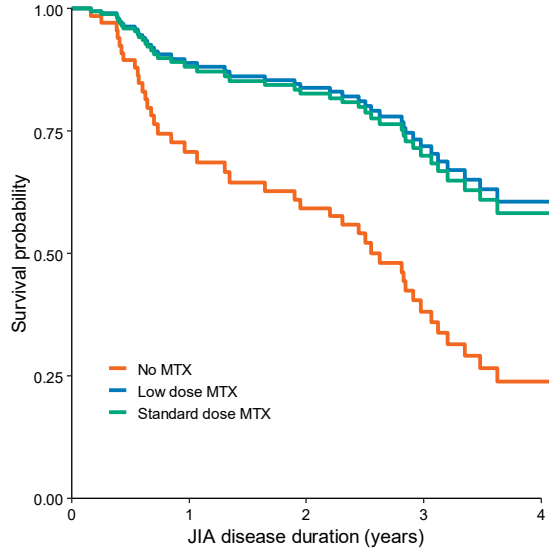

Figure 4. Diagram of average survival curves for new-onset uveitis in current case-control study. The separate curves for subpopulations with and without low (<10 mg/m2/wk) or standard dose (≥10 mg/m2/wk) MTX use are calculated based on the adjusted time-varying Cox model, therefore they follow a similar pattern and do not represent generalisable absolute numbers of patients at risk over time.
JIA: juvenile idiopathic arthritis, MTX: methotrexate.

DISCUSSION

This study reports a significant protective effect of MTX therapy on new-onset uveitis in JIA patients not treated with biologicals. This effect was not different for low versus standard dose MTX. Fifty percent of JIA-U patients that discontinued MTX therapy and did not restart, developed uveitis within one year after discontinuation.

The results of this study are supported by current guidelines that consider MTX as effective systemic treatment for JIA-U[5,23–25]. The current findings are also in line with two previous observational studies in which JIA patients who had ever received MTX had developed less JIA-U than patients who had not received MTX[6,7]. These studies, however, did not perform adjusted analyses and also did not analyse the effect of MTX as a time-varying exposure, introducing the risk of significant immortal time bias. In contrast, a RCT reported more new-onset uveitis events in oligoarticular JIA patients treated with intraarticular corticosteroids plus MTX (n = 6, 8%) than in oligoarticular JIA patients treated with intraarticular corticosteroids only (n = 3, 4%) in an additional exploratory analysis. This result was however not statistically significant and follow-up time was only 12 months.

Considering that untreated JIA-U can potentially lead to significant visual impairment, physicians might consider early initiation of MTX therapy especially in patients at high risk of developing JIA-U, commonly girls with ANA positive oligoarthritis onset at a young age[26]. In fact, in most JIA treatment guidelines these are exactly the patients that now often receive intra-articular corticosteroid injections instead of MTX[27]. This study indicated that MTX therapy is protective against JIA-U in both low and standard doses. If future studies confirm this finding, low-dose MTX therapy (<10 mg/m2/wk) could be offered to JIA patients with low arthritis disease activity but high risk of developing JIA-U. This might also have a beneficial effect on the risk of MTX side effects, which are common and include nausea, gastro-intestinal complaints, mouth ulcers and hepatotoxicity[25,28].

Our study found that the risk of JIA-U in patients who discontinued MTX therapy was highest shortly after discontinuation. This is in line with a German national register study that highlighted MTX discontinuation upon successful remission of arthritis as an apparent risk factor for JIA-U[29]. For this reason, physicians should consider more frequent ophthalmologic screening after MTX discontinuation in patients at high risk of developing JIA-U, which is dependent on JIA subtype, ANA status, JIA disease duration and age (at JIA onset)[26]. This practice is also recommended in the British Society for Paediatric and Adolescent Rheumatology and Royal College of Ophthalmology screening guidelines for JIA-U[4]. Here, we recommend to increase screening frequency in the first 6-12 months after MTX discontinuation and then revert to current screening guidelines. It has long been recommended to increase screening frequency for uveitis to every two months in the highest risk group of JIA patients[30]. Furthermore, it could be considered especially early in the disease course not to stop MTX therapy in the group of patients with highest risk of JIA-U, but rather switch to a low dose of MTX. This is in line with our finding that patients who developed JIA-U within one year after MTX discontinuation had used MTX therapy for a shorter time than patients who developed JIA-U more than one year after MTX discontinuation. The above suggestions have been discussed within the Multinational Interdisciplinary Working Group for Uveitis in Childhood (MIWGUC), which aims to improve current international uveitis screening guidelines for JIA based on the principle of evidence-based medicine, and has expressed its support for increasing screening frequency after MTX discontinuation.

Like MTX, the monoclonal antibody tumour necrosis factor (TNF) inhibitors adalimumab (ADA) and infliximab (IFX) are considered effective in the treatment of JIA-U. A RCT reported the effectiveness of ADA combined with MTX over MTX monotherapy[31] and current guidelines recommend MTX combined with ADA or IFX in patients with severe JIA-U[5,23–25]. Although there are to date no strong data from observational studies in support of a preventive effect of monoclonal antibody TNF inhibitors due to the problem of confounding by indication, paediatric rheumatologists commonly opt for ADA instead

of etanercept as the biological DMARD therapy of choice in patients at high risk of JIA-U[32]. Large scale observational studies comparing the effects of MTX, IFX and ADA on the development of JIA-U report contradicting results[29,33–35]. Still, TNF inhibitors are currently not considered an alternative to MTX as a first-line DMARD for treating JIA, but they are effective therapies after MTX failure or intolerance.

Our study has limitations. First, as with every case-control design, there is a certain risk of bias due to sampling of controls. However, this bias was minimized by selecting control patients from the same source population as the identified cases and who would have been selected as cases had they developed the outcome of interest[9]. JIA-U cases and JIA control patients furthermore showed similar characteristics. Secondly, we only identified eligible JIA-U cases with oligoarthritis or RF- polyarthritis. Consequently, we cannot state with certainty that our findings are applicable for patients with psoriatic and undifferentiated arthritis, who also run a notable risk of developing JIA-U[2]. Third, we were unable to study the effect of MTX doses below 5 mg/m^2/wk on JIA-U onset rates due to very few data.

Future research should focus on studying the time-varying effect of JIA disease activity scores such as the cJADAS[36] on the relationship between MTX use and new-onset JIA-U. Studies have reported higher disease activity in JIA to be associated with JIA-U, both temporarily and as a long-term predictor[35,37–39]. There is a possibility that disease activity is an unmeasured confounder in the effect of MTX on new-onset JIA-U for the current study, since higher disease activity in general provides more rationale for treatment with MTX. Therefore, it could be that the independent protective effect of MTX on new-onset JIA-U is even stronger than reported here. A high disease activity could also explain why we still observed nine patients who developed JIA-U while on MTX treatment. Secondly, the observed protective effect of (different doses of) MTX on new-onset JIA-U should ideally be confirmed in a RCT in order to eliminate any risk of selection bias. Such a study could also provide a number of patients who need to be treated over a specific time-period to prevent one case of JIA-U.

In conclusion, we report a significantly reduced rate of new-onset chronic uveitis in biological-naïve JIA patients treated with MTX therapy. Treating physicians might consider early initiation of MTX therapy in JIA patients at high risk for uveitis and we advocate more frequent ophthalmologic screening especially in the first 6-12 months after MTX discontinuation.

ACKNOWLEDGEMENTS

The authors thank Kirsten van der Velden, Marit Bijl and Annelies Suijs for facilitating the collection of informed consents.

FUNDING

This study was financially supported by the Dutch Ophthalmology Foundation 'UitZicht' and 'ODAS stichting', and by longstanding research support from the Dutch Arthritis Foundation (ReumaNederland), grant number LLP10. Funding entities had no role in the conducting or presentation of this study.

COMPETING INTERESTS

None declared.

ETHICS APPROVAL

This study was classified by the institutional review board of the UMC Utrecht as exempt of the Medical Research Involving Human Subjects Act (22/604) and was carried out in compliance with the Helsinki Declaration. All included patients provided informed consent for the use of their data for scientific purposes.

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CHAPTER 10

10

Real-world comparison of the effects of adalimumab and etanercept on well-being in non-systemic juvenile idiopathic arthritis: a propensity score-matched cohort study

Joeri W. van Straalen[1,2], Sytze de Roock[1,2], Gabriella Giancane[3,4], Alessandro Consolaro[3,4], Marite Rygg[5,6], Ellen B. Nordal[7,8], Nadina Rubio-Pérez[9], Marija Jelusic[10], Jaime De Inocencio[11], Jelena Vojinovic[12,13], Nico M. Wulffraat[1,2], Patricia C.J. Bruijning-Verhagen[14], Nicolino Ruperto[15] and Joost F. Swart[1,2], for the Paediatric Rheumatology International Trials Organisation (PRINTO)

[1]Department of Paediatric Immunology and Rheumatology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, the Netherlands
[2]Faculty of Medicine, Utrecht University, Utrecht, the Netherlands
[3]Clinica Pediatrica e Reumatologia, IRCCS Istituto Giannina Gaslini, Genoa, Italy
[4]Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili (DiNOGMI), Università degli Studi di Genova, Genoa, Italy
[5]Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, NTNU - Norwegian University of Science and Technology, Trondheim, Norway
[6]Department of Paediatrics, St. Olavs University Hospital of Trondheim, Trondheim, Norway
[7]Department of Paediatrics, University Hospital of North Norway, Tromsø, Norway
[8]Department of Clinical Medicine, UiT the Arctic University of Norway, Tromsø, Norway
[9]Departamento de Pediatria, Facultad de Medicina, Hospital Universitario "Dr. J. E. González", Universidad Autónoma de Nuevo León, Monterrey, Mexico
[10]Department of Paediatrics, University of Zagreb School of Medicine, Zagreb, Croatia
[11]Department of Paediatric Rheumatology, University Hospital 12 de Octubre, Madrid, Spain.
[12]Department of Paediatric Immunology and Rheumatology, Faculty of Medicine, University of Nis, Nis, Serbia
[13]Department of Paediatric Rheumatology, Clinic of Pediatrics, Clinical Center Nis, Nis, Serbia
[14]Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, the Netherlands
[15]UOSID centro trial, IRCCS Istituto Giannina Gaslini, Genoa, Italy

Pediatr Rheumatol Online J. 2022;20(1):96.

ABSTRACT

Background

Etanercept (ETN) and adalimumab (ADA) are considered equally effective biologicals in the treatment of arthritis in juvenile idiopathic arthritis (JIA) but no studies have compared their impact on patient-reported well-being. The objective of this study was to determine whether ETN and ADA have a differential effect on patient-reported well-being in non-systemic JIA using real-world data.

Methods

Biological-naive patients without a history of uveitis were selected from the international Pharmachild registry. Patients starting ETN were matched to patients starting ADA based on propensity score and outcomes were collected at time of therapy initiation and 3-12 months afterwards. Primary outcome at follow-up was the improvement in Juvenile Arthritis Multidimensional Assessment Report (JAMAR) visual analogue scale (VAS) well-being score from baseline. Secondary outcomes at follow-up were decrease in active joint count, adverse events and uveitis events. Outcomes were analysed using linear and logistic mixed effects models.

Results

Out of 158 eligible patients, 45 ETN starters and 45 ADA starters could be propensity score matched resulting in similar VAS well-being scores at baseline. At follow-up, the median improvement in VAS well-being was 2 (interquartile range (IQR): 0.0 – 4.0) and scores were significantly better (P = 0.01) for ETN starters (median 0.0, IQR: 0.0 – 1.0) compared to ADA starters (median 1.0, IQR: 0.0 – 3.5). The estimated mean difference in VAS well-being improvement from baseline for ETN versus ADA was 0.89 (95% CI: -0.01 – 1.78; P = 0.06). The estimated mean difference in active joint count decrease was -0.36 (95% CI: -1.02 – 0.30; P = 0.28) and odds ratio for adverse events was 0.48 (95% CI: 0.16 –1.44; P = 0.19). One uveitis event was observed in the ETN group.

Conclusions

Both ETN and ADA improve well-being in non-systemic JIA. Our data might indicate a trend towards a slightly stronger effect for ETN, but larger studies are needed to confirm this given the lack of statistical significance.

Keywords: juvenile idiopathic arthritis, etanercept, adalimumab, patient-reported outcomes, epidemiology, real-world data, propensity score analysis

BACKGROUND

Juvenile idiopathic arthritis (JIA) is the most common chronic disease in childhood with a global prevalence varying between 3.8 – 400 per 100,000[1]. It is not a single disease, but comprises all forms of idiopathic arthritis lasting for more than six weeks before the age of 16[2,3]. The International League of Associations for Rheumatology (ILAR) has classified seven categories of JIA with distinct clinical and laboratory features[4]. JIA may cause severe disability and a reduced quality of life. Drugs used in the management of JIA are nonsteroidal anti-inflammatory drugs (NSAIDs), intraarticular and systemic glucocorticoids, and conventional synthetic (cs-) and biological (b-) disease-modifying antirheumatic drugs (DMARDs)[5–7]. Due to therapeutic advances in the last two decades, such as the availability of b-DMARDs, disease remission has become a realistic goal for most children with JIA[8].

Two of the most used b-DMARDs in the management of non-systemic arthritis in JIA are the TNF-α inhibitors etanercept (ETN) and adalimumab (ADA). Current treatment recommendations for JIA consider ETN and ADA equal alternatives[5]. Unlike ADA, ETN is not effective against uveitis, an ocular manifestation that affects roughly one in every five JIA patients[9]. A 2013 study found that ETN is prescribed more often than ADA in daily practice, although JIA patients with a history or at high risk of developing uveitis are more commonly treated with ADA[10]. According to this study, the choice for ETN or ADA treatment primarily depends on physician and patient preferences such as experience with the drug.

While ETN and ADA are considered equally effective in treating arthritis in JIA, no studies have compared their impact on patient-reported evaluation of overall well-being. Patient-reported outcomes such as well-being are important measures in a treat-to-target approach to the management of JIA since they provide a more holistic view of health condition and treatment efficacy than merely disease activity[11–14]. Data on patient well-being after drug therapies might therefore be valuable for making treatment guidelines and recommendations.

The objective of this research was to determine whether ETN and ADA have a differential effect on well-being in patients with non-systemic JIA from the international observational Pharmachild registry[15–18]. We hypothesized that such a difference might be caused by differences in type of side effects, methotrexate (MTX) co-medication (which is more common with ADA in order to prevent anti-drug antibody development) and frequency of the injection (which is higher for ETN).

METHODS

Patients

The "Pharmacovigilance in JIA patients treated with biologic agents and/or MTX" (Pharmachild) registry started in 2011 and is currently ongoing. Its primary objective is to assess safety and efficacy of DMARD therapies in patients with JIA. Inclusion criteria are children with JIA as per ILAR classification criteria that are receiving NSAIDs, glucocorticoids, cs-DMARDs or b-DMARDs per physician decision. Currently, patients are enrolled from 85 centres that are part of the Paediatric Rheumatology International Trials Organization (PRINTO) from 31 countries worldwide[19]. Pharmachild consists of patients for whom only retrospective data have been collected at enrolment and patients for whom also prospective data is collected. In brief, Pharmachild collects demographic, clinical and laboratory data, information on drug exposure and adverse events and the cross-culturally adapted version of the Juvenile Arthritis Multidimensional Assessment Report (JAMAR)[20]. The JAMAR assesses patient-reported outcomes in JIA, including functional status, pain, disease activity, health-related quality of life, well-being and satisfaction with disease status[21]. It has been translated into 54 languages and both a parent and child version exist. JAMAR questionnaires in Pharmachild are only available for patients with prospective data. Further details of the Pharmachild registry are available elsewhere[15].

Data of patients with prospective data were extracted on 12 November 2020. For inclusion into the current study, patients or their parents should have completed a "baseline" JAMAR on the day of starting ETN or ADA therapy or at maximum one month earlier, provided they had not received any b-DMARD previously. In case both a parent and child JAMAR was completed for the same visit, the child version was selected. In this way, patient-reported outcomes were prioritized over parent-reported outcomes, without excluding information of visits for which only a parent or child JAMAR was available. Other exclusion criteria were systemic JIA, and a history of uveitis. Systemic JIA patients were excluded since this form of JIA is distinct from other subtypes with different clinical features and therapy options[2]. Furthermore, a "follow-up" JAMAR should have been completed 3-12 months after having started ETN or ADA. In case two or more follow-up JAMARs were completed by/for one patient, the JAMAR closest to six months after start of ETN or ADA was selected.

Determinant and outcomes

We compared study outcomes between patients who started ETN versus patients who started ADA. The primary outcome in this study was the improvement in JAMAR visual analogue scale (VAS) well-being score compared to baseline at the follow-up time-point closest to six months, with a minimum of three and maximum of 12 months. This 21-point VAS score reflects the answer to the following question: "considering all the ways the

illness affects you/your child, please evaluate how you/he/she feels at the moment", and ranges from 0 (very well) to 10 (very poorly). Secondary outcomes were the decrease in active joint count from baseline to follow-up, the number of adverse events reported by the patient or their parent(s) at follow-up and the number of uveitis events that occurred during follow-up.

Other covariates measured at baseline were patient/parent-reported pain, patient/parent-reported evaluation of disease activity, the physician global assessment of disease activity (all measured on a 21-point VAS), the physical and psychosocial domains of the paediatric rheumatology quality of life scale (composite scores of five items measured on a 4-point Likert scale), the juvenile arthritis functional score (a composite score of 15 items measured on a 4-point Likert scale), the patient acceptable symptom state (satisfied or not satisfied with current condition) and the Juvenile Arthritis Disease Activity Score (a composite measure consisting of the physician global assessment, VAS well-being, erythrocyte sedimentation rate and the active joint count)[22].

Propensity score matching

It is difficult to ascertain causal relationships from observational studies due to the lack of randomization typical of clinical trials, which often leads to confounding by indication. This latter term means that certain patients are more likely to receive a treatment of interest than others and therefore run a different risk for the outcome of interest. We addressed this problem by propensity score matching: ETN and ADA starters were matched at baseline on the probability of being prescribed ADA instead of ETN. The following variables at baseline that could play a role in the decision between ETN or ADA therapy[10] were used in a logistic regression model to predict the propensity score: ILAR category of JIA, sex, age, country of medical centre, VAS pain, adverse events while on methotrexate therapy and VAS well-being. Before matching the patients, a distribution of propensity scores for ETN and ADA starters was made and patients outside the range of propensity scores that was common for both groups were excluded. This was done in order to eliminate violation of the positivity assumption, which requires that there are no subjects in one treatment group that are not comparable to subjects in the other treatment group based on propensity score[23]. Subsequently, patients were matched 1 to 1 without replacement based on the logit propensity score. For this matching, we used an acceptable distance (i.e. calliper) of 0.2 times the standard deviation of the logit propensity score, as recommended in the literature[24]. Patients with propensity scores outside of the calliper remained unmatched and were excluded for further analysis. After matching, balance in covariates at baseline was assessed by comparing descriptive statistics and by means of the area under the receiver operating characteristic curve (AUC) of the propensity model fitted in the balanced cohort. Several examples of propensity score matching studies exist within the

field of rheumatic diseases[25–29], and the authors believe that innovative statistical methods like these are of additive value for evidence-based practice in (paediatric) rheumatology.

Statistical analysis

Covariates at baseline were compared between ETN and ADA starters using the Mann-Whitney U test, Chi-squared test or Fischer's exact test. In addition, VAS well-being scores at follow-up, time from baseline measurements to start of the b-DMARD, and time from start of the b-DMARD to follow-up measurements were compared between ETN and ADA starters using the Mann-Whitney U test. Missing outcomes at follow-up were handled by multiple imputation using chained equations. All analyses were run for 20 imputed datasets and the different estimates were combined using the theory of Rubin's rules, which takes into account both uncertainty from one imputed dataset (within-imputation variability) and uncertainty due to the missing information (between-imputation variability)[30]. Outcomes were analysed using linear and logistic mixed effects models with a random intercept per treatment centre to correct for dependence of observations. We performed an intention-to-treat analysis, that is, patients who started ETN or ADA were analysed in their respective groups regardless if they stopped or changed initial therapy. The analyses of improvement in VAS well-being and decrease in active joint count (quantitative variables) were adjusted for baseline VAS well-being and baseline active joint count respectively in order to increase statistical power and address the problem of regression to the mean[31]. As a sensitivity analysis, all analyses were repeated for the unmatched cohort of patients meeting the positivity assumption while adjusting for the propensity score (instead of matching). For this analysis, we transformed the propensity score using restricted cubic splines with four knots in order to correctly model the relation between this numerical variable and the outcomes of interest[32]. For all analyses, statistical significance was set at $P < 0.05$. All analyses were performed with R version 4.0.0 and the packages rms, mice, lme4, pROC and Matching[33].

RESULTS

Matched baseline cohort

As of 12 November 2020, a total of 2,907 non-systemic JIA patients without a history of uveitis were enrolled in the prospective cohort of Pharmachild. Out of these, 158 patients completed a JAMAR at start of ETN/ADA and 3-12 months thereafter (Figure 1). After calculating propensity scores, another 24 patients who had started ETN had to be excluded because of violation of the positivity assumption. The distribution of propensity scores is provided in Supplementary Figure 1. Clinical characteristics were similar between included and excluded patients (Supplementary Table 1). 45/60 ETN starters and 45/74 ADA starters were subsequently matched on propensity score, for whom characteristics

used in the propensity score model were similar (Table 1). Further characteristics of the matched patients are summarized in Supplementary Table 2. The AUC of the propensity score model fitted in the matched baseline cohort was low (0.56, 95% CI: 0.32 – 0.56), indicating a good balance of confounders between ETN and ADA starters. The percentage of patients with a child version JAMAR was comparable for ETN (33.3%) and ADA starters (37.8%). Moreover, the median year of starting ETN (2015, interquartile range (IQR): 2015 – 2016) was close to the median year of starting ADA (2016, IQR: 2015 – 2016). Patients who started ETN had a longer disease duration than patients who started ADA (median 2.9 years versus median 1.5 years, $P = 0.31$). The median VAS pain score in the overall matched cohort was 4.0 (IQR: 1.0 – 6.5), median VAS well-being score was 4.0 (IQR: 1.5 – 6.0) and median active joint count was 3.0 (IQR: 1.0 – 5.8). The median duration from completing a JAMAR to starting a b-DMARD was similar ($P = 0.15$) for ETN (0 days, IQR: 0 – 1) and ADA starters (0 days, IQR: 0 – 7).

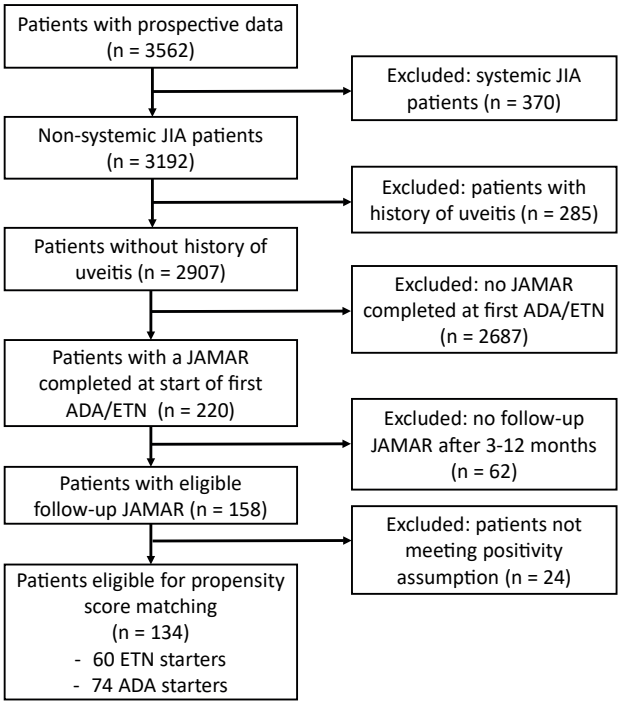

Figure 1. Flowchart of included patients. ADA: adalimumab, ETN: etanercept, JAMAR: juvenile arthritis multidimensional assessment report, JIA: juvenile idiopathic arthritis.

Table 1. Patient characteristics at baseline.

Variable	Cohort before matching (n = 134)			Cohort after matching (n = 90)		
	ETN starters (n = 60)	ADA starters (n = 74)	P	ETN starters (n = 45)	ADA starters (n = 45)	P
Demographics						
Age in years, median (IQR)	8.6 (5.1 – 13.5)	10.7 (6.1 – 14.9)	0.18	8.0 (5.3 – 13.9)	9.8 (5.9 – 14.7)	0.57
Country, n (%)			0.05			1.00
Czech Republic	13 (21.7%)	9 (12.2%)		9 (20.0%)	8 (17.8%)	
France	11 (18.3%)	7 (9.5%)		6 (13.3%)	5 (11.1%)	
Greece	5 (8.3%)	20 (27.0%)		5 (11.1%)	5 (11.1%)	
Italy	19 (31.7%)	20 (27.0%)		16 (35.6%)	18 (40.0%)	
Latvia	0 (0.0%)	1 (1.4%)		0 (0.0%)	0 (0.0%)	
Lithuania	2 (3.3%)	1 (1.4%)		2 (4.4%)	1 (2.2%)	
Netherlands	9 (15.0%)	8 (10.8%)		6 (13.3%)	7 (15.6%)	
Norway	1 (1.7%)	2 (2.7%)		1 (2.2%)	1 (2.2%)	
Poland	0 (0.0%)	1 (1.4%)		0 (0.0%)	0 (0.0%)	
Singapore	0 (0.0%)	2 (2.7%)		0 (0.0%)	0 (0.0%)	
Slovakia	0 (0.0%)	1 (1.4%)		0 (0.0%)	0 (0.0%)	
Spain	0 (0.0%)	2 (2.7%)		0 (0.0%)	0 (0.0%)	
Clinical characteristics						
Disease duration in years, median (IQR)	2.4 (1.2 – 5.4)	1.8 (0.8 – 4.1)	0.19	2.9 (1.3 – 5.1)	1.5 (0.8 – 4.4)	0.31
ILAR category, n (%)			0.21			1.00
ERA	7 (11.7%)	17 (23.0%)		6 (13.3%)	7 (15.6%)	
Persistent oligoarthritis	14 (23.3%)	21 (28.4%)		13 (28.9%)	13 (28.9%)	
Extended oligoarthritis	8 (13.3%)	7 (9.5%)		5 (11.1%)	5 (11.1%)	
Polyarthritis RF-	21 (35.0%)	24 (32.4%)		18 (40.0%)	16 (35.6%)	
Polyarthritis RF+	4 (6.7%)	1 (1.4%)		0 (0.0%)	1 (2.2%)	
Psoriatic arthritis	0 (0.0%)	1 (1.4%)		0 (0.0%)	0 (0.0%)	
Undifferentiated arthritis	6 (10.0%)	3 (4.1%)		3 (6.7%)	3 (6.7%)	
Active joint count, median (IQR)	3.0 (2.0 – 7.0)	3.0 (1.0 – 4.8)	0.15	3.0 (1.0 – 6.0)	3.0 (1.0 – 5.0)	0.69
Co-medication, n (%)						
NSAIDs	20 (33.3%)	16 (21.6%)	0.19	16 (34.8%)	10 (22.2%)	0.24
Steroids	9 (15.0%)	12 (16.2%)	1.00	6 (13.0%)	5 (11.1%)	1.00
Synthetic DMARDs	47 (78.3%)	61 (82.4%)	0.71	35 (80.4%)	38 (84.4%)	0.59

Table 1. Continued

Variable	Cohort before matching (n = 134)			Cohort after matching (n = 90)		
	ETN starters (n = 60)	ADA starters (n = 74)	P	ETN starters (n = 45)	ADA starters (n = 45)	P
Patient/parent-reported outcomes						
Adverse events on MTX	20 (33.3%)	27 (36.5%)	0.84	16 (35.6%)	16 (35.6%)	1.00
VAS pain, median (IQR)	4.0 (1.8 – 6.0)	3.3 (0.63 – 6.4)	0.25	4.0 (2.0 – 6.0)	4.5 (1.0 – 6.5)	0.90
VAS well-being, median (IQR)	3.0 (1.5 – 5.1)	4.0 (1.1 – 6.0)	0.74	4.0 (2.0 – 6.0)	4.0 (1.5 – 6.0)	0.78

ADA: adalimumab, ERA: enthesitis-related arthritis, ETN: etanercept, ILAR: International League of Associations for Rheumatology, IQR: interquartile range, n: number, MTX: methotrexate, RF: rheumatoid factor, VAS: visual analogue scale

Follow-up results

The median duration from starting a b-DMARD to completing a follow-up JAMAR was not significantly different ($P = 0.51$) for ETN (183 days, IQR: 168 – 199) and ADA (176 days, IQR: 168 – 195) starters (Supplementary Figure 2). At follow up, 42/45 (93%) ETN starters still used ETN and 36/45 (80%) ADA starters still used ADA ($P = 0.12$). VAS well-being scores at follow-up were better ($P = 0.01$) for ETN starters (median 0.0, IQR: 0.0 – 1.0) than ADA starters (median 1.0, IQR: 0.0 – 3.5) (Figure 2). Nevertheless, a median improvement in VAS well-being of 2 was observed for both ETN (IQR: 0.0 – 5.0) and ADA (IQR: 0.0 – 4.0). The estimated mean difference in VAS well-being improvement for ETN versus ADA starters was 0.89 (95% CI: -0.01 – 1.78) (Table 2). For both groups, three patients reported considerable worsening of well-being (VAS well-being increase of ≥2). Median active joint count at follow-up was 0 for both ETN and ADA starters (Figure 3). The estimated mean difference in active joint count decrease for ETN versus ADA starters was -0.36 (95% CI: -1.02 – 0.30). At follow-up, 11 (24.4%) ETN starters and 15 (34.9%) ADA starters reported adverse events. The estimated odds ratio for adverse events between the two groups was 0.48 (95% CI: 0.16 – 1.44). MTX co-medication at follow-up was common for both ETN (60%) and ADA (67%) starters. Patients who started ETN reported more gastric complaints than patients who started ADA, whereas the latter group reported more mood swings and sleep disturbances (Table 3). During follow-up, one event of uveitis occurred in the ETN group.

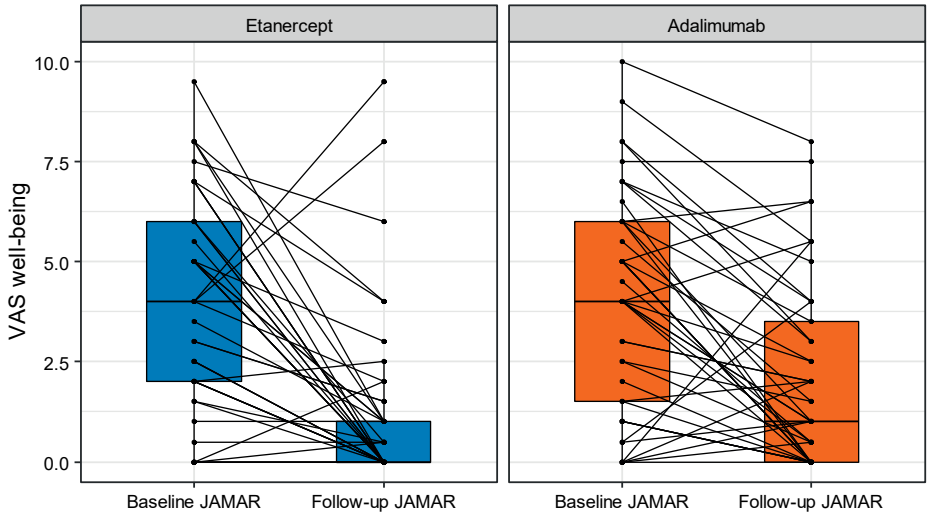

Figure 2. Visual analogue scale (VAS) well-being scores at baseline and follow. Boxplots represent median and interquartile range. Connected dots represent measurements from the same patient.
JAMAR: juvenile arthritis multidimensional assessment report.

Table 2. Results from follow-up measurements.

	ETN starters (n = 45)	**ADA starters (n = 45)**	**Effect estimate for ETN vs. ADA (95% CI)**	***P*-value**
Improvement in VAS well-being compared to baseline, median (IQR)	2.0 (0.0 – 5.0)	2.0 (0.0 – 4.0)	0.89 (-0.01 – 1.78)[a]	0.06
Decrease in active joint count compared to baseline, median (IQR)	3 (1 – 6)[b]	2 (1 – 4)	-0.36 (-1.02 – 0.30)[a]	0.28
Adverse events, n (%)	11 (24.4%)	15 (34.9%)[c]	0.48 (0.16 – 1.44)[d]	0.19
Uveitis events, n (%)	1 (2.2%)	0 (0.0%)	-	-

Missing values were handled by multiple imputation.
ADA: adalimumab, ETN: etanercept, IQR: interquartile range, n: number, VAS: visual analogue scale.
[a]mean difference as determined from linear mixed effects model
[b]there was one missing observation
[c]there were two missing observations
[d]odds ratio as determined from logistic mixed effects model

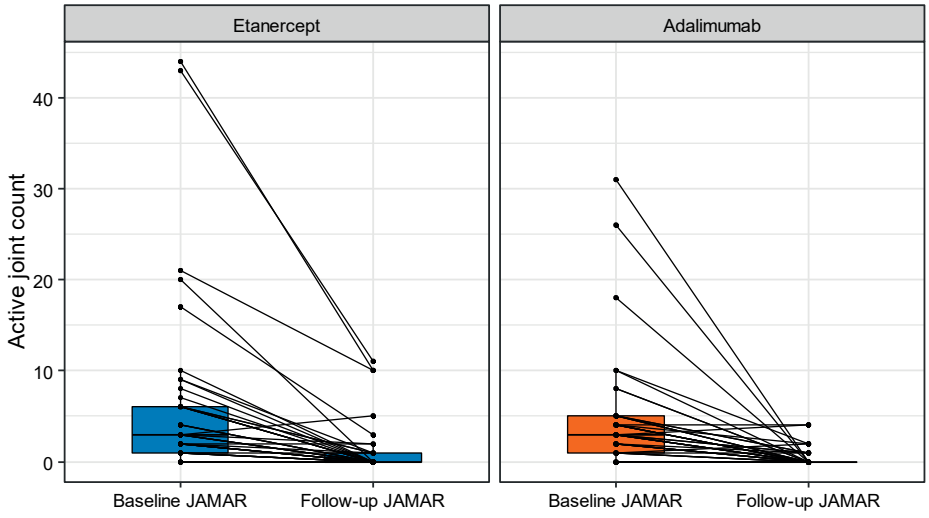

Figure 3. Active joint counts at baseline and follow-up. Boxplots represent median and interquartile range. Connected dots represent measurements from the same patient.
JAMAR: juvenile arthritis multidimensional assessment report.

Table 3. Adverse events reported at follow-up.

Adverse event reported, n (%)	ETN starters (n = 45)	ADA starters (n = 43)	*P*-value
Fever	1 (2.2%)	0 (0.0%)	1
Aphthae	1 (2.2%)	2 (4.5%)	1
Gingivitis	1 (2.2%)	0 (0.0%)	1
Headache	3 (6.7%)	4 (9.1%)	1
Rash	1 (2.2%)	1 (2.3%)	1
Mood swings	1 (2.2%)	5 (11.4%)	0.20
Sleep disturbances	0 (0.0%)	5 (11.4%)	0.06
Gastric complaints	4 (8.9%)	1 (2.3%)	0.36
Nausea	3 (6.7%)	6 (13.6%)	0.48
Vomiting	1 (2.2%)	1 (2.3%)	1
Constipation	1 (2.2%)	0 (0.0%)	1
Injection site reactions	2 (4.4%)	4 (9.1%)	0.68
Dehydration	1 (2.2%)	0 (0.0%	1
Hair loss	0 (0.0%)	2 (4.5%)	0.24
Fatigue	0 (0.0%)	1 (2.3%)	0.49
Urinary incontinence	1 (2.2%)	0 (0.0%)	1
Leukopenia	1 (2.2%)	0 (0.0%)	1

ADA: adalimumab, ETN: etanercept, n: number

Sensitivity analysis

When analysing all follow-up measurements of the full unmatched cohort of patients meeting the positivity assumption (n = 134), median VAS well-being was 0.5 (IQR: 0.0 – 2.0), median active joint count was 0 (IQR: 0 – 0), 36/132 patients (27.3%) reported adverse events and no additional events of uveitis were reported. Median improvement of VAS well-being and decrease in active joint count from baseline was 2.0 (IQR: 0.0 – 4.3) and 3.0 (IQR: 1.0 – 6.5) for ETN starters and 1.8 (IQR: 0.0 – 4.0) and 2.0 (IQR: 1.0 – 4.0) for ADA starters, respectively. 15 ETN starters (25.0%) and 21 ADA starters (29.2%) reported adverse events. While adjusting for propensity score, the estimated mean difference in VAS well-being improvement for ETN versus ADA starters was 0.70 (95% CI: -0.05 – 1.45) (Supplementary Table 3). The estimated mean difference in active joint count decrease for ETN versus ADA starters, adjusted for propensity score, was -0.37 (95% CI: -1.27 – 0.52). Finally, the adjusted odds ratio for adverse events between the two groups was 0.45 (95% CI: 0.17 – 1.19).

DISCUSSION

In our study, ETN and ADA both improved VAS well-being following 3-12 months of treatment. Analysis of 90 matched patients indicates improvement of well-being may be larger when ETN therapy is prescribed compared to ADA, but results were non-significant. The same conclusions were drawn following a sensitivity analysis in which we used the transformed propensity score for statistical adjustment instead of matching.

Propensity score matching at baseline resulted in overall equally distributed covariates for ETN and ADA starters. However, a difference in median disease duration of over one year was observed. It could be that ADA was used earlier in the disease course due to risk of uveitis, which is highest during the first years after onset of arthritis[34]. Nevertheless, when adjusting for baseline disease duration in our analyses, similar results were observed.

We report the first head-to-head comparison of the effects of ETN and ADA on patient-reported evaluation of overall well-being in JIA. Previous studies have reported patient-reported well-being after initiation of ETN or ADA therapy, but did not compare the two drugs[35–37]. In these studies, well-being after anti-TNF therapy improved more compared to the current study, although patients were older, had higher disease activity and could have had systemic arthritis or a history of uveitis. In the current study, VAS well-being scores at follow-up were significantly better for ETN starters compared to ADA starters and the estimated improvement in VAS well-being from baseline was 0.89 points larger for ETN starters compared to ADA starters. The latter difference was however not statistically significant. This may reflect equality between the treatments or a lack of statistical power of our study, given the estimated effect with a significance level of 0.05 was extremely

close to statistical significance with a *P*-value of 0.06. A true difference in effect on VAS well-being might be explained by pain caused by ADA injection[10]. Pain on ADA injection used to be associated with a citrate buffer, which was removed from the drug in 2018[38]. In our study, 89% (40/45) of patients who started ADA did so before 2018. Therefore, it could be that the possible difference in effect on VAS well-being between ETN and ADA is currently smaller than observed in this study.

Similar to the results of our research, previous studies have concluded that ETN and ADA have comparable efficacy in reducing disease activity in JIA[37,39–42]. However, the evidence from these studies is limited given differences in patient characteristics between the groups of included ETN and ADA users. These differences were mostly observed in uveitis history or earlier b-DMARD use. One study suggested that children younger than 4 years without uveitis show a better response to ETN than ADA[43]. But more research on this subject is required given the risk of de novo uveitis and the fact that ETN and ADA users within this study were also not comparable.
Since the current study did not demonstrate a statistically significant difference in effect on well-being, disease activity and adverse events, presence or risk of uveitis remains the most important factor for physicians to consider when choosing between ETN and ADA. ADA but not ETN is effective against uveitis[9], although development of uveitis has also been reported under ADA therapy[44]. JIA-associated uveitis is extremely rare in patients with systemic arthritis or RF+ polyarthritis and occurs most often in ANA positive patients with a young age at JIA onset[17]. Too few uveitis events were observed in the current study to make any comparisons, although the only case of uveitis occurred in the ETN group. Another important factor in choosing between ETN or ADA therapy is possible treatment failure due to development of anti-drug antibodies, which can occur under ADA therapy and can be prevented with MTX co-medication[45]. Adverse events related to MTX are however common and include nausea, gastro-intestinal complaints, mouth ulcers and hepatotoxicity[7]. For these reasons, physicians might opt for ETN instead of ADA therapy, especially in patients with MTX intolerance.

An interesting finding of our study was that well-being considerably worsened during follow-up in six patients, although disease activity improved in nearly all patients included in the study. This could possibly be explained by fear of injection, but we could not confirm this hypothesis from JAMARs at follow-up of the concerned patients. Another reason might be chronic pain due to central sensitization, which is not uncommon in JIA[46]. We indeed observed that four out of the six patients reported a suboptimal VAS pain score and persistent activity or relapse, despite that disease activity, as indicated by physician-reported active and painful joint counts, was absent or minimal. Also, none of these patients developed uveitis. These results show that physician-reported disease activity does not translate directly to well-being in children with JIA.

Our study has limitations. Almost all patients were eventually included from European centres, which might hamper generalization of our results to other settings around the world where b-DMARDs are not widely available[47]. Patients from non-European centres were mostly excluded for not having completed a JAMAR on the day of starting ETN or ADA therapy or at maximum one month earlier. Furthermore, the number of patients included in our study was not large enough to draw conclusions about differences in the type of adverse events reported between ETN and ADA starters. Especially considering that a proportion of the reported adverse events were likely caused by MTX co-medication[48], which was common and similar for both ETN and ADA starters at baseline and follow-up. Also, given the observational nature of this study, JAMARs of included patients were not completed at the exact same time points from starting a b-DMARD, further factors associated with uveitis risk such as ANA status and erythrocyte sedimentation rate[49] could not be used in the propensity score model as predictors of ETN or ADA therapy due to missing data, and there is a possibility of unmeasured confounding variables such as the treating physician. The latter could be a confounder given that some physicians might have a preference for ETN or ADA based on previous experiences.

Nonetheless, propensity score matching is a strong method for dealing with bias in (retrospective) observational studies[50]. This method mimics the randomization process of a RCT in the context of a non-interventional study[51]. Indeed, we observed good balance of the many covariates measured in our propensity score-matched cohort. Furthermore, whereas RCTs may prove efficacy of interventions, their results often suffer from limited applicability to clinical practice due to strict inclusion and exclusion criteria. On the other hand, propensity score methods allow for valid comparison of effectiveness of different interventions from "real-world evidence", which closely resembles the actual clinical practice[52].

To our knowledge, we report the first comparison between similar groups of b-DMARD therapy-naive ETN and ADA starters in JIA, with a focus on patient-reported well-being. Given the scarcity of such data but its value for treatment guidelines and recommendations, more studies on the effects of drugs from the same classes on patient-reported outcomes in JIA should be performed in the future.

CONCLUSIONS

In conclusion, both ETN and ADA resulted in improved well-being in patients with non-systemic JIA. Our data might indicate a trend towards a slightly stronger effect for ETN, but larger studies are needed to confirm this given the lack of statistical significance. Presence

or high risk of uveitis and MTX intolerance remain the most important factors to consider when choosing between these two drugs.

ACKNOWLEDGEMENTS

The authors thank all PRINTO centers for contributing to the data collection and PRINTO research assistants (Chiara Pallotti, Silvia Scala, Simona Angioloni and Luca Villa). The authors would also like to express their acknowledgements to the European Reference Network for Immunodeficiency, Autoinflammatory, Autoimmune and Pediatric Rheumatic diseases (ERN-RITA). Lastly, we thank all patients and their parents for consenting to this research.

FUNDING

Pharmachild has been supported by a grant from the European Union (grant 260353), by the Dutch ZonMW (grant PharmachildNL 80-83600-98-21012) and by funding from the IRCCS Istituto Giannina Gaslini (Genoa, Italy).

COMPETING INTERESTS

AC reports speaking fees from AbbVie and Pfizer and a research grant from Pfizer. NR has received honoraria for consultancies or speaker bureaus from the following pharmaceutical companies in the past 3 years: 2 Bridge, Amgen, AstraZeneca, Aurinia, Bayer, Brystol Myers and Squibb, Celgene, inMed, Cambridge Healthcare Research, Domain Therapeutic, EMD Serono, Glaxo Smith Kline, Idorsia, Janssen, Eli Lilly, Novartis, Pfizer, Sobi, UCB.

All other authors declare no conflict of interest for this manuscript.

ETHICS APPROVAL

Pharmachild and all participating centers obtained approval from their respective ethics committees and were conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent/assent based on existing national regulations.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Characteristics of included and excluded patients.

Variable	Excluded patients (n = 2773)	Included patients (n = 134)
Demographics		
Female subjects, n (%)	1991 (71.8%)	97 (72.4%)
Country, n (%)		
Austria	1 (0.0%)	0 (0.0%)
Brazil	48 (1.7%)	0 (0.0%)
Croatia	21 (0.8%)	0 (0.0%)
Czech Republic	60 (2.2%)	22 (16.4%)
Denmark	11 (0.4%)	0 (0.0%)
Ecuador	21 (0.8%)	0 (0.0%)
France	237 (8.5%)	18 (13.4%)
Greece	165 (6.0%)	25 (18.7%)
Hungary	68 (2.5%)	0 (0.0%)
India	63 (2.3%)	0 (0.0%)
Israel	23 (0.8%)	0 (0.0%)
Italy	927 (33.4%)	39 (29.1%)
Latvia	13 (0.5%)	1 (0.7%)
Libya	5 (0.2%)	0 (0.0%)
Lithuania	129 (4.7%)	3 (2.2%)
Mexico	83 (3.0%)	0 (0.0%)
Netherlands	175 (6.3%)	17 (12.7%)
Norway	213 (7.7%)	3 (2.2%)
Poland	18 (0.6%)	1 (0.7%)
Romania	78 (2.8%)	0 (0.0%)
Russia	26 (0.9%)	0 (0.0%)
Saudi Arabia	35 (1.3%)	0 (0.0%)
Singapore	37 (1.3%)	2 (1.5%)
Slovakia	20 (0.7%)	1 (0.7%)
Spain	295 (10.6%)	2 (1.5%)
Switzerland	1 (0.0%)	0 (0.0%)
Clinical characteristics		
Age at JIA onset in years, median (IQR)	4.5 (2.2 – 9.0)	5.0 (2.4 – 10.2)
ILAR category, n (%)		
ERA	294 (10.6%)	24 (17.9%)
Persistent oligoarthritis	793 (28.6%)	35 (26.1%)
Extended oligoarthritis	455 (16.4%)	15 (11.2%)

Supplementary Table 1. Continued

Variable	Excluded patients (n = 2773)	Included patients (n = 134)
Polyarthritis RF-	777 (28.0%)	45 (33.6%)
Polyarthritis RF+	131 (4.7%)	5 (3.7%)
Psoriatic arthritis	100 (3.6%)	1 (0.7%)
Undifferentiated arthritis	223 (8.0%)	9 (6.7%)
Immunological markers, n (%)		
ANA positive	1436 (56.0%) n = 2564	73 (56.2%) n = 130
HLA-B27 positive	387 (26.1%) n = 1482	14 (19.4%) n = 72
RF positive	146 (6.2%) n = 2353	5 (4.1%) n = 121

ANA: antinuclear antibodies, ERA: enthesitis-related arthritis, HLA: human leukocyte antigen, ILAR: International League of Associations for Rheumatology, IQR: interquartile range, RF: rheumatoid factor

Supplementary Table 2. Extended patient characteristics at baseline.

Variable	Cohort before matching (n = 134)			Cohort after matching (n = 90)		
	ETN starters (n = 60)	ADA starters (n = 74)	*P*	ETN starters (n = 45)	ADA starters (n = 45)	*P*
Child version of JAMAR	19 (31.7%)	32 (43.2%)	0.23	15 (33.6%)	17 (37.8%)	0.83
Demographics						
Female subjects, n (%)	46 (76.7%)	51 (68.9%)	0.42	33 (73.3%)	31 (68.9%)	0.82
Age in years, median (IQR)	8.6 (5.1 – 13.5)	10.7 (6.1 – 14.9)	0.18	8.0 (5.3 – 13.9)	9.8 (5.9 – 14.7)	0.57
Country, n (%)			0.05			1.00
Czech Republic	13 (21.7%)	9 (12.2%)		9 (20.0%)	8 (17.8%)	
France	11 (18.3%)	7 (9.5%)		6 (13.3%)	5 (11.1%)	
Greece	5 (8.3%)	20 (27.0%)		5 (11.1%)	5 (11.1%)	
Italy	19 (31.7%)	20 (27.0%)		16 (35.6%)	18 (40.0%)	
Latvia	0 (0.0%)	1 (1.4%)		0 (0.0%)	0 (0.0%)	
Lithuania	2 (3.3%)	1 (1.4%)		2 (4.4%)	1 (2.2%)	
Netherlands	9 (15.0%)	8 (10.8%)		6 (13.3%)	7 (15.6%)	
Norway	1 (1.7%)	2 (2.7%)		1 (2.2%)	1 (2.2%)	
Poland	0 (0.0%)	1 (1.4%)		0 (0.0%)	0 (0.0%)	
Singapore	0 (0.0%)	2 (2.7%)		0 (0.0%)	0 (0.0%)	
Slovakia	0 (0.0%)	1 (1.4%)		0 (0.0%)	0 (0.0%)	
Spain	0 (0.0%)	2 (2.7%)		0 (0.0%)	0 (0.0%)	
Clinical characteristics						
Disease duration in years, median (IQR)	2.4 (1.2 – 5.4)	1.8 (0.8 – 4.1)	0.19	2.9 (1.3 – 5.1)	1.5 (0.8 – 4.4)	0.31
ILAR category, n (%)			0.21			1.00
ERA	7 (11.7%)	17 (23.0%)		6 (13.3%)	7 (15.6%)	
Persistent oligoarthritis	14 (23.3%)	21 (28.4%)		13 (28.9%)	13 (28.9%)	
Extended oligoarthritis	8 (13.3%)	7 (9.5%)		5 (11.1%)	5 (11.1%)	
Polyarthritis RF-	21 (35.0%)	24 (32.4%)		18 (40.0%)	16 (35.6%)	
Polyarthritis RF+	4 (6.7%)	1 (1.4%)		0 (0.0%)	1 (2.2%)	
Psoriatic arthritis	0 (0.0%)	1 (1.4%)		0 (0.0%)	0 (0.0%)	
Undifferentiated arthritis	6 (10.0%)	3 (4.1%)		3 (6.7%)	3 (6.7%)	
Co-medication, n (%)						
NSAIDs	20 (33.3%)	16 (21.6%)	0.19	16 (34.8%)	10 (22.2%)	0.24
Steroids	9 (15.0%)	12 (16.2%)	1.00	6 (13.0%)	5 (11.1%)	1.00
Synthetic DMARDs	47 (78.3%)	61 (82.4%)	0.71	35 (80.4%)	38 (84.4%)	0.59

Supplementary Table 2. Continued

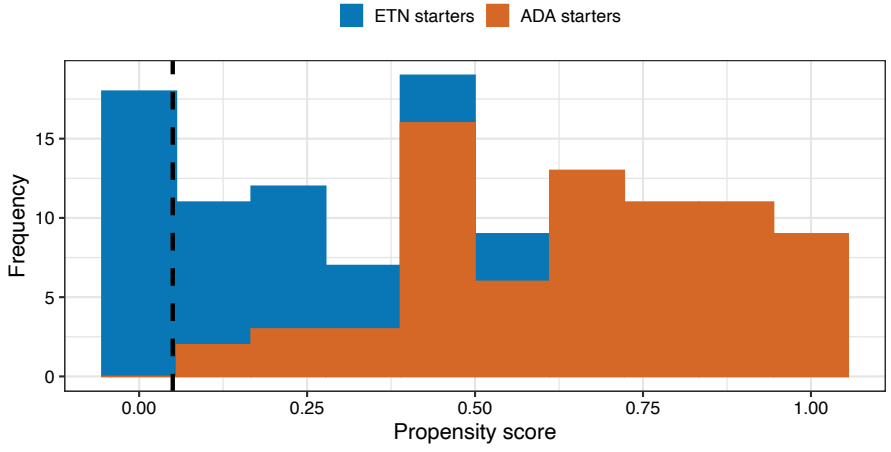
Variable	Cohort before matching (n = 134)			Cohort after matching (n = 90)		
	ETN starters (n = 60)	ADA starters (n = 74)	*P*	ETN starters (n = 45)	ADA starters (n = 45)	*P*
Patient/parent-reported outcomes						
Adverse events on MTX	20 (33.3%)	27 (36.5%)	0.84	16 (35.6%)	16 (35.6%)	1.00
VAS pain, median (IQR)	4.0 (1.8 – 6.0)	3.3 (0.63 – 6.4)	0.25	4.0 (2.0 – 6.0)	4.5 (1.0 – 6.5)	0.90
VAS disease activity, median (IQR)	4.3(2.0 – 6.6)	3.5 (1.0 – 6.0)	0.25	5.0 (2.0 – 7.0)	4.5 (1.5 – 6.5)	0.64
VAS well-being, median (IQR)	3.0 (1.5 – 5.1)	4.0 (1.1 – 6.0)	0.74	4.0 (2.0 – 6.0)	4.0 (1.5 – 6.0)	0.78
JQL physical health score, median (IQR)	4.0 (2.0 – 8.3) n = 52	3.0 (1.0 – 6.0) n = 69	0.16	5.0 (2.0 – 8.0) n = 38	4.0 (1.0 – 6.0) n = 41	0.31
JQL psychosocial health score, median (IQR)	1.5 (1.0 – 4.0) n = 50	2.0 (0.8 – 4.0) n = 68	0.79	2.0 (1.0 – 4.0) n = 37	2.0 (1.0 – 4.0) n = 41	0.62
JAFS score, median (IQR)	3.0 (1.0 – 6.5) n = 51	3.0 (0.0 – 6.0) n = 71	0.20	3.0 (1.0 – 6.0) n = 39	3.0 (0.0 – 6.0) n = 42	0.70
Patient acceptable symptom state, n (%)						1.00
Disease activity, median (IQR)						
Active joint count	3.0 (2.0 – 7.0)	3.0 (1.0 – 4.8)	0.15	3.0 (1.0 – 6.0)	3.5 (2.5 – 5.0)	0.69
PGA	4.0 (2.9 – 5.0)	3.5 (2.5 – 5.5)	0.98	3.5 (3.0 – 4.5)	3.5 (2.5 – 5.0)	0.72
JADAS-71 score	11.8 (8.0 – 16.6) n = 52	11.6 (7.0 – 16.0) n = 62	0.53	11.5 (8.1 – 15.0) n = 39	11.7 (6.8 – 15.0) n = 35	0.82

ADA: adalimumab, DMARD: disease-modifying antirheumatic drug, ERA: enthesitis-related arthritis, ETN: etanercept, ILAR: International League of Associations for Rheumatology, IQR: interquartile range, JADAS: juvenile arthritis disease activity score, JAFS: juvenile arthritis functional score, JAMAR: juvenile arthritis multidimensional assessment report, JQL: paediatric rheumatology quality of life scale, n: number, MTX: methotrexate, NSAID: non-steroidal anti-inflammatory drug, PGA: physician global assessment, RF: rheumatoid factor, VAS: visual analogue scale

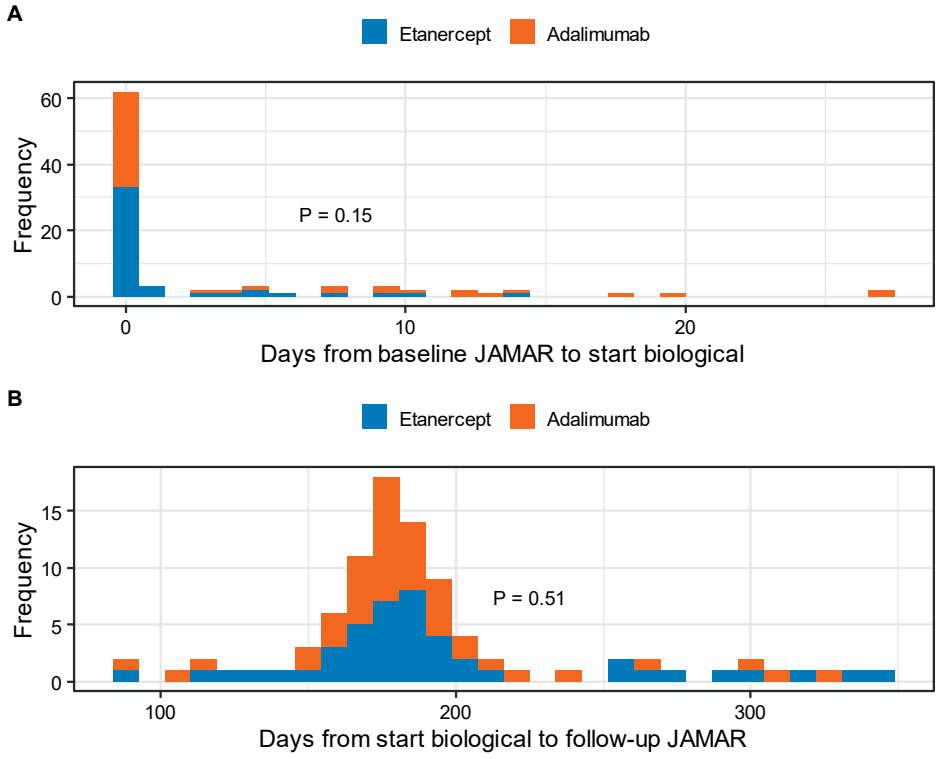
Supplementary Table 3. Results from follow-up measurements for the unmatched cohort.

	ETN starters (n = 60)	ADA starters (n = 74)	PS-adjusted effect estimate for ETN vs. ADA (95% CI)
Improvement in VAS well-being compared to baseline, median (IQR)	2.0 (0.0 – 4.3)	1.8 (0.0 – 4.0)	0.70 (-0.05 – 1.45)[a]
Decrease in active joint count compared to baseline, median (IQR)	3.0 (1.0 – 6.5)[b]	2.0 (1.0 – 4.0)	-0.37 (-1.27 – 0.52)[a]
Adverse events, n (%)	15 (25.0%)	21 (29.2%)[c]	0.45 (0.17 – 1.19)[d]
Uveitis events, n (%)	1 (1.7%)	0 (0.0%)	-

Missing values were handled by multiple imputation.
ADA: adalimumab, ETN: etanercept, IQR: interquartile range, PS: propensity score, VAS: visual analogue scale.
[a]mean difference as determined from propensity score-adjusted linear mixed effects model
[b]there was one missing observation
[c]there were two missing observations
[d]odds ratio as determined from propensity score-adjusted logistic mixed effects



Supplementary Figure 1. Overlapping histograms of propensity score for receiving adalimumab (ADA), n = 158. Vertical black dashed line indicates border of common propensity scores for etanercept (ETN) and ADA starters and patients left from this margin were excluded (n = 24).



Supplementary Figure 2. Stacked histograms of time intervals between start of etanercept/adalimumab therapy and baseline/follow-up measurements. A: duration from baseline juvenile arthritis multidimensional assessment report (JAMAR) to start biological. B: duration from start biological to follow-up JAMAR.

CHAPTER 11

11

Meningococcal ACWY conjugate vaccine immunogenicity and safety in adolescents with juvenile idiopathic arthritis and inflammatory bowel disease: a prospective observational cohort study

Milou Ohm[1*], Joeri W. van Straalen[2*], Marieke Zijlstra[3], Gerrie de Joode-Smink[2], Anne Jasmijn Sellies[2], Joost F. Swart[2], Sebastiaan J. Vastert[2], Joris M. van Montfrans[2,4], Marije Bartels[5], Annet van Royen-Kerkhof[2], Joanne G. Wildenbeest[4], Caroline A. Lindemans[2,6], Victorien Wolters[3], Roos A.W. Wennink[7], Joke H. de Boer[7], Mirjam J. Knol[1], Marloes W. Heijstek[8], Elisabeth A.M. Sanders[1,2], Frans M. Verduyn-Lunel[9], Guy A.M. Berbers[1], Nico M. Wulffraat[2], Marc H.A. Jansen[2]

[1]Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, Netherlands
[2]Department of Paediatric Immunology and Rheumatology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, Netherlands
[3]Department of Paediatric Gastroenterology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, Netherlands
[4]Department of Paediatric Infectious Diseases, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, Netherlands
[5]Department of Paediatric Haematology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, Netherlands
[6]Princess Máxima Centre for Paediatric Oncology, Utrecht, Netherlands
[7]Department of Ophthalmology, University Medical Centre Utrecht, Utrecht, Netherlands
[8]Department of Rheumatology & Clinical Immunology, University Medical Centre Utrecht, Utrecht, Netherlands
[9]Department of Medical Microbiology, University Medical Centre Utrecht, Utrecht, Netherlands

**Milou Ohm and Joeri W. van Straalen contributed equally*

Vaccine. 2023;S0264-410X(23)00480-2

ABSTRACT

Background

Immunogenicity to meningococcal serogroup ACWY (MenACWY) conjugate vaccine has not been studied in immunocompromised minors with juvenile idiopathic arthritis (JIA) or inflammatory bowel disease (IBD). We determined immunogenicity of a MenACWY-TT vaccine in JIA and IBD patients at adolescent age and compared results to data from aged-matched healthy controls (HCs).

Methods

We performed a prospective observational cohort study in JIA and IBD patients (14–18 years old), who received a MenACWY vaccination during a nationwide catch-up campaign (2018–2019) in the Netherlands. Primary aim was to compare MenACWY polysaccharide-specific serum IgG geometric mean concentrations (GMCs) in patients with HCs and secondary between patients with or without anti-TNF therapy. GMCs were determined before and 3–6, 12, and 24 months postvaccination and compared with data from HCs at baseline and 12 months postvaccination. Serum bactericidal antibody (SBA) titres were determined in a subset of patients at 12 months postvaccination.

Results

We included 226 JIA and IBD patients (66 % and 34 % respectively). GMCs were lower for MenA and MenW (GMC ratio 0.24 [0.17-0.34] and 0.16 [0.10-0.26] respectively, $p < 0.01$) in patients compared to HCs at 12 months postvaccination. Anti-TNF users had lower MenACWY GMCs postvaccination compared with those without anti-TNF ($p < 0.01$). The proportion protected (SBA ≥ 8) against MenW was reduced in anti-TNF users (76 % versus 92 % in non-anti-TNF and 100 % in HCs, $p < 0.01$).

Conclusion

The MenACWY conjugate vaccine was immunogenic in the vast majority of JIA and IBD patients at adolescent age, but seroprotection was lower in patients using anti-TNF agents. Therefore, an extra booster MenACWY vaccination should be considered.

Keywords: MenACWY vaccination, juvenile idiopathic arthritis, inflammatory bowel disease, adolescents, anti-TNF agents, immunocompromised, immunogenicity, safety, biologicals

INTRODUCTION

Paediatric patients with autoimmune inflammatory diseases are more susceptible for (a severe course of) infections, which is either caused by the disease itself and/or the use of immunosuppressive or immunomodulating medication[1]. Immunosuppressive/modulatory drugs are fundamental to suppress disease activity, but can lead to a compromised immune system. Juvenile idiopathic arthritis (JIA) is the most common rheumatic condition in children[2] and inflammatory bowel disease (IBD) is an important gastro-intestinal inflammatory disorder in the paediatric population[3]. Even though these disorders vary widely in clinical manifestation, tumour necrosis factor (TNF) plays an important role in the pathophysiology of these diseases and is a key target for therapy for both diseases[4].

Vaccination in immunocompromised patients is crucial to provide better protection against infections. Over the years, trials have proved that the risk of adverse events, such as disease flares, is limited and vaccinations are now advocated for (paediatric) patients with immune disorders[5,6]. Yet, vaccine immunogenicity was not always found to be as good as in healthy individuals, although data are conflicting[5]. Progress towards better treatment of many immune diseases was made with the introduction of biological disease modifying anti-rheumatic drugs (bDMARDs), of which anti-TNF agents are most commonly used. Next to improvement of therapy, bDMARDS as well as conventional synthetic DMARDS (csDMARDs) may impact the immune system in an unwanted way. Studies show that B-cell depleting therapies and high-dose glucocorticoids hamper the humoral response upon vaccination in children[7]. In addition, recent studies showed that children on TNF inhibitors generally have adequate immune responses upon vaccination but antibody levels were lower and tended to decline more rapidly compared with healthy controls[7,8].

Previously, meningococcal C (MenC) conjugate vaccination was shown to be immunogenic and safe in patients with JIA[9]. However, data on vaccine-induced antibody responses (including the effect of medication use) and safety in immunocompromised paediatric patients receiving a MenACWY vaccination is lacking. Due to an outbreak of serogroup W invasive meningococcal disease (IMD-W), the MenACWY vaccination was introduced in the national immunization programme (NIP) in the Netherlands for toddlers aged 14 months (replacing MenC conjugate vaccination at 14 months of age) in 2018 and adolescents 14 years of age (newly introduced) in 2020[10]. Furthermore, a catch-up campaign for all adolescents aged 14-18 years took place in 2018-2019. In order to assess immunogenicity of the MenACWY conjugate vaccine (MenACWY-TT, Nimenrix©) in adolescents with JIA or IBD, we conducted a prospective observational study in a cohort of adolescent patients 14-18 years of age. Vaccine responses – overall, as well as in relation to medication use – were measured in sera collected pre- and postvaccination, with a follow-up of two years.

Safety was evaluated by analysing the effect of meningococcal vaccination on disease activity and (serious) adverse events in patients.

METHODS

Study design and participants

The MenACWY vaccination was included in the NIP in the Netherlands since 2020 for adolescents aged 14 years, preceded by a nationwide catch-up campaign in 2018 –2019 for 14-18 year-olds[10]. An observational cohort study that started at the beginning of the campaign in 2018 was performed in adolescent patients with immune disorders (autoimmune inflammatory rheumatic diseases including JIA, IBD, SLE, MCTD, vasculitis, uveitis, immune deficiencies [cellular and humoral], 22q11 deletion syndrome, sickle cell disease or (functional) asplenia, and patients that underwent stem cell transplantation after bone marrow failure/aplasia). Patients were recruited from the Wilhelmina Children's Hospital of the University Medical Centre Utrecht. For the current study, we asked all JIA and IBD patients who were 14-18 years of age and eligible for vaccination during the campaign to participate. The adolescent patients with other immune disorders as mentioned hereabove will be described elsewhere. All participants received a single dose of MenACWY-TT (Nimenrix®) from the local public health centre. Written informed consent was obtained from participants and also their parents/guardians if the participant was under 16 years of age at time of enrolment. The Medical Research Ethics Committee Utrecht decided that the study was exempt from the Medical Research Involving Human Subjects Act (WMO) (local RIB protocol number 18/558/C). Clinical data and collection of blood samples occurred as part of routine follow-up visits with the clinician. Thus, blood samples were collected before, and at 3-6 months, 12 months (+/- 3 months) and 24 months (+/- 3 months) after vaccination. Serology results were compared with healthy control data (15 years of age) at baseline and 12 months postvaccination from a randomized controlled trial that was previously performed and published by the National Institute for Public Health and the Environment (RIVM)[11,12]. The reported drug therapy is the medication that was used at the time of vaccination.

Outcome measures

Serology

Meningococcal serogroup A, C, W and Y polysaccharide (PS)-specific serum IgG concentrations were determined by fluorescent bead-based multiplex immunoassay (MIA), as described previously[13]. The lower level of quantitation was set at 0.01 µg/mL. Functional antibodies were determined with the serum bactericidal antibody (SBA) assay in an arbitrarily chosen subset of sera (n = 97) at 12 months postvaccination, with

a titre ≥ 8 considered as the protective threshold (internationally-accepted correlate of protection)[14,15].

Safety

Safety was assessed by determining disease activity and patient's self-reported adverse events (interviewed by the clinician) after vaccination in all participants. Disease activity was assessed at every visit and measured in JIA patients with the clinical Juvenile Arthritis Disease Activity Score including 27 joints (cJADAS-27) with a range from 0 (low activity) to 47 (high activity)[16] and in IBD patients either by the weighted Paediatric Crohn's Disease Activity Index (wPCDAI)[17] or by the Paediatric Ulcerative Colitis Activity Index (PUCAI)[18]. Medication use was noted at each visit. All participants were asked at every visit for (serious) adverse events, which were registered if present.

Statistical analysis

Baseline and follow-up MenACWY-PS specific IgG concentrations were log-transformed prior to all statistical analyses and presented as GMCs with corresponding 95% confidence intervals (CI). GMCs of JIA and IBD patients were compared with data from aged-matched healthy controls (HCs) at baseline and 12 months postvaccination using the ANOVA test[11,12]. GMCs were compared between anti-TNF users, non-anti-TNF users (i.e. patients who did not use anti-TNF agents, regardless if other biologicals were used) and HCs at baseline and 12 months postvaccination using the ANOVA test. Post-hoc tests were performed using the t-test with Bonferroni correction. GMCs at 3-6 and 24 months postvaccination were compared between anti-TNF and non-anti-TNF users using the t-test. Also, pairwise comparisons of GMCs in anti-TNF and non-anti-TNF users per visit were performed to determine differences between timepoints using the t-test with Bonferroni correction. In order to study the independent effect of anti-TNF use on log-transformed MenACWY IgG concentrations postvaccination in IBD and JIA patients, we performed crude and adjusted linear mixed model analyses[19]. Variables adjusted for in the analyses were sex, disease, age at vaccination, baseline IgG concentration (constant variables), follow-up time and drug therapy (other than anti-TNF) (time-varying variables). The regression coefficient was exponentiated to obtain (adjusted) GMC ratios and 95% CIs for anti-TNF users versus non-anti-TNF users. For these analyses, we used a random intercept per patient and a random slope for the anti-TNF effect. Missing GMC data were handled by multiple imputation using chained equations[20]. All analyses were run for 20 imputed datasets and estimates were pooled using Rubin's rules. Furthermore, we decided a-priori to perform linear mixed model analyses to study the adjusted effect of follow-up time on MenACWY IgG concentrations postvaccination. In order to assess if this effect was different for anti-TNF and non-anti-TNF users, we added an interaction term between anti-TNF use and follow-up time to the regression models. We aimed to determine a cut-off for the PS-specific IgG concentrations using antibody data from patients and HCs. The threshold for

seroprotectivity was defined as the minimal IgG concentration for which 100% of the SBA titres 12 months postvaccination were protective (SBA ≥ 8) in the healthy controls.

Log-transformed SBA titres for the different serogroups at 12 months postvaccination were compared between anti-TNF users, non-anti-TNF users and healthy controls using the ANOVA test and post-hoc tests were performed using the t-test with Bonferroni correction. Proportions of participants with seroprotective SBA titres (SBA ≥ 8) were compared using Fisher's exact test and post-hoc tests were performed with Bonferroni correction.

An overall difference in disease activity score (cJADAS, PUCAI, wPCDAI) between study visits was tested with the Skillings-Mack test for unbalanced dependent samples[21]. Pairwise comparisons of disease activity scores per visit were performed using the Wilcoxon rank sum test with Bonferroni correction.

A p-value < 0.05 was considered statistically significant for all analyses. All analyses were performed using R version 4.0.3 and the mice and lme4 packages.

Role of the funding source

The funders of the study had no role in study design, data-collection, data analysis, data interpretation, or writing of the report.

RESULTS

Baseline characteristics

Between October 2018 and March 2020, 226 participants (59% female, 134/226) were included (Figure 1) with a median age of 15.7 years (Table 1). Among them, two-thirds of the patients was diagnosed with JIA (150/226, 66%) of which the main subgroups were oligo- and polyarthritis. One-third of the patients had IBD (76/226, 34%), with Crohn's disease as most common subtype. A total of 113 out of 226 patients (50%) used csDMARDs and 109 out of 226 (48.2%) used bDMARDs, mostly anti-TNF agents (89 out of 109).

Table 1. Study participant characteristics at baseline.

	Total patient cohort (n = 226)	**JIA (n = 150)**	**IBD (n = 76)**	**Healthy controls (n = 75)**
Female sex, n (%)	134 (59.3%)	95 (63.3%)	39 (51.3%)	36 (48%)
Age in years, median (IQR)	15.7 (14.3 – 17.3)	15.6 (14.1 – 17.3)	16.3 (14.9 – 16.7)	15.2 (14.9 – 15.5)
Medication use, n (%)				N/A
No immunosuppressive drugs/NSAIDs	61 (27.0%)	52 (34.7%)	9 (11.8%)	
Systemic corticosteroids	14 (6.2%)	4 (2.7%)	10 (13.2%)	
csDMARDs	113 (50.0%)	67 (44.7%)	46 (60.5%)	
MTX	54 (23.9%)	52 (34.7%)	2 (2.6%)	
AZA	39 (17.3%)	3 (2.0%)	36 (47.4%)	
SSZ	15 (6.6%)	0 (0.0%)	15 (19.7%)	
LEF	7 (3.1%)	7 (4.7%)	0 (0.0%)	
bDMARDs	109 (48.2%)	67 (44.7%)	42 (55.3%)	
Anti-TNF	89 (39.4%)	54 (36.0%)	35 (46.1%)	
Non-anti-TNF bDMARD	20 (8.8%)	13 (8.7%)	7 (9.2%)	
Anti-TNF + csDMARD	55 (24.3%)	36 (24.0%)	19 (25.0%)	
Disease, n (%)				N/A
JIA	150 (66.4%)	150 (100.0%)	N/A	
Persistent oligoarthritis	49 (21.7 %)	49 (32.7 %)		
Extended oligoarthritis	16 (7.1%)	16 (10.7%)		
Polyarthritis	47 (20.8%)	47 (31.3%)		
Systemic arthritis	14 (6.2%)	14 (9.3%)		
Enthesitis-related arthritis	11 (4.9%)	11 (7.3%)		
Psoriatic arthritis	8 (3.5%)	8 (5.3%)		
Other JIA	5 (2.2%)	5 (3.3%)		
IBD	76 (33.6%)	N/A	76 (100.0%)	
Crohn's disease	44 (19.5%)		44 (57.9%)	
Ulcerative colitis	21 (9.3%)		21 (27.6%)	
IBD-unclassified	11 (4.9%)		11 (14.5%)	

AZA = azathioprine; bDMARDS = biological disease modifying anti-rheumatic drugs; csDMARDS = conventional synthetic disease modifying anti-rheumatic drugs; IBD = inflammatory bowel disease; IQR = interquartile range; JIA = juvenile idiopathic arthritis; LEF = leflunomide; MTX = methotrexate; N/A = not applicable; NSAIDs = non-steroidal anti-inflammatory drugs; SSZ = sulfasalazine

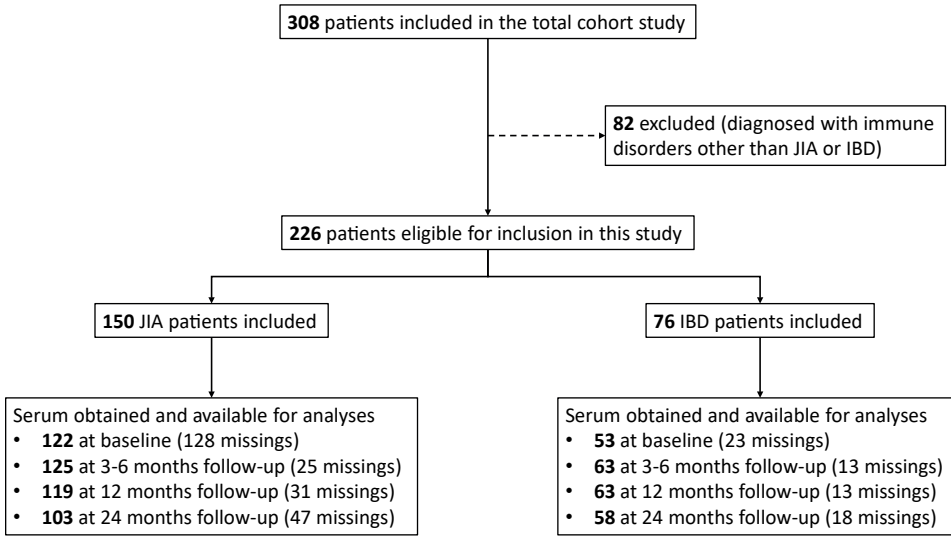


Figure 1. Flowchart of inclusion.

Meningococcal polysaccharide-specific IgG concentrations in JIA and IBD patients

GMCs of PS-specific IgG concentrations were below 0.5 µg/mL for all serogroups at baseline in patients, but notably higher for MenC compared to MenAWY which is presumably due to priming with MenC vaccination during childhood (Table 2). Compared with HCs, IgG PS-specific GMCs were significantly lower in patients for serogroup A and W (2.0 [1.6-2.4] and 0.7 [0.5-1.0] respectively versus 8.2 [6.5-10.4] and 4.5 [3.3-6.3] in HCs) at 12 months postvaccination and also at baseline (Table 2). GMCs did not differ between patients and HCs for serogroup C and Y at 12 months postvaccination. Three months after vaccination, GMCs significantly increased compared to baseline and the GMC for MenC was significantly higher than for MenAWY (data not shown). MenA and MenC antibodies waned over time between 3-6 months and 12 months postvaccination ($p < 0.01$), and between 3-6 months and 24 months postvaccination for all serogroups ($p < 0.01$).

Effect of anti-TNF agents on PS-specific IgG concentrations in JIA and IBD patients

Within the patient cohort, non-anti-TNF users were more often female (66%) while anti-TNF users were slightly more often male (52%) (Supplementary Table 1). No difference in systemic corticosteroid use was found between anti-TNF users and non-anti-TNF users. Among non-anti-TNF users, 42% used sDMARDS, 22% used methotrexate and 15% used bDMARDS other than anti-TNF. For all serogroups, significant differences in PS-specific IgG GMCs between anti-TNF users and non-anti-TNF users were already present 3-6 months postvaccination (Figure 2) and these differences persisted until 24 months postvaccination. Both the crude and adjusted effect of anti-TNF therapy at baseline on PS-specific IgG concentrations were statistically significant for all serogroups in the linear mixed model (Table 3). The GMC ratio between anti-TNF users and non-anti-TNF users was lowest for serogroup Y (0.19 [0.10-0.34]) and highest for serogroup A (0.50 [0.33-0.76]) in the adjusted analysis (Table 3), but also significant for serogroup C (0.47 [0.32-0.70]) and serogroup W (0.23 [0.14-0.39]). A difference in GMC between 12 and 24 months postvaccination was observed for serogroup C and W ($p < 0.01$) but not for A and Y in anti-TNF users.

Table 2. Geometric mean concentrations (95% CIs) of meningococcal serogroup A, C, W and Y (MenACWY) polysaccharide-specific IgG concentrations (µg/ml) for juvenile idiopathic arthritis (JIA) and inflammatory bowel disease (IBD) patients with and without anti-TNF use at baseline.

Time-point	Serogroup	HC	All patients	Anti-TNF	Non-anti-TNF	*P*-value			
						All patients vs. HC	Anti-TNF vs. HC[1]	Non-anti-TNF vs. HC[1]	Non-anti-TNF vs. anti-TNF[1]
Baseline		n = 75	n = 175	n = 80	n = 95				
	MenA	0.6 (0.5 – 0.8)[2]	0.1 (0.1 – 0.1)	0.1 (0.1 – 0.1)	0.1 (0.1 – 0.1)	<0.01*	<0.01*	<0.01*	1.00
	MenC	0.3 (0.2 – 0.5)	0.4 (0.3 – 0.6)	0.4 (0.3 – 0.6)	0.5 (0.3 – 0.7)	0.19	1.00	0.45	1.00
	MenW	0.2 (0.1 – 0.3)	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)	<0.01*	<0.01*	<0.01*	1.00
	MenY	0.1 (0.1 – 0.1)	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.1)	<0.01*	<0.01*	0.02*	1.00
3-6 months		n = 0	n = 188	n = 82	n = 106				
	MenA	-	3.6 (2.8 – 4.6)	1.8 (1.3 – 2.6)	6.2 (4.6 – 8.2)				<0.01*
	MenC	-	50.5 (40.0 – 63.8)	33.6 (22.6 – 49.9)	69.2 (52.8 – 90.7)				<0.01*
	MenW	-	0.7 (0.5 – 1.0)	0.2 (0.2 – 0.4)	1.6 (1.1 – 2.3)				<0.01*
	MenY	-	2.5 (1.8 – 3.5)	0.8 (0.5 – 1.3)	5.9 (4.2 – 8.5)				<0.01*
12 months		n = 75	n = 182	n = 76	n = 106				
	MenA	8.2 (6.5 – 10.4)	2.0 (1.6 – 2.4)	1.2 (0.9 – 1.6)	2.8 (2.2 – 3.6)	<0.01*	<0.01*	<0.01*	<0.01*
	MenC	16.9 (14.0 – 20.4)	14.8 (12.3 – 17.8)	9.2 (6.8 – 12.5)	20.8 (16.9 – 25.6)	0.32	<0.01*	0.64	<0.01*
	MenW	4.5 (3.3 – 6.3)	0.7 (0.5 – 1.0)	0.2 (0.1 – 0.3)	1.7 (1.3 – 2.4)	<0.01*	<0.01*	<0.01*	<0.01*
	MenY	2.5 (1.7 – 3.8)	1.5 (1.1 – 2.1)	0.4 (0.2 – 0.7)	3.9 (2.8 – 5.5)	0.05	<0.01*	0.41	<0.01*
24 months		n = 0	n = 161	n = 67	n = 94				
	MenA	-	1.0 (0.8 – 1.4)	0.6 (0.4 – 1.0)	1.5 (1.1 – 2.2)[2]				<0.01*
	MenC	-	7.7 (6.2 – 9.5)	4.3 (3.0 – 6.1)	11.6 (9.0 – 14.8)[2]				<0.01*
	MenW	-	0.4 (0.3 – 0.5)	0.1 (0.0 – 0.2)	1.0 (0.7 – 1.4)				<0.01*
	MenY	-	1.1 (0.8 – 1.5)	0.3 (0.2 – 0.5)	2.5 (1.7 – 3.7)				<0.01*

*$P < 0.05$

[1]*P*-values at baseline and 12 months were adjusted for multiple testing with Bonferroni correction

[2]one missing observation

HC = healthy controls

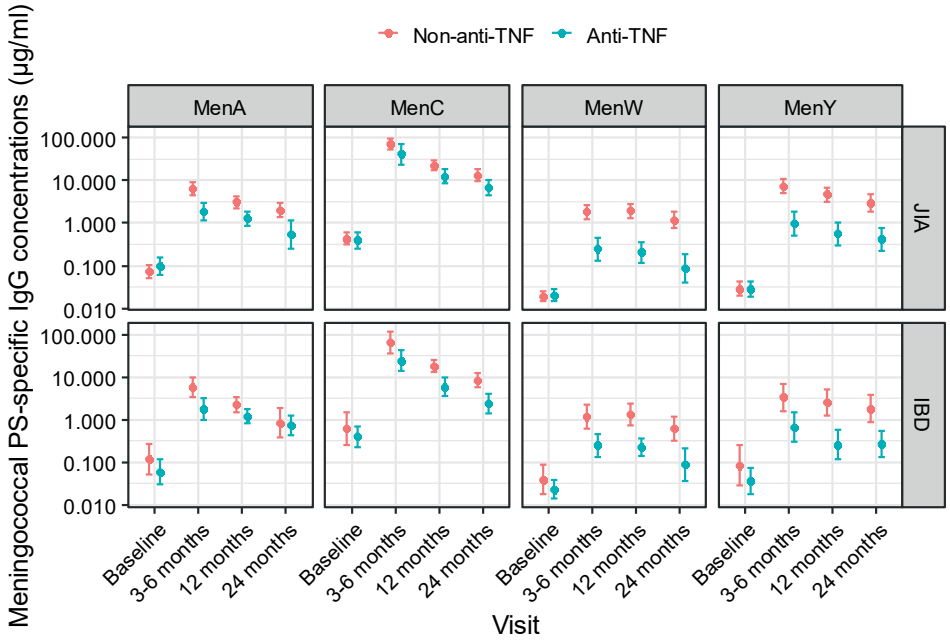


Figure 2. Meningococcal serogroup A, C, W and Y polysaccharide-specific serum IgG concentrations in anti-TNF users and non-anti-TNF users per disease cohort (in JIA and IBD patients) at baseline and during follow-up. Dots indicate geometric mean concentrations with 95% confidence intervals.
IBD = inflammatory bowel disease; JIA = juvenile idiopathic arthritis; PS = polysaccharide

Table 3. Linear mixed model analyses for the independent effect of anti-TNF use at baseline on log-transformed meningococcal IgG concentrations at all postvaccination timepoints for JIA and IBD patients.

Serogroup	Analysis	GMC ratio for anti-TNF users vs. non-anti-TNF users (95% CI)
MenA	Crude	0.44 (0.31 - 0.63)*
	Adjusted[1]	0.50 (0.33 - 0.76)*
MenC	Crude	0.50 (0.35 - 0.71)*
	Adjusted[1]	0.47 (0.32 - 0.70)*
MenW	Crude	0.17 (0.11 - 0.28)*
	Adjusted[1]	0.23 (0.14 - 0.39)*
MenY	Crude	0.14 (0.08 - 0.24)*
	Adjusted[1]	0.19 (0.10 - 0.34)*

GMC = geometric mean concentration
Missing values were handled by multiple imputation.
*statistically significant effect
[1]adjusted for sex, disease, age at vaccination, baseline IgG concentration (constant variables), follow-up time and immunosuppressive drug therapy other than anti-TNF (time-varying variables)

Functional antibodies at 12 months postvaccination

Serum samples from a random subset of n = 97 patients (of which 65 diagnosed with JIA and 32 diagnosed with IBD) collected at 12 months postvaccination were tested in the SBA assay. We compared three different groups: anti-TNF users, non-anti-TNF users and HCs. At baseline, SBA titres were low for all serogroups but higher in MenC compared to MenAWY, again presumably induced by a MenC vaccination at young age (Supplementary Table 2). The seroprotection rates (proportion with SBA titre ≥ 8) between patients using anti-TNF, patients not using anti-TNF and HCs were significantly different for MenW (76%, 92%, and 100% respectively, $p < 0.01$), but not for MenACY (Table 4). Furthermore, SBA GMTs at 12 months postvaccination were significantly lower ($p < 0.05$) for serogroup C and W in the anti-TNF group in comparison with the non-anti-TNF group (Supplementary Table 2). There were no significant differences in GMTs between the anti-TNF and non-anti-TNF group for serogroup A and Y. However, significant differences between GMTs were found for all serogroups when anti-TNF users were compared with HCs (data not shown). The lowest SBA GMT was observed for serogroup W, with a GMT of 188 (80-440) in the anti-TNF group, compared with 533 (304-934) in the non-anti-TNF group and 1546 (1257-1903) in HCs. We did not find a difference between boys and girls in the protected proportion of JIA and IBD patients (Supplementary Table 3). Because functional antibody titres did not correlate with PS-specific IgG concentrations except for serogroup C ($r = 0.88$, $p < 0.01$), a cut-off for IgG seroprotection could not be determined; not all children with a low SBA titre also showed a low IgG concentration, some had IgG concentrations above 0.5 or even 1.0 µg/mL (Figure 3).

Table 4. Frequency (%) of seroprotective SBA titres (≥ 8) 12 months postvaccination in JIA and IBD patients with and without anti-TNF use at baseline and in healthy 15 year-old controls (HC).

Serogroup	Non-anti-TNF (n = 52)	Anti-TNF (n = 45)	HC (n = 75)	*P*-value			
				Overall difference	Non-anti-TNF vs. anti-TNF[1]	Non-anti-TNF vs. HC[1]	Anti-TNF vs. HC[1]
MenA	50 (96%)	41 (91%)	74 (99%)	0.11	1.00	1.00	0.20
MenC	49 (94%)	44 (98%)	75 (100%)	0.06	1.00	0.20	1.00
MenW	48 (92%)	34 (76%)	74 (100%)[2]	<0.01*	0.08	0.08	<0.01*
MenY	49 (96%)[2]	43 (96%)	73 (97%)	0.88	1.00	1.00	1.00

*$P < 0.05$

[1]*P*-values were adjusted for multiple testing with Bonferroni correction

[2]one missing observation

Safety: disease activity and adverse events

No severe adverse events were reported during the study. Three patients reported an event of special interest during routine care at 3-6 months follow-up, which included worsening of alopecia areata, low serum adalimumab level, and sinusitis. All events were transient. No significant overall difference was observed in disease activity scores (wPCDAI, PUCAI and cJADAS) during follow-up and at 3-6 months postvaccination compared to baseline (data not shown).

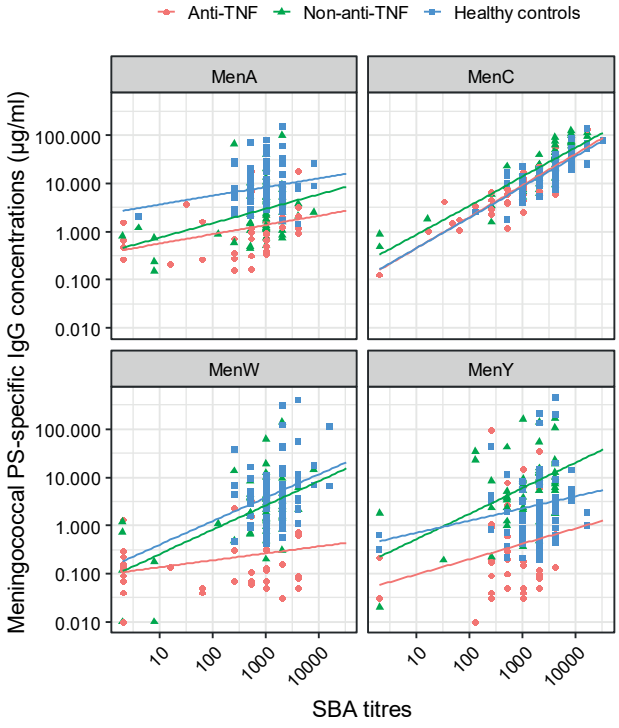


Figure 3. Plots of meningococcal serogroup A, C, W and Y polysaccharide-specific serum IgG concentrations versus serum bactericidal antibody (SBA) titres for participants with available data 12 months postvaccination. Coloured lines indicate linear trends.

DISCUSSION

In this study, we found that a single dose of meningococcal ACWY conjugate vaccine is immunogenic and in general elicited seroprotective antibody titres in adolescents diagnosed with JIA or IBD. However, the vaccine was less immunogenic in patients using anti-TNF agents compared with patients not using anti-TNF agents and compared with healthy controls. More specifically, one-fourth of the patients on anti-TNF did not have a protective functional antibody titre against serogroup W 12 months after vaccination. No severe adverse events or increase in disease activity was detected after vaccination.

The few studies reporting on the vaccine response in paediatric patients treated with bDMARDs are contradictory and not always in line with our results. In a recently published systematic literature review that assessed all available data on vaccines except for the COVID-19 vaccines, paediatric patients with autoimmune inflammatory rheumatic diseases did not have lower seroprotection rates when bDMARDS were used except for B-cell depleting therapies[7]. The only available reports on meningococcal vaccines found that MenC vaccination was safe and immunogenic in JIA patients[9], although an accelerated decline of antibodies was observed when biologicals were used[22]. Current guidelines recommend regular vaccinations according to the NIP[7], but recommendations on determination of seroprotection levels postvaccination, and consequently a booster vaccination in case of low antibody levels, are lacking.

TNF inhibitors suppress the response to TNF, a cytokine involved in immune and inflammatory responses such as proliferation and activation of T-cells, B-cells, macrophages, dendritic cells and NK cells[23]. Although the pathogenesis of some immune-mediated inflammatory diseases – including JIA and IBD - remains incompletely understood, an excessive production of proinflammatory cytokines including TNFα is involved and plays a crucial role in treatment. The immune response to a conjugate vaccine includes the activation of B- and T-cells that results in the production of antibodies and induction of a cellular memory response. TNF promotes the activation and proliferation of T-cells, both naïve and effector, and can thereby provide help to B-cells for antibody production. Anti-TNF may alter the T-cell dependent B-cell response, which is especially important in the polysaccharide-specific B-cell response that is induced by conjugate vaccines[24]. Furthermore, TNF induces dendritic cell maturation, which promotes an efficient antigen presentation[25]. CD40 and the CD40 ligand, which are important proteins in the carrier-peptide-specific T-cell response, have been reported to be down-regulated by anti-TNF agents in patients with Crohn's disease[24,26]. Future research should investigate how the recall response to an extra booster vaccination (while being treated with anti-TNF) is influenced.

In this study, most patients were primed with a MenC vaccination (vaccine uptake was around 95% in 2006-2008[27]) at the age of 14 months. The response to a new antigen differs from a recall response and secondary responses are less likely to be impaired by immunosuppressive therapy[28]. We indeed observed a higher GMC in MenC compared to the other serogroups in both patients with or without anti-TNF treatment. This probably predicts a promising booster response for the other three meningococcal serogroups as well - even when anti-TNF agents are used - which underlines the importance of a booster vaccination, especially in patients who did not respond (fully) to the primary vaccination. Since the MenC vaccination was replaced for a MenACWY vaccination in the Dutch NIP, future patients (the first children primed at the age of 14 months with MenACWY vaccination in 2019 will receive a booster at 14 years around the year 2032) will probably respond to all serogroups as a recall. Thus, an additional booster vaccination for these patients might become unnecessary by the time MenACWY-primed toddlers receive the MenACWY booster vaccination as an adolescent.

One year postvaccination, a quarter of the patients using anti-TNF was not protected against MenW in this study and we expect that this proportion will further increase over time. We found that vaccine-induced PS-specific serum IgG concentrations were unreliable as cut-off for seroprotection as measured by SBA, as not all children with a low SBA titre also showed a low IgG concentration, some even had IgG concentrations above 0.5 or even 1.0 µg/mL. The functionality of the antibodies next to serum components as complement proteins (as reflected by the SBA) involves not only PS-specific IgG, but also other antibodies not restricted to the capsule and also for example IgM. Children that have a low SBA titre despite adequate PS-specific IgG concentrations may therefore actually benefit from an extra booster vaccination. Thus, PS-specific IgG concentrations were unreliable to use as a cut-off, which hampers individual-based advice on a booster vaccination for each patient by physicians. The SBA assay is however an expensive and time-consuming assay, and only validated for research purposes. Since the antibody decay, rather than hyporesponsiveness to the initial vaccination, might play a role in the reduced protection induced by vaccination[22], a booster vaccination should be considered. Usually, a two-dose schedule or a vaccination 3-5 years after the primary vaccination is advised in risk groups. A two-dose schedule may induce a good initial vaccine response, but does not necessarily lead to a longer duration of protection[29]. A booster could provide this, but earlier boosting (earlier than after 3-5 years) is required to provide protection for at least one-fourth of the patients that would otherwise be unprotected during the period in life in which an individual has high risk of contracting the meningococcal bacterium. For the clinical practice, therefore, we propose that an extra MenACWY vaccination should be considered for all adolescents treated with anti-TNF, regardless of IgG concentration, one year after the regular vaccination.

While safety has not been investigated before in immunocompromised adolescents receiving a MenACWY vaccination, for MenC vaccination safety was proved to be assured and no adverse events were reported[9]. We did not find altered disease activity three months after MenACWY vaccination in JIA and IBD patients and no safety issues were reported in patients using immunosuppressive/modulating agents. This is in line with what was found for other vaccines[30].

Our study comes with limitations, especially because we performed an observational cohort study. Serum sampling depended on routine visits with the clinician and the COVID-19 pandemic has led to dropouts during follow-up. Furthermore, the age of vaccination in this study was 14-18 years, while currently in the NIP adolescents receive MenACWY vaccination at 14 years. Therefore, we might have overestimated the vaccine response since this may increase with age[12].

Strengths of the study were that we assessed functional antibody activity (SBA assay) – next to IgG concentrations – to actually assess seroprotection rates. We were able to take into account medical data including disease activity and medication use such as anti-TNF agents. We prospectively followed-up on patients for 24 months and could therefore optimize the recommendations for a possible booster vaccination. Furthermore, we investigated both differences between anti-TNF users and non-anti-TNF users as well as the difference between healthy adolescents and patients (with or without medication use) by including healthy age-matched control data. In addition, we performed analyses to adjust for dependent measurements within patients over time and factors that could have led to confounding, which is a frequent problem in observational studies. We encourage that our results are validated in another prospective cohort.

In conclusion, vaccination of immunocompromised adolescents with a MenACWY conjugate vaccine was immunogenic, but patients using anti-TNF agents demonstrated lower antibody concentrations for all serogroups and even reduced seroprotection rates for MenW. An extra booster vaccination in those adolescents should be considered, which we would now advise one year after the regular adolescent vaccination at the age of 14 years. Future research should evaluate the effect and optimal timing of a booster vaccination.

ACKNOWLEDGEMENTS

We thank all adolescents who participated in the study. Furthermore, we thank Debbie van Rooijen for her help with laboratory measurements.

FUNDING

This study was funded by the UMC Utrecht and the Ministry of Health, Welfare and Sport. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Study participant baseline characteristics in anti-TNF users and non-anti-TNF users.

	Non-anti-TNF (n = 137)	**Anti-TNF (n = 89)**
Female sex, n (%)	91 (66.4%)	43 (48.3%)
Age in years, median (IQR)	15.9 (14.4 - 17.3)	15.7 (13.9 - 16.8)
Medication use, n (%)		
No immunosuppressive drugs/NSAIDs	61 (44.5%)	0 (0.0%)
Systemic corticosteroids	7 (5.1%)	7 (7.9%)
csDMARDs	58 (42.3%)	55 (61.8%)
MTX	30 (21.9%)	24 (27.0%)
AZA	20 (14.6%)	19 (21.3%)
SSZ	9 (6.6%)	6 (6.7%)
LEF	1 (0.7%)	6 (6.7%)
bDMARDs	20 (14.6%)	89 (100.0%)
Anti-TNF	0 (0.0%)	89 (100.0%)
Non-anti-TNF bDMARD	20 (14.6%)	0 (0.0%)
Anti-TNF + sDMARD	0 (0.0%)	55 (61.8%)
Disease, n (%)		
JIA	96 (70.1%)	54 (60.7%)
Persistent oligoarthritis	32 (23.4%)	17 (19.1%)
Extended oligoarthritis	7 (5.1%)	9 (10.1%)
Polyarthritis	28 (20.4%)	19 (21.3%)
Systemic arthritis	14 (10.2%)	0 (0.0%)
Enthesitis-related arthritis	7 (5.1%)	4 (4.5%)
Psoriatic arthritis	5 (3.6%)	3 (3.4%)
Other JIA	3 (2.2%)	2 (2.2%)
IBD	41 (29.9%)	35 (39.3%)
Crohn's disease	22 (16.1%)	22 (24.7%)
Ulcerative colitis	12 (8.8%)	9 (10.1%)
IBD-unclassified	7 (5.1%)	4 (4.5%)

AZA = azathioprine; bDMARDS = biological disease modifying anti-rheumatic drugs; csDMARDS = conventional synthetic disease modifying anti-rheumatic drugs; IBD = inflammatory bowel disease; IQR = interquartile range; JIA = juvenile idiopathic arthritis; LEF = leflunomide; MTX = methotrexate; NSAIDs = non-steroidal anti-inflammatory drugs; SSZ = sulfasalazine

Supplementary Table 2. Geometric mean titres (95% CI) of meningococcal serogroup A, C, W and Y (MenACWY) serum bactericidal antibody (SBA) results per serogroup 12 months postvaccination for juvenile idiopathic arthritis (JIA) and inflammatory bowel disease (IBD) patients with and without anti-TNF use at baseline and healthy aged-matched controls (HC).

Serogroup	No anti-TNF (n = 52)	Anti-TNF (n = 45)	HC (n = 75)	P-value			
				Overall	No anti-TNF vs. anti-TNF[1]	No anti-TNF vs. HC[1]	Anti-TNF vs. HC[1]
MenA	625 (385 – 1015)	413 (222 – 768)	875 (687 – 1115)	0.04*	0.60	0.72	0.04*
MenC	1611 (911 – 2850)	671 (406 – 1111)	2964 (2340 – 3755)	<0.01*	0.02*	0.10	<0.01*
MenW	533 (304 – 934)	188 (80 – 440)	1546 (1257 – 1903)[2]	<0.01*	0.03*	<0.01*	<0.01*
MenY	983 (611 – 1581)[2]	708 (442 – 1133)	1611 (1154 – 2247)	0.02*	0.91	0.25	0.02*

*$P < 0.05$

[1]*P*-values were adjusted for multiple testing with Bonferroni correction

[2]one missing observation

Supplementary Table 3. Frequency (%) of seroprotective meningococcal serogroup A, C, W and Y (MenACWY) serum bactericidal antibody (SBA) titres (≥ 8) 12 months postvaccination in male and female juvenile idiopathic arthritis (JIA) and inflammatory bowel disease (IBD) patients.

Serogroup	Girls (n = 60)	Boys (n = 37)	P-value
MenA	55 (91.7%)	36 (97.3%)	0.40
MenC	56 (93.3%)	37 (100.0%)	0.29
MenW	51 (85.0%)	31 (83.8%)	1.00
MenY	57[1] (96.6%)	35 (94.6%)	0.64

[1]one missing observation

CHAPTER 12

12

Testing an increased visit interval scheme using web-based self-monitoring in patients with juvenile idiopathic arthritis: protocol and interim results of the THUIS study

Joeri W. van Straalen[1,2], Gerrie C.J. de Joode-Smink[1,2], Martijn J.H. Doeleman[1,2], Marc H.A. Jansen[1,2], Erika van Nieuwenhove[1,2], Annet van Royen-Kerkhof[1,2], Bas J. Vastert[1,2], Nico M. Wulffraat[1,2], Joost F. Swart[1,2*] and Sytze de Roock[1,2*]

[1]Department of Paediatric Immunology and Rheumatology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, the Netherlands
[2]Faculty of Medicine, Utrecht University, Utrecht, the Netherlands

**Joost F. Swart and Sytze de Roock contributed equally*

ABSTRACT

Background

Children with juvenile idiopathic arthritis (JIA) commonly visit their paediatric rheumatologist every three months. This is time consuming and expensive for the patient, their parents or guardian, the hospital and other stakeholders. The THUIS study aims to demonstrate that JIA patients with inactive disease can safely increase their visit interval by home-monitoring disease activity using the EuroQol five-dimensional youth questionnaire with five levels (EQ-5D-Y-5L) and Juvenile Arthritis Multidimensional Assessment Report (JAMAR).

Methods

JIA patients with inactive disease from the Wilhelmina Children's Hospital in Utrecht, the Netherlands, will skip one three-monthly control visit and instead complete an online EQ-5D-Y-5L and JAMAR questionnaire at home. The home-monitoring results will be evaluated by a research nurse in order to determine if the patient can safely remain at home or if a short-term control visit at the hospital has to be scheduled. Clinical Juvenile Arthritis Disease Activity scores (cJADAS) after six months will be compared with a historical cohort of matched JIA patients in order to prove non-inferiority. Secondary outcomes are adverse events during follow-up, patient satisfaction with home-monitoring, the number of reminders sent for home-monitoring and the number of patients that fail to home-monitor.

Discussion

As of 17 October 2022, 76 patients have been recruited, of which 55 have completed home-monitoring and 11 have been followed-up after six months. Preliminary results indicate that home-monitoring using web-based questionnaires is a feasible and much appreciated method of tracking disease activity in JIA patients. Final results of the THUIS study might also be relevant for other chronic paediatric diseases.

Keywords: juvenile idiopathic arthritis, remote monitoring, e-health, patient-reported outcomes, disease activity, healthcare costs

Trial registration

The THUIS study is registered at ClinicalTrials.gov (NCT05603286).

BACKGROUND

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood and may cause severe disability and a reduced quality of life[1–3]. Treatment includes immunosuppressive drugs for reducing arthritis, which are commonly prescribed in a step-up approach[4–6]. Following a treat-to-target strategy, the main aim of JIA treatment is to achieve and sustain inactive disease, or at least minimal levels of disease activity[7]. A commonly used disease activity measure in the treat-to-target approach to treating JIA is the clinical Juvenile Arthritis Disease Activity (cJADAS) score[8,9], which takes into account the number of joints with active arthritis, a physician global assessment of disease activity, and a patient or parent assessment of well-being. Due to therapeutic advances in the last three decades, such as the availability of biologicals, inactive disease has become a realistic goal for most children with JIA[10].

At the Wilhelmina Children's Hospital in Utrecht, the Netherlands, JIA patients commonly visit their paediatric rheumatologist every three months for monitoring disease activity and medication-related side effects. Occasionally, patients with inactive disease have less frequent visits. Control visit intervals also had to be increased during the peak of the COVID-19 pandemic. Systematically increasing the visit interval of JIA patients with inactive disease might be safely facilitated by remote self-monitoring of disease activity using patient-reported outcomes. A recent study reported that four JIA-specific parent/child-reported outcome measures for disease activity showed good criterion validity and excellent reliability and thus can be considered for remote patient assessment[11]. Another study demonstrated that moderate to high disease activity in JIA patients could be identified well by remote self-monitoring with the EuroQol five-dimensional youth questionnaire with five levels (EQ-5D-Y-5L)[12].

Here, we present the methodology and interim results of the "Testing an increased visit interval scheme using web-based self-evaluation" (THUIS) study. The THUIS (acronym for "home" in Dutch) study aims to demonstrate that JIA patients with inactive disease can safely skip a hospital visit by self-monitoring disease activity using both the EQ-5D-Y-5L and Juvenile Arthritis Multidimensional Assessment Report (JAMAR) questionnaires, saving time and costs for both patients, parents or guardians, physicians and other stakeholders.

METHODS

Objectives

Primary objective

To investigate if the time interval in between hospital control visits can be safely increased in JIA patients with inactive disease by home-monitoring disease activity using online EQ-5D-Y-5L and JAMAR questionnaires.

Secondary objectives

- To investigate the relationship between EQ-5D-Y-5L and JAMAR answers and disease activity at follow-up three months later.
- To validate EQ-5D-and EQ-VAS-score cut-offs as indicators of disease activity.
- To investigate how JIA patients experienced online home-monitoring as an alternative for visiting the hospital.
- To investigate how often patients need to be reminded or fail to home-monitor.

Outcomes

Primary endpoint

The number of disease flares six months after baseline visit. A disease flare was defined as a cJADAS score of >3[13].

Secondary endpoints

- The number of rescheduled visits due to presumed disease worsening.
- The number of disease flares observed at rescheduled visits.
- The number and type of adverse events (AEs) reported during follow-up of home-monitoring patients.
- Patient satisfaction with home-monitoring, measured using a separate five-item questionnaire.
- The number of reminders for home-monitoring sent to patients.
- The number of patients that fail to home-monitor or withdraw from the study. The former is defined as the number of patients that do not complete a EQ-5D-Y-5L and JAMAR questionnaire for home-monitoring, even after two reminders.

Study participants

Inclusion criteria

- JIA diagnosis of ≥1 year (all subtypes can be included).
- Inactive disease (defined as a cJADAS of ≤3).
- Age 6-20 years.

Exclusion criteria

- Insufficient mastering of the Dutch language.
- Not able or willing to use e-mail.

Study design

This trial has a non-inferiority design in which an intervention cohort of 85 JIA patients will be compared to a historical cohort of 85 JIA patients. Participants in the intervention cohort and data of historical controls will be included from the Paediatric Immunology and Rheumatology department of the Wilhelmina Children's Hospital, a tertiary care centre. At baseline, which is a regular control visit, the treating paediatric rheumatologist will determine if a patient who meets the inclusion criteria can participate in the THUIS study. Possible reasons which could make participation not possible include a disease flare, tapering or stopping treatment, not being capable of self-monitoring or not feeling comfortable with skipping a hospital visit. After inclusion, participants are supposed to skip one regular three-monthly control visit and instead complete an online EQ-5D-Y-5L and JAMAR questionnaire. This can be completed together with a parent or guardian, if needed. Questionnaires will be send to the participants or a parent or guardian 11 weeks after the baseline visit via e-mail using Castor EDC (Electronic Data Capture) software[14]. Completed questionnaires will be evaluated by an experienced research nurse who is part of the study and paediatric rheumatology care team. Evaluation will be done in consultation with the treating paediatric rheumatologist if needed. In case there is a suspicion of disease worsening based on the home-monitoring results, the participant will be called via telephone for additional questions and if needed rescheduled for a control visit as soon as possible. In case no suspicion of disease worsening arises, the participant will be followed-up at the hospital six months (range 5-7) after the baseline visit. Patients who wish to visit the hospital anytime sooner can always contact their treating physician to do so. Patients who fail to home-monitor after two reminders (via e-mail and telephone) or who withdraw from the study will be excluded from the main analysis and replaced by new participants until follow-up results are available for 85 participants. During the study, participants will take their prescribed medication as usual. Since it is not possible to provide patients with biological (b-) disease-modifying antirheumatic drug (DMARD) therapy for longer than three months, we will send these drugs to patients who live ≥30 kilometres away from the hospital by cooled transport three months after the baseline visit. Patients who live <30 kilometres away from the hospital and are using biologicals can pick up their medication after three months at the hospital at any time they prefer. If indicated by the paediatric rheumatologist, a blood sample will be collected from participants in their local area (mostly at their general practitioner office) three months after inclusion such that blood test results for monitoring drug toxicity can be send to the study team.

Data collection

Three months after inclusion (range: 11-14 weeks), participants in the intervention cohort will complete an online version of the EQ-5D-Y-5L and JAMAR questionnaire from home. The EQ-5D-Y-5L is the youth version of the EQ-5D-5L questionnaire, which measures health using five Likert scale items (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a vertical visual analogue scale (VAS)[15]. Higher scores for the Likert scale items (range 1-5) indicate worse health. Higher scores for the VAS (range 0-100) indicate better health. The JAMAR has been developed specifically for the assessment of JIA patients and includes 15 parent or patient-centred items including functional status, pain, disease activity, quality of life, well-being and satisfaction with current disease status[16]. All JIA patients who are treated in the Wilhelmina Children's Hospital already fill in a JAMAR questionnaire shortly before each regular control visit. Physical function is captured in the JAMAR by the Juvenile Arthritis Functionality Scale (JAFS) lower limbs, hand and wrist and upper segment components. Each component consists of five items with a four-point Likert scale (range 0-3), where higher scores indicate a higher degree of disability. Pain, disease activity and well-being are captured in the JAMAR using a horizontal 21-numbered circle VAS (range 0-10) with higher scores indicating a worse valuation. Quality of life is captured in the JAMAR using the paediatric rheumatology quality of life scale (JQL) physical and psychosocial health components. Both of these components consist of five items with a four-point Likert scale (range 0-3), where higher scores indicate worse quality of life. At intended follow-up (5-7 months after inclusion), and after skipping one three-monthly control visit, the paediatric rheumatologist will record a cJADAS and possible AEs. Furthermore, participants will complete a short five-item questionnaire to indicate their satisfaction with home-monitoring.

Statistical analysis

The number of disease flares at follow-up in the intervention cohort will be compared to the number of disease flares in a historical cohort of matched JIA patients. Patients will be matched 1:1 on age (in years), disease duration (in years), gender, drug therapy and JIA subtype. As calculated from data from the Wilhelmina Children's Hospital between January 2015 and May 2019, a disease flare was observed in 14% of the visits after a JIA patient had had inactive disease, regardless of the visit interval. The maximal acceptable proportion of flares in the intervention cohort is set to 15% more than the historical cohort, which comes down to a relative risk of approximately two. Therefore, the 95% confidence interval upper limit of the relative risk for experiencing a disease flare in the intervention cohort compared to the historical cohort should not exceed two in order to prove non-inferiority. The total sample size of 170 patients will give the study a statistical power of 80% to establish non-inferiority for a margin of 15% more disease flares in the intervention cohort compared to the historical cohort. This margin was considered clinically relevant based on expert consensus from paediatric rheumatologists of the Wilhelmina Children's Hospital and takes into account that a disease flare can be the result of changes in multiple

parameters, does not directly lead to joint damage and at times even goes unnoticed by the patient. The sample size was calculated using the "SampleSize4ClinicalTrials" package in R version 3.6.2[17]. Previously reported EQ-5D and EQ-VAS score cut-offs as indicators of moderate to high disease activity (cJADAS >1.5 and >2.5 for oligoarthritis and polyarthritis, respectively)[12] will be validated by calculating their diagnostic values (accuracy, sensitivity, specificity, positive predictive value, negative predictive value and corresponding 95% confidence intervals) in the THUIS study. The remaining secondary outcomes will be analysed using descriptive statistics.

PRELIMINARY RESULTS

Characteristics of included patients

As of 17 October 2022, a total of 76 JIA patients with a median disease duration of 6.2 years had been enrolled in the THUIS study intervention cohort. Six eligible patients (7%) had refused to participate (Figure 1). The majority of included patients were girls and the most common subtype was oligoarticular JIA (Table 1). At inclusion, no medication or NSAID was used by 39% of the patients, synthetic DMARD (sDMARD) therapy without biological was used by 17%, bDMARD monotherapy was used by 21%, and sDMARD and bDMARD combination therapy was used by 22%.

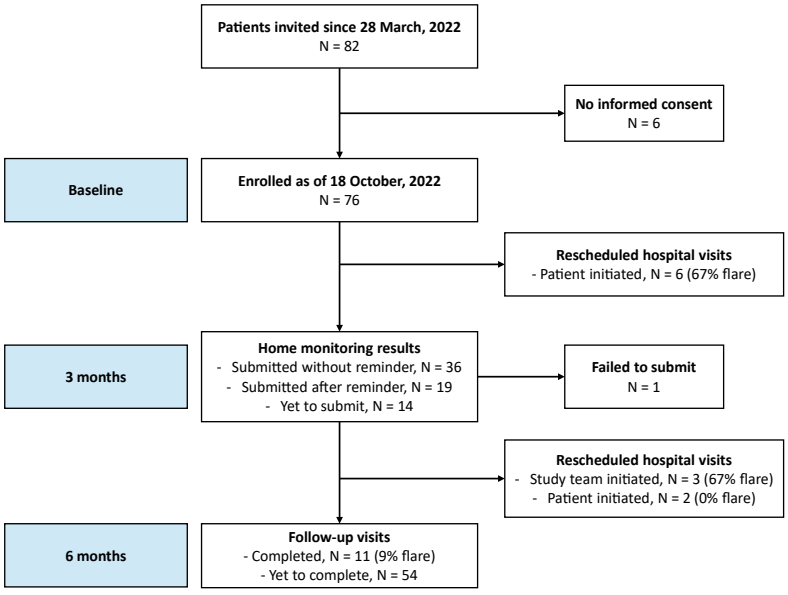

Figure 1. Flowchart of patients in the THUIS study intervention cohort as of 18 October, 2022.

Table 1. Characteristics of patients in the THUIS study intervention cohort at enrolment.

Characteristics at enrolment	Enrolled patients (n = 76)
Age in years, median (IQR)	13.9 (11.8 – 16.7)
Girls, n (%)	48 (63.2%)
JIA subtype, n (%)	
Oligoarthritis	38 (50.0%)
RF- polyarthritis	11 (14.5%)
Psoriatic arthritis	10 (13.2%)
Enthesitis-related arthritis	8 (10.5%)
Systemic arthritis	6 (7.9%)
RF+ polyarthritis	2 (2.6%)
Undifferentiated arthritis	1 (1.3%)
Disease duration in years, median (IQR)	6.2 (3.2 – 10.6)
Medication use, n (%)	
No medication/NSAID	30 (39.5%)
sDMARD therapy	13 (17.1%)
Methotrexate	8 (10.5%)
Leflunomide	2 (2.6%)
Tofacitinib	2 (2.6%)
Tofacitinib + methotrexate	1 (1.3%)
bDMARD monotherapy	16 (21.1%)
Adalimumab	2 (2.6%)
Golimumab	5 (6.6%)
Tocilizumab	5 (6.6%)
Canakinumab	1 (1.3%)
Etanercept	3 (3.9%)
bDMARD combination therapy	17 (22.4%)
Adalimumab + methotrexate	14 (18.4%)
Adalimumab + leflunomide	1 (1.3%)
Adalimumab + mycophenolate mofetil	1 (1.3%)
Abatacept + methotrexate	1 (1.3%)
Disease activity, median (IQR)	
VAS well-being	0 (0 – 1)
Physician global assessment	0 (0 – 0)
Active joint count	0 (0 – 0)
cJADAS score	0 (0 – 1)
Previous visit ≥6 months ago, n (%)	28 (36.8%)

bDMARD: biological disease-modifying antirheumatic drug, cJADAS: clinical Juvenile Arthritis Disease Activity Score, IQR: interquartile range, JIA: juvenile idiopathic arthritis, n: number, NSAID: non-steroidal anti-inflammatory drugs, RF: rheumatoid factor, sDMARD: synthetic disease-modifying antirheumatic drug, VAS: visual analogue scale

Home-monitoring and follow-up results

Thus far, 55 patients had submitted home-monitoring results after three months and one patient failed to home-monitor (i.e. did not submit home-monitoring results, even after two reminders). Nineteen patients (34%) had to be reminded via e-mail or telephone to complete a questionnaire for home-monitoring. Eight patients had requested to reschedule a hospital visit themselves, of which six patients did so before home-monitoring (67% flare rate) and two patients thereafter (0% flare rate). The study team rescheduled another three hospital visits based on home-monitoring results (67% flare rate). In this group, all three patients had reported painful or swollen joints, a slightly worsened illness compared to the baseline visit and that they were not satisfied with their current symptom state (Table 2). Full home-monitoring results are provided in Supplementary Table 1. Eleven patients had completed a hospital visit after six months (9% flare rate). Of all patients who developed a flare after inclusion (n = 7), four (57%) used no medication at baseline or NSAIDs only, one (14%) used tofacitinib monotherapy, one (14%) used golimumab monotherapy and one (14%) used etanercept monotherapy.

Table 2. JAMAR and EQ-5D-Y-5L home-monitoring results at 3 months follow-up (shortened).

Question	No rescheduled visit by study team (n = 52)	Rescheduled visit by study team (n = 3)
EQ-5D-Y-5L questionnaire		
Problem of mobility, n (%)	7 (13.5%)	2 (66.7%)
Problem of self-care, n (%)	4 (7.7%)	0 (0.0%)
Problem of usual activity, n (%)	11 (21.2%)	2 (66.7%)
Problem of pain/discomfort, n (%)	15 (28.8%)	3 (100.0%)
Problem of anxiety/depression, n (%)	8 (15.4%)	0 (0.0%)
VAS health, median (IQR)	91.5 (80.0 – 100.0)	82.0 (73.5 – 84.0)
JAMAR questionnaire		
JAFS lower limbs score, median (IQR)	0 (0 – 1)	1 (1 – 2)
JAFS hand and wrist score, median (IQR)	0 (0 – 0)	0 (0 – 1)
JAFS upper segment score, median (IQR)	0 (0 – 0)	0 (0 – 2)
VAS pain, median (IQR)	0.3 (0.0 – 1.5)	3.0 (2.5 – 5.3)
Painful or swollen joint(s), n %)	8 (15.4%)	3 (100.0%)
Morning stiffness, n (%)	8 (15.4%)	2 (66.7%)
Fever, n %)	0 (0.0%)	0 (0.0%)
Skin rash, n (%)	1 (1.9%)	0 (0.0%)
VAS disease activity, median (IQR)	0.0 (0.0 – 1.0)	2.5 (2.5 – 4.8)
State of illness, n (%)		
Remission	42 (80.8%)	0 (0.0%)
Persistent activity	6 (11.5%)	1 (33.3%)

Table 2. Continued

Question	No rescheduled visit by study team (n = 52)	Rescheduled visit by study team (n = 3)
Relapse	4 (7.7%)	2 (66.7%)
Course of illness, n (%)		
Much improved	5 (9.6%)	0 (0.0%)
Slightly improved	4 (7.7%)	0 (0.0%)
Stable/unchanged	40 (76.9%)	0 (0.0%)
Slightly worsened	3 (5.8%)	3 (100.0%)
Much worsened	0 (0.0%)	0 (0.0%)
Taking medication, n (%)	31 (59.6%)	2 (66.7%)
Adverse events from medication, n (%)	4 (7.7%)	0 (0.0%)
Attending school, n (%)	51 (98.1%)	3 (100.0%)
Problems at school, n (%)	7 (13.7%)	0 (0.0%)
JQL physical health score, median (IQR)	1 (0 – 3)	3 (2 – 5)
JQL psychosocial health score, median (IQR)	0 (0 – 2)	2 (1 – 3)
VAS well-being, median (IQR)	0.5 (0.0 – 1.6)	2.0 (1.5 – 2.5)
Satisfied with current symptom state, n (%)	47 (90.4%)	0 (0.0%)

EQ-5D-Y-5L : EuroQol five-dimensional 'youth' questionnaire with five levels, IQR: interquartile range, JAFS: Juvenile Arthritis Functionality Scale, JAMAR: Juvenile Arthritis Multidimensional Assessment Report, JQL: paediatric rheumatology quality of life scale, n: number, VAS: visual analogue scale

During follow-up, one patient suffered from a cold with coughing due to COVID-19 infection. This mild AE was transient. No other AEs were reported. No paediatric rheumatologist requested blood test results for monitoring drug toxicity. Nine participants completed a patient satisfaction questionnaire and all indicated they would like to skip a hospital control visit more often using home-monitoring (Table 3).

Table 3. Results of patients satisfaction questionnaires at 6 months follow-up visit (n = 9).

Question	Results (n, %)
1. How easy was it for you to complete the questionnaires from home?	
Very easy	3 (33.3%)
Easy	6 (66.7%)
Neutral	0 (0.0%)
Difficult	0 (0.0%)
Very difficult	0 (0.0%)
2. How safe did you feel during the study?	
Very safe	5 (55.6%)
Safe	4 (44.4%)
Neutral	0 (0.0%)
Unsafe	0 (0.0%)
Very unsafe	0 (0.0%)
3. How satisfied are you about home-monitoring?	
Very satisfied	5 (55.6%)
Satisfied	3 (33.3%)
Neutral	1 (11.1%)
Unsatisfied	0 (0.0%)
Very unsatisfied	0 (0.0%)
4. Would you like to skip a hospital visit using home-monitoring more often?	
Yes	9 (100.0%)
No	0 (0.0%)

DISCUSSION

From the current preliminary THUIS study results we can already draw some conclusions. In general, most JIA patients do like to skip a hospital visit by home-monitoring, as reflected by the high proportion of eligible patients that wanted to participate and the results of the already completed patient satisfaction questionnaires. Furthermore, almost no patients fail to home-monitor, although some need to be reminded to do so. So far, 9% of all included patients had experienced a flare during the study. This number is lower than the proportion of flares observed after a JIA patient had had inactive disease between January 2015 and May 2019 (14%), which was used in our sample size calculation.

JIA typically requires long-lasting complex care which poses a considerable economic burden on patients, parents/caregivers, health care providers and insurance companies[18–20]. Remote monitoring of children with chronic disease has the potential of reducing these costs as a result of a decrease in hospital visits[21]. This will also remove part of the burden

on paediatric rheumatology units, especially in areas with few available paediatric rheumatologists. As a consequence, patients with acute problems can be scheduled for a control visit more quickly. Most importantly, patients who can safely home-monitor themselves will miss less days of school and their parents or guardians will miss less days of work, benefiting society in general.

The expected risk of any articular or extra-articular damage while skipping a hospital visit in the THUIS study is negligible due to several measures. First of all, only patients with inactive disease are being included. This group of patients is the least likely to develop damage within the six months of our study. Second, an increase in disease activity (underlying the damage) will likely be reflected in the home-monitoring results and thus timely observed by the study team, as one previous study already demonstrated that self-assessment with the EQ-5D-Y-5L can distinguish between inactive disease and moderate to high disease activity with high discriminatory power[12]. Third, patients can always call their treating physician and reschedule a control visit if they feel this is necessary or that signals have not been picked up (yet) via the web-based questionnaires. Fourth, patients that fail to monitor themselves will be contacted by the study team and have a rescheduled 3-month visit if deemed necessary.

Nevertheless, some prior knowledge about the patient is desirable for assessing home-monitoring results since JIA patients and their parents can have the tendency to over- or underestimate their health status[22]. Since there could be several and specific reasons for which a home-monitoring patient might need to be rescheduled for a control visit as soon as possible, we believe that no single automated score for the patient-reported outcomes can or should be used. Rather, the home-monitoring results should be carefully assessed on a case by case basis, preferably by a health professional who knows the specific patient to some extent. Nevertheless, it would be interesting to study the diagnostic value of a combination of home-monitoring questions once the THUIS study has been completed. Such a combined score could be useful for pre-screening patients that might need to be rescheduled. As previously reported, the evaluation of pain and level of disease activity, the assessment of morning stiffness duration, and an active joint count for proxy/self-assessment are promising outcome measures for remote patient monitoring of disease activity[11]. These measures are also captured in the THUIS study, and therefore it is possible to study their (combined) diagnostic value in actual home-monitoring patients once data collection is completed.

The final results of this study might also be promising for the care of patients with chronic diseases other than JIA, such as inflammatory bowel disease, chronic kidney disease and chronic lung disease (including remote laboratory results, if deemed necessary). However, the current literature about remote monitoring of disease activity using patient-

reported outcome measures in paediatric chronic diseases is scarce. One study remotely monitored disease activity of 71 children with chronic urticaria over a period of 13 months and reported favourable treatment outcomes[23]. This monitoring however also included consultations via telephone or video call. Still, due to the need of limiting social contacts during the COVID-19 pandemic and technological advances such as mobile apps, we expect more results on self-monitoring of disease activity in paediatric chronic diseases to be published in the coming years. In adult patients with chronic disease, studies have demonstrated a beneficial effect of remote monitoring on early clinical assessment and treatment, but also shared-decision making and disease-specific knowledge[24].

The THUIS study has limitations. First of all, most hospital pharmacies only supply biological DMARDs for three months in order to avoid home stacking with possible waste of costly medication (e.g. due to switching to other medication or issues with the refrigerator). Since JIA is commonly treated in a tertiary care hospital, many patients would have to travel a long distance for picking up their medication after three months. In addition, long distance travel to pick up medication is in stark contrast with the rationale of home-monitoring. In our study, we resolved this issue by transporting biologicals to the home address of the latter group of patients. Unfortunately, this involves substantial costs since this requires cooled transport. For sDMARD and small molecule targeted therapies (only tofacitinib is registered yet for JIA) the transport does not need to be cooled however. Second, the JAMAR questionnaire does not distinguish between painful or swollen joints. This difference could be informative in determining whether or not a patient should be rescheduled for a hospital visit. The JAMAR is also validated only in JIA patients[16] and hence not a suitable tool for home-monitoring of (children with) other chronic diseases. Third, there is a risk that the use of home-based self-monitoring creates disparities based on digital literacy of patients and their parents or guardians[25]. Lastly, we realize that not all patients might be willing to skip a control visit, as already observed in the interim results. Some patients who have had regular control visits for years might feel as though these visits are a comfortable or maybe even warranted safeguard against possible disease worsening, or simply a pleasant opportunity for asking their physician any questions.

To conclude, interim results of the THUIS study have so far indicated that home-monitoring using web-based questionnaires is a feasible and a much appreciated method of tracking disease activity in JIA patients. Depending on the final results of this study, it remains to be sorted out how home-monitoring of JIA disease activity can be systematically implemented in clinical practice. It might also be of interest to perform a cost-effectiveness analysis taking into account the costs of transporting medication and reminding patients who forget to home-monitor at the agreed time-period.

ACKNOWLEDGEMENTS

The authors thank Mark Klein for contributing to the institutional review board submission and Regina de Geus, Kirsten van der Velden, Marit Bijl and Annelies Suijs for contributing to the collection of informed consents.

FUNDING

There is no funding to be reported for this study.

COMPETING INTERESTS

The authors declare that they have no competing interests.

ETHICS APPROVAL

The THUIS study has been approved by the Medical Research Ethics Committee of the UMC Utrecht, the Netherlands (21-767). All participants (and their parents) have to provide written informed consent/assent to enter the THUIS study. The study is conducted according to the principles of the Declaration of Helsinki and in accordance with the WMO and ICH Good Clinical Practice (GCP) guidelines.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. JAMAR and EQ-5D-Y-5L home-monitoring results at 3 months follow-up (extensive).

Question	No rescheduled visit by study team (n = 52)	Rescheduled visit by study team (n = 3)
EQ-5D-Y-5L questionnaire		
Mobility, n (%)		
No problems	45 (86.5%)	1 (33.3%)
A little bit of a problem	6 (11.5%)	1 (33.3%)
Some problems	1 (1.9%)	1 (33.3%)
A lot of problems	0 (0.0%)	0 (0.0%)
Cannot	0 (0.0%)	0 (0.0%)
Self-care, n (%)		
No problems	48 (92.3%)	3 (100.0%)
A little bit of a problem	3 (5.8%)	0 (0.0%)
Some problems	1 (1.9%)	0 (0.0%)
A lot of problems	0 (0.0%)	0 (0.0%)
Cannot	0 (0.0%)	0 (0.0%)
Usual activity, n (%)		
No problems	41 (78.8%)	1 (33.3%)
A little bit of a problem	10 (19.2%)	2 (66.7%)
Some problems	1 (1.9%)	0 (0.0%)
A lot of problems	0 (0.0%)	0 (0.0%)
Cannot	0 (0.0%)	0 (0.0%)
Pain/discomfort, n (%)		
No pain	37 (71.2%)	0 (0.0%)
A little bit of pain	11 (21.2%)	2 (66.7%)
Some pain	4 (7.7%)	1 (33.3%)
A lot of pain	0 (0.0%)	0 (0.0%)
Extreme pain	0 (0.0%)	0 (0.0%)
Anxiety/depression, n (%)		
Not worried	44 (8.5%)	3 (100.0%)
A little bit worried	6 (11.5%)	0 (0.0%)
Quite worried	0 (0.0%)	0 (0.0%)
Really worried	2 (3.8%)	0 (0.0%)
Extremely worried	0 (0.0%)	0 (0.0%)
VAS health, median (IQR)	91.5 (80.0 – 100.0)	82.0 (73.5 – 84.0)

Supplementary Table 1. Continued

Question	No rescheduled visit by study team (n = 52)	Rescheduled visit by study team (n = 3)
JAMAR questionnaire		
Functional ability		
Running on flat ground, n (%)		
No difficulty	46 (88.5%)	2 (66.7%)
Some difficulty	6 (11.5%)	1 (33.3%)
Much difficulty	0 (0.0%)	0 (0.0%)
Unable to do	0 (0.0%)	0 (0.0%)
Walking up 5 steps, n (%)		
No difficulty	49 (94.2%)	3 (100.0%)
Some difficulty	3 (5.8%)	0 (0.0%)
Much difficulty	0 (0.0%)	0 (0.0%)
Unable to do	0 (0.0%)	0 (0.0%)
Jumping forward, n (%)		
No difficulty	44 (84.6%)	2 (66.7%)
Some difficulty	8 (15.4%)	1 (33.3%)
Much difficulty	0 (0.0%)	0 (0.0%)
Unable to do	0 (0.0%)	0 (0.0%)
Squatting, n (%)		
No difficulty	40 (76.9%)	1 (33.3%)
Some difficulty	10 (19.2%)	1 (33.3%)
Much difficulty	2 (3.8%)	1 (33.3%)
Unable to do	0 (0.0%)	0 (0.0%)
Bending down, n (%)		
No difficulty	47 (90.4)	3 (100.0%)
Some difficulty	5 (9.6%)	0 (0.0%)
Much difficulty	0 (0.0%)	0 (0.0%)
Unable to do	0 (0.0%)	0 (0.0%)
Carrying out activities with fingers, n (%)		
No difficulty	46 (88.5%)	2 (66.7%)
Some difficulty	4 (7.7%)	1 (33.3%)
Much difficulty	2 (3.8%)	0 (0.0%)
Unable to do	0 (0.0%)	0 (0.0%)
Opening and closing fists, n (%)		
No difficulty	51 (98.1%)	2 (66.7%)
Some difficulty	1 (1.9%)	1 (33.3%)
Much difficulty	0 (0.0%)	0 (0.0%)
Unable to do	0 (0.0%)	0 (0.0%)

Supplementary Table 1. Continued

Question	No rescheduled visit by study team (n = 52)	Rescheduled visit by study team (n = 3)
Squeezing with hands, n (%)		
No difficulty	48 (92.3%)	3 (100.0%)
Some difficulty	4 (7.7%)	0 (0.0%)
Much difficulty	0 (0.0%)	0 (0.0%)
Unable to do	0 (0.0%)	0 (0.0%)
Opening a door, n (%)		
No difficulty	50 (96.2%)	3 (100.0%)
Some difficulty	2 (3.8%)	0 (0.0%)
Much difficulty	0 (0.0%)	0 (0.0%)
Unable to do	0 (0.0%)	0 (0.0%)
Opening and closing a tap, n (%)		
No difficulty	49 (94.2%)	3 (100.0%)
Some difficulty	2 (3.8%)	0 (0.0%)
Much difficulty	1 (1.9%)	0 (0.0%)
Unable to do	0 (0.0%)	0 (0.0%)
Stretching out arms, n (%)		
No difficulty	51 (98.1%)	3 (100.0%)
Some difficulty	1 (1.9%)	0 (0.0%)
Much difficulty	0 (0.0%)	0 (0.0%)
Unable to do	0 (0.0%)	0 (0.0%)
Putting hands behind neck, n (%)		
No difficulty	52 (100.0%)	3 (100.0%)
Some difficulty	0 (0.0%)	0 (0.0%)
Much difficulty	0 (0.0%)	0 (0.0%)
Unable to do	0 (0.0%)	0 (0.0%)
Looking over shoulders, n (%)		
No difficulty	52 (100.0%)	2 (66.7%)
Some difficulty	0 (0.0%)	1 (33.3%)
Much difficulty	0 (0.0%)	0 (0.0%)
Unable to do	0 (0.0%)	0 (0.0%)
Looking at ceiling, n (%)		
No difficulty	52 (100.0%)	2 (66.7%)
Some difficulty	0 (0.0%)	1 (33.3%)
Much difficulty	0 (0.0%)	0 (0.0%)
Unable to do	0 (0.0%)	0 (0.0%)
Biting into sandwich, n (%)		
No difficulty	50 (96.2%)	2 (66.7%)

Supplementary Table 1. Continued

Question	No rescheduled visit by study team (n = 52)	Rescheduled visit by study team (n = 3)
Some difficulty	1 (1.9%)	1 (33.3%)
Much difficulty	1 (1.9%)	0 (0.0%)
Unable to do	0 (0.0%)	0 (0.0%)
VAS pain, median (IQR)	0.3 (0.0 – 1.5)	3.0 (2.5 – 5.3)
Pain or swelling in finger(s), n (%)	2 (3.8%)	0 (0.0%)
Pain or swelling in wrist(s), n (%)	1 (1.9%)	1 (33.3%)
Pain or swelling in elbow(s), n (%)	0 (0.0%)	0 (0.0%)
Pain or swelling in shoulder(s), n (%)	0 (0.0%)	0 (0.0%)
Pain or swelling in hip(s), n (%)	1 (1.9%)	1 (33.3%)
Pain or swelling in knee(s), n (%)	5 (9.6%)	0 (0.0%)
Pain or swelling in ankle(s), n (%)	1 (1.9%)	2 (66.7%)
Pain or swelling in toe(s), n (%)	3 (5.8%)	0 (0.0%)
Pain or swelling in neck, n (%)	0 (0.0%)	1 (33.3%)
Pain or swelling in lower back, n (%)	1 (1.9%)	0 (0.0%)
Morning stiffness, n (%)	8 (15.4%)	2 (66.7%)
Duration of morning stiffness, n (%)		
15 minutes or less	3 (5.8%)	1 (33.3%)
15 to 30 minutes	2 (3.8%)	0 (0.0%)
30 minutes to 1 hour	1 (1.9%)	0 (0.0%)
1 to 2 hours	2 (3.8%)	1 (33.3%)
More than 2 hours	0 (0.0%)	0 (0.0%)
Fever, n %)	0 (0.0%)	0 (0.0%)
Skin rash, n (%)	1 (1.9%)	0 (0.0%)
VAS disease activity, median (IQR)	0.0 (0.0 – 1.0)	2.5 (2.5 – 4.8)
State of illness, n (%)		
Remission	42 (80.8%)	0 (0.0%)
Persistent activity	6 (11.5%)	1 (33.3%)
Relapse	4 (7.7%)	2 (66.7%)
Course of illness, n (%)		
Much improved	5 (9.6%)	0 (0.0%)
Slightly improved	4 (7.7%)	0 (0.0%)
Stable/unchanged	40 (76.9%)	0 (0.0%)
Slightly worsened	3 (5.8%)	3 (100.0%)
Much worsened	0 (0.0%)	0 (0.0%)
Taking medication, n (%)	31 (59.6%)	2 (66.7%)
Adverse events from medication, n (%)	4 (7.7%)	0 (0.0%)
Attending school, n (%)	51 (98.1%)	3 (100.0%)
Problems at school, n (%)	7 (13.7%)	0 (0.0%)

Supplementary Table 1. Continued

Question	No rescheduled visit by study team (n = 52)	Rescheduled visit by study team (n = 3)
Quality of life		
Difficulty with self-care, n (%)		
Never	45 (86.5%)	2 (66.7%)
Sometimes	4 (7.7%)	1 (33.3%)
Often	1 (1.9%)	0 (0.0%)
Every day	1 (1.9%)	0 (0.0%)
Difficulty taking a 15 minute walk, n (%)		
Never	38 (73.1%)	1 (33.3%)
Sometimes	11 (21.2%)	1 (33.3%)
Often	2 (3.8%)	0 (0.0%)
Every day	0 (0.0%)	1 (33.3%)
Difficult carrying out energetic activities, n (%)		
Never	32 (61.5%)	1 (33.3%)
Sometimes	12 (23.1%)	2 (66.7%)
Often	6 (11.5%)	0 (0.0%)
Every day	1 (1.9%)	0 (0.0%)
Difficulty doing at-school activities, n (%)		
Never	42 (80.8%)	2 (66.7%)
Sometimes	7 (13.5%)	1 (33.3%)
Often	2 (3.8%)	0 (0.0%)
Every day	0 (0.0%)	0 (0.0%)
Have had pain, n (%)		
Never	29 (55.8%)	0 (0.0%)
Sometimes	19 (36.5%)	3 (100.0%)
Often	0 (0.0%)	0 (0.0%)
Every day	3 (5.8%)	0 (0.0%)
Have felt sad or depressed, n (%)		
Never	40 (76.9%)	3 (100.0%)
Sometimes	9 (17.3%)	0 (0.0%)
Often	0 (0.0%)	0 (0.0%)
Every day	2 (3.8%)	0 (0.0%)
Have felt nervous or anxious, n (%)		
Never	42 (80.8%)	2 (66.7%)
Sometimes	7 (13.5%)	1 (33.3%)
Often	1 (1.9%)	0 (0.0%)
Every day	1 (1.9%)	0 (0.0%)

Supplementary Table 1. Continued

Question	No rescheduled visit by study team (n = 52)	Rescheduled visit by study team (n = 3)
Trouble getting along with children, n (%)		
Never	43 (82.7%)	3 (100.0%)
Sometimes	6 (11.5%)	0 (0.0%)
Often	2 (3.8%)	0 (0.0%)
Every day	0 (0.0%)	0 (0.0%)
Difficulty concentrating, n (%)		
Never	35 (67.3%)	1 (33.3%)
Sometimes	11 (21.2%)	0 (0.0%)
Often	3 (5.8%)	2 (66.7%)
Every day	2 (3.8%)	0 (0.0%)
Felt dissatisfied with appearance, n (%)		
Never	40 (76.9%)	2 (66.7%)
Sometimes	7 (13.5%)	1 (33.3%)
Often	2 (3.8%)	0 (0.0%)
Every day	2 (3.8%)	0 (0.0%)
VAS well-being, median (IQR)	0.5 (0.0 – 1.6)	2.0 (1.5 – 2.5)
Satisfied with current symptom state, n (%)	47 (90.4%)	0 (0.0%)

EQ-5D-Y-5L: EuroQol five-dimensional 'youth' questionnaire with five levels, IQR: interquartile range, JAMAR: Juvenile Arthritis Multidimensional Assessment Report, n: number, VAS: visual analogue scale

PART V

V

General discussion and appendices

CHAPTER 13

13

Summary, discussion and future perspectives

In this thesis, I applied traditional and advanced epidemiological methods to answer clinically relevant questions for the management of children with juvenile idiopathic arthritis (JIA). Throughout the thesis, questions have been addressed ranging from diagnosing JIA to predicting comorbidity and providing evidence for therapy choice. In this part of the thesis, I will first provide a summary of the main findings and then discuss broader implications for improving patient care by epidemiological methods.

SUMMARY

In the first two chapters of this thesis I presented studies relevant to the diagnosis of JIA.

In **Chapter 2** I concluded that the Juvenile Arthritis Multidimensional Assessment Report (JAMAR) performs well in distinguishing JIA from chronic musculoskeletal pain syndrome (CMPS) in patients with corresponding symptoms. I furthermore provided a validated tool for clinical use to predict a diagnosis of JIA in patients with corresponding symptoms. Given that JIA and CMPS are the most common diagnoses in paediatric rheumatology and physical examination by experienced paediatric rheumatologist is required to separate the two, this prediction tool might be of added value for timely referrals of JIA especially in settings with a shortage of paediatric rheumatologists.

In **Chapter 3** I provided a comprehensive overview of the prevalence of autoimmune diseases in parents of children with JIA from the international Pharmachild registry. The most common familial autoimmune diseases were psoriasis, autoimmune thyroid disease, rheumatoid arthritis (RA) and ankylosing spondylitis. Paediatric rheumatologists should therefore not overlook these diseases during family health history at the diagnosis stage of a potential new JIA patient. The prevalence of several autoimmune diseases was higher in parents of JIA patients compared to prevalence rates in the healthy population reported in the literature, confirming that familial autoimmune disease is a risk factor for JIA development. A family history of autoimmune disease was also associated with the JIA category but not severity of the disease course.

Subsequently, I focused on the prevalence and predictors of common comorbidities in JIA.

In **Chapter 4** I reported the incidence of macrophage activation syndrome (MAS), tuberculosis, varicella and uveitis on drug therapy in JIA patients as a result of a collaboration between three of the largest European JIA registries: the UK JIA Biologic Registries (BCRD/BSPAR-ETN), the German BiKeR and JuMBO biologic registries and the multinational Pharmachild registry. Occurrence of varicella in the German registers was

lower due to a higher vaccination coverage. This study demonstrated the opportunities of international collaboration in studying relatively rare diseases and disease outcomes but also highlighted challenges for successful harmonization of data.

In **Chapter 5** I provided a clinical prediction model for the development of both acute and chronic uveitis in JIA patients such that clinicians can obtain individualised predicted probabilities instead of the three subjective risk-categories from ophthalmologic screening guidelines. Predicted probabilities could be used to assist in determining screening frequencies, provide rationale for drug therapy and inform patients and parents. This was the first ever study to present a prediction model for JIA-associated uveitis intended for clinical application.

In **Chapter 6** I developed and externally validated a clinical prediction model specifically for chronic uveitis at different disease durations in JIA. This was the first ever study to report an externally validated prediction model for JIA-associated uveitis. This article also provides recommendations for clinical application of the prediction model, which will be further discussed in the Multinational Interdisciplinary Working Group for Uveitis in Childhood (MIWGUC).

In **Chapter 7** I studied the prevalence and predictors of autoimmune thyroid disease in JIA patients. I reported that the strongest predictor of autoimmune thyroid disease in JIA is a positive family history. The article therefore suggests that physicians should consider screening for thyroid disease in patients with positive family history, which is based on standard blood tests.

In **Chapter 8** I reported that the incidence of inflammatory bowel disease (IBD) is increased in JIA patients on etanercept (ETN) therapy, irrespective of combination therapy with methotrexate (MTX). IBD was furthermore associated with enthesitis-related arthritis (ERA) and a family history of autoimmune disease. Hence, adalimumab (ADA) therapy, which is effective in the treatment of IBD, might be preferred over ETN in this group of JIA patients at high risk of developing IBD.

In the next chapters, I studied the effect of drug therapy on clinical outcomes in JIA.

In **Chapter 9** I conducted a matched case-control study in order to assess the effect of MTX therapy on the rate of new-onset uveitis in biological-naïve JIA patients. MTX was associated with an almost three times lower hazard for uveitis development on adjusted, time-varying analysis. There was no significantly different effect between low and normal dose MTX therapy. Half of the patients who developed uveitis after discontinuation of MTX did so within one year. Therefore, it was suggested in this article to early initiate (low dose)

MTX therapy in JIA patients at high risk for uveitis and consider frequent ophthalmologic screening shortly after MTX discontinuation.

In **Chapter 10** I used real-world data (RWD) and propensity score analyses to make a valid comparison of the effects of ADA and ETN on clinical outcomes in JIA. Both drugs improved disease activity to a similar extent but the study data might indicate a slightly stronger improvement of patient-reported well-being for ETN compared to ADA, although results were not significant. Larger studies are needed to confirm this effect but a true difference might be caused by pain on injection due to a citrate buffer in ADA, which is currently removed from the drug. In this study it was observed that disease activity as scored by the physician does not always directly translate to patient-reported well-being which indicates that patient-reported outcome measures (PROMs) should always be included in a treat-to-target approach to the management of JIA.

In **Chapter 11** I reported the results of a prospective cohort study to assess the long-term safety and immunogenicity of the meningococcal ACWY (MenACWY) vaccine in JIA and IBD patients. It was observed that the vaccine did not lead to serious adverse events and did not increase disease activity. IgG antibody concentrations against all four serogroups were lower in patients who used anti-tumour necrosis factor (TNF) therapy compared to patients not on anti-TNF therapy and healthy age-matched controls. One year after vaccination, the proportion of patients who used anti-TNF agents with protective antibody titres against serogroup W was just 76%. Thus, it was advised in this article to offer all patients on anti-TNF therapy a booster vaccine after one year.

Finally, I outline the methodology and preliminary findings of an ongoing clinical trial which focuses on remote disease monitoring in JIA.

In **Chapter 12** I present the study protocol and interim results of the THUIS study, which aims to demonstrate that hospital visits can be safely replaced by home-monitoring using web-based questionnaires for JIA patients in clinical remission. As of 17 October 2022, 76 participants were included of which 72% have completed a questionnaire for home-monitoring and 14% have been followed-up after skipping one hospital visit. Disease flares were observed in 9% of the participants, which is not higher compared to historical data of patients with stable disease from the Wilhelmina Children's hospital. In addition, all followed-up participants indicated that they would like to make use of home-monitoring more often in the future.

DISCUSSION

Range of utilised study designs

This thesis is a reflection of the usefulness and relative strengths and weaknesses of various epidemiological study designs in answering different types of research questions, both diagnostic, etiologic, prognostic, and interventional. Study designs used in this thesis are prospective and retrospective observational cohort studies, a case-control study, a cross-sectional study and a clinical trial. It should be noted that a specific study design follows naturally from a well-designed research question, and not the other way around.

Data from the Pharmachild registry were used in Chapter 10 of this thesis to compare treatment effects between ADA and ETN in JIA, and in Chapter 8 of this thesis to compare incidence rates of IBD between different drug therapies. Making use of such existing prospective data for comparing (new) drug therapies or healthcare interventions is often more practical and ethical than setting up a prospective cohort study or clinical trial, as was done for studying safety and immunogenicity of the MenACWY vaccine (Chapter 11) and home-monitoring of disease activity (Chapter 12) in this thesis. For example, it would not have been ethical to set up a clinical trial to compare treatment effects between ADA and ETN in JIA, since some patients run a higher risk of developing uveitis for which ADA is an effective therapy[1]. Nevertheless, when using existing prospective data for comparing treatment effects, researchers should use statistical methods to adjust for confounding by indication.

In Chapter 9 of this thesis, I presented a case-control study in which I studied the potential protective effect of MTX on uveitis onset in biological-naïve JIA patients using a cohort of previously-identified JIA-associated uveitis patients. Compared to a prospective study, case-control studies are more efficient, especially when studying rare outcomes, saving valuable time and money[2]. The current study was a particularly efficient procedure since no readily available data about uveitis history were available in the paediatric rheumatology registry of the Wilhelmina Children's Hospital, and it would have been a disproportionately time-consuming process to collect these from electronic health records. Although case-control studies can be highly efficient in determining causal relationships, researchers should make sure to sample controls from the same pool where the cases emerged from in order to prevent selection bias[3].

In order to provide long-term predictions for several comorbidities in JIA (Chapters 5-8), I used long-term prospective cohort data from the Pharmachild registry[4]. To develop prediction models that can provide absolute predicted probabilities for use in clinical practice, outcomes and exposures should be measured in all patients from a cohort instead of a selection of patients (i.e. a census approach instead of a sampling approach)[2].

For this reason, it is not possible to perform (diagnostic or prognostic) prediction research with a case-control study design. While a clinical trial could be appropriate for carrying out short-term prediction research given treatment (options), a prospective cohort study is oftentimes more practical for long-term prediction given the generally lower costs for study duration. Like clinical trials, prospective cohort studies are also appropriate for studying rare exposures such as specific immunosuppressive drugs in JIA patients. A common methodological pitfall in prediction research is using analyses for binary outcomes in patients with variable follow-up durations, since patients with a short follow-up might later develop the outcome event to be predicted[5]. For this reason, we only included JIA patients with a disease duration of at least four years for developing a prediction model for uveitis in Chapter 5 of this thesis.

In Chapter 2 of this thesis, I presented a cross-sectional study in which I developed a diagnostic prediction model for separating JIA from CMPS in patients with corresponding symptoms. Questions of diagnosis are preferably answered using cross-sectional study designs, in which diagnostic tests or determinants and the outcome (a disease of interest as determined with a reference test) are ascertained simultaneously. In diagnostic research, determinants and outcomes do not necessarily have to be collected at the exact same moment in time. However, it is a prerequisite that outcome measurements can assure the presence or absence of the disease of interest at the time of measuring the diagnostic tests, or vice versa[2]. In the study presented in Chapter 2, JAMAR questionnaires where completed for almost 300 patients shortly before a definite diagnosis by the paediatric rheumatologist. A cross-sectional study design can often not be used to determine causal relationships and make predictions.

Added value of advanced epidemiological methods

Throughout this thesis, I used advanced epidemiological methods and analyses in order to obtain valid answers to various research objectives. Examples of advanced epidemiological methods in this thesis include: random effects models, propensity score analyses, regularization, bootstrap resampling, model recalibration, multiple imputation and time-varying analysis. These methods have advantages compared to conventional statistical analyses, but should also be used with caution.

In Chapter 10 and 11 I used random effects models to adjust for correlated observations. These included study outcomes of patients with ADA or ETN therapy from the Pharmachild registry who were treated in the same country and prospective MenACWY serology results from the same patient. Briefly, these analyses allow regression intercepts and slopes to vary on a level for which there are multiple dependent observations, such as individual patients or single hospitals[6]. Because of this, the data is no longer assumed to include independent observations, as is the case in traditional regression analyses. The

importance of adjusting for dependent observations is illustrated in Figure 1, where the dots indicate four observations in six patients (represented by different shades of black). When analysing these observations with an ordinary regression analysis which assumes that all 24 observations are independent, the estimated trend which is indicated by the red arrow will be severely biased (i.e. a negative effect of the exposure on the outcome). The green arrow represents the valid trend as estimated from a random effects model, which is a positive effect of the exposure on the outcome. As such, random effects models are appropriate for analysing longitudinal data with repeated measurements over time. However, these models have assumptions, including normality of errors and constant error variance[6].

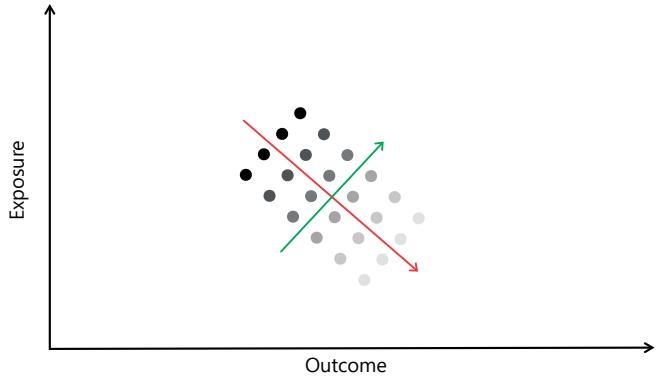

Figure 1. Schematic example of estimated trends when analysing dependent observations of different patients (n = 6, represented by different shades of black) with a random effects model (green arrow) and a conventional regression analysis (red arrow), the latter of which incorrectly assumes that all 24 observations are independent.

In Chapter 10 of this thesis, propensity score analyses were used as a method to adjust for multiple confounding variables in the relationship between ADA or ETN therapy and patient-reported well-being. In this method, an often large number of (presumed) confounding variables in the relationship between the exposure and outcome of interest is used to predict the prior probability of receiving the exposure for every patient in a dataset (i.e. the propensity score). These propensity scores can subsequently be used in different ways to remove confounding by indication and obtain valid estimates of the relationship between the exposure and outcome[2]. Therefore, compared to traditional variable adjustment, a propensity score analysis adjusts for multiple variables without risking an overfit model, which could lead to invalid treatment effect estimates. In essence, propensity score analysis mimics the design of a randomised controlled trial (RCT) using observational data and already several studies making use of propensity score analysis in the field of rheumatology have been published[7–11]. The most used methods for propensity

score analysis are matching, weighting and (quintile) adjustment. The type of propensity score analysis can be influential as research has shown that different methods can lead to different effect estimates[12]. For this reason, I used not one but two methods for propensity score analysis in Chapter 10 to confirm robustness of the study results. Furthermore, it is important to select as many relevant confounding variables for inclusion in the propensity score model, including any transformations of non-linear relationships with the exposure variable to be predicted[13]. Also, researchers should make sure that propensity scores which only occur in either the exposed or unexposed group are trimmed, since according to the propensity score model, patients with these scores never had any chance of ending up in the other group[14]. Because of this, patients who received ETN therapy with a low predicted probability for ADA had to be excluded from the study in Chapter 10 of this thesis.

Another technique for dealing with a large number of variables and even high-dimensional data (i.e. data where the number of columns is larger than the number of rows) is regularization using penalised regression models. Common regularization techniques are ridge regression and least absolute shrinkage and selection operator (LASSO) regression[15]. The latter model was used in Chapter 2 of this thesis to select useful variables for a diagnostic prediction model and shrink coefficients of variables with relatively less predictive value. In contrast to propensity score analysis, regularization can be used for prediction or diagnostic research, and shrinkage of coefficients prevents overfitting of prediction models. Regularization can be used in ordinary linear or logistic regression, and therefore the same assumptions apply. A disadvantage of regularization is that it is not straightforward to calculate confidence intervals around effect estimates.

Bootstrap resampling (Chapter 5) and model recalibration (Chapter 6) following external validation are other methods used in this thesis to adjust prediction models for uveitis for overfitting (i.e. optimism) in the model development cohort. By applying these methods, prediction models should provide predictions that are less specific for patients in the development cohort and better in patients from further settings. Briefly, in bootstrap resampling, prediction models with the same predictor variables are fitted in multiple datasets derived from the original data[16]. Subsequently, the average difference between the resulting model coefficients and the original coefficients is used to adjust the original model coefficients, resulting in an optimism-adjusted prediction model. The amount of adjustment or shrinkage provides an idea about the magnitude of optimism of the original prediction model in the model development data. Because bootstrap resampling makes use of all the available data, it is a more efficient method for internal model validation than a split-sample or k-fold cross validation approach[16]. Following external validation by assessing discrimination and calibration in another dataset, there are a number of methods to recalibrate a prediction model to the new setting. Commonly used methods

are recalibration in the large, which re-estimates a models intercept or baseline survival probability, and logistic recalibration, which adds a constant shrinkage factor to the original model coefficients[17]. Obviously, researchers have to carefully think about which external datasets to use for recalibration, since this can have an impact on the resulting prediction model. For instance, in Chapter 6 of this thesis, both external validation cohorts included only Western European JIA patients, which might hamper generalizability of the recalibrated prediction model for uveitis to non-Western European settings. The methodology for model development and subsequent recalibration as presented in this chapter was selected for the February 2023 *Arthritis & Rheumatology* journal club feature, which aims to facilitate discussion on important and innovative research methods in rheumatology.

Time-varying analysis was used in Chapter 9 of this thesis to prevent immortal time bias in the effect of MTX therapy on uveitis development, which is the case when exposed or unexposed follow-up time is misclassified in the data analysis[18]. Immortal time bias typically occurs when study participants are classified as exposed or unexposed to a treatment or therapy without taking into account that exposure could be varying over time and not just constant. Figure 2 shows a simplified example of the concept of immortal time bias. In this example, the total survival time is misclassified in the ("ever") exposed group, leading to a biased ratio of survival time compared to the unexposed group (12 months / 6 months = 2). However, when taking into account that exposure only started after 6 months, the survival ratio will be different (6 months / [6 + 6] months = 0.5). This example demonstrates the importance of correctly analysing time-varying exposure in clinical research, a practice which is often overlooked.

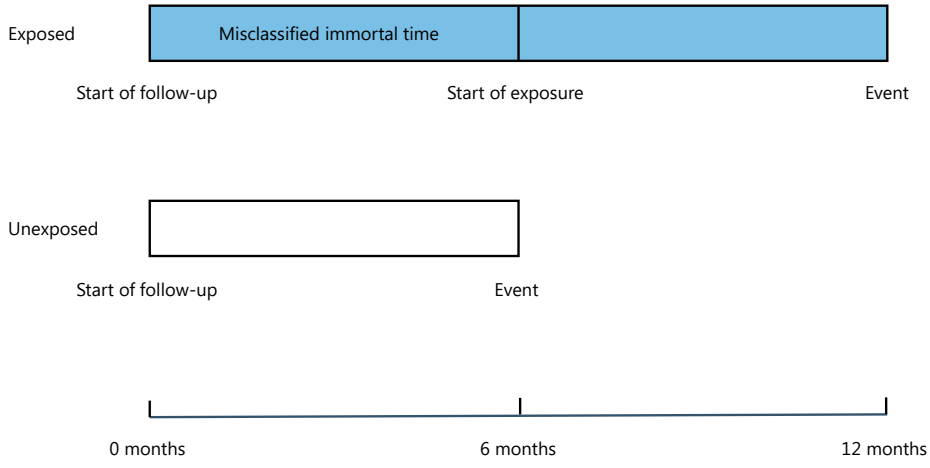

Figure 2. Schematic example of immortal time bias as a result of misclassified exposure time.

Lastly, multiple imputation was used in Chapters 6, 10 and 11 of this thesis to avoid selection bias, which could result from restricting the data to cases without missing information (i.e. a complete case analysis). In multiple imputation, a specified number of datasets with complete information for all patients are created by repeatedly predicting missing values from observed variables. Subsequently, analyses of interest are performed in the multiple imputed datasets and the resulting estimates are combined to obtain a final effect size, for instance using the theory of Rubin's rules[19]. Multiple imputation also increases statistical power since patients with missing information are not excluded. However, this technique is only possible for data which is considered missing at random (which means that missing data can be predicted from observed data of other patients)[19]. Also, the percentage of missing data should not be too large, although there is no consensus on a universally acceptable threshold value.

Potential of machine learning in rheumatology research

Some of the analyses used in this thesis such as LASSO regression for separating JIA and CMPS can be considered machine learning methods. Machine learning can be defined as a field of artificial intelligence which uses algorithms to uncover patterns from provided data without following specific instructions[20]. Machine learning methods can be classified into supervised learning (e.g. neural networks, support vector machines, decision trees) in which outcomes of interest such as the presence of comorbidity are defined in the data, and unsupervised learning (e.g. principal component analysis, k-means clustering), in which these outcomes are not defined.

Since the field of rheumatology concerns mostly chronic and often long-lasting conditions for which long-term follow-up data are collected, machine learning models could be useful by detecting complex non-linear patterns and generating prediction models for informing clinical decision making more efficiently and precisely than conventional methods[21]. Examples of clinically relevant outcomes to predict in JIA patients are the success of stopping or tapering treatment or the chances of adverse events, disease progression or clinical remission. A study has also demonstrated that JIA patients could be distinguished from healthy controls using a machine learning algorithm in immune phenotyping data with 90% accuracy[22]. Furthermore, unsupervised machine learning can be used to identify clusters of biomarkers such as pro-inflammatory cytokines from high-dimensional multi-omics data which explain a high percentage of variability between patients[23]. This could gain new insights into the pathophysiology of JIA or predict for instance which groups of patients will respond well to a particular drug or have a specific disease course. As an example, a study of 640 new-onset JIA patients identified seven distinct patterns of joint involvement using an unsupervised machine learning approach[24]. In the future, deep learning algorithms could be used for image interpretation in musculoskeletal radiology, saving valuable time[20]. Several studies making use of machine learning approaches in

the field of rheumatology and JIA have already been published[20,21,25]. Although machine learning methods are relatively new in clinical research, already several guidelines exist that could be used for reporting research or assessing published studies[26–28].

Nevertheless, machine learning methods require extensive training, testing and validation and large patient numbers are needed to make optimal use of high-dimensional data[25]. Furthermore, machine learning algorithms sometimes perform no better than traditional statistical techniques but are less interpretable[29]. Lastly, just like conventional statistical methods, machine learning algorithms can suffer from overfitting and should always be validated in independent external datasets before being used in the clinic.

Increasing relevance of real-world data

Due to worldwide digitalization of healthcare information and the need for evidence that can be translated to the clinical practice, RWD are becoming an increasingly important source for clinical research[30]. Examples of RWD are electronic health records, insurance claims, pharmacy data and data from monitoring devices such as smartphones and smartwatches. Also, improved knowledge of advanced statistical methods including machine learning have made it possible to handle the often large volume and heterogeneity of RWD[25]. Compared to evidence from other types of data, real-world evidence has advantages and disadvantages (Table 1).

RWD are often abundant in the field of rheumatic conditions, since these are most of the time chronic and result in long-term follow-up. While RCTs are excellent study designs for proving efficacy of an intervention, i.e. an effect under ideal circumstances, the added value of the same intervention in a real-world setting (i.e. effectiveness) might be different[30]. As an example, research from the UK "Biologics for Children with Rheumatic Diseases" (BCRD) cohort has reported that drug continuation of anakinra in systemic JIA patients was significantly shorter compared to tocilizumab with one-third of the patients reporting injection-related problems[31]. This goes to show that a drug might suffer from suboptimal effectiveness in its intended setting due to side-effects resulting in non-compliance. Performing a RWD study is also relatively cheap and for this reason can be used to provide multiple (head-to-head) comparisons between drugs of similar classes in the treatment of JIA, as was done with ADA and ETN in Chapter 10 of this thesis. In addition, compared to a RCT, there are no extra study visits apart from routine control visits and patients do not have to be randomised to placebo therapy in a RWD study.

Disadvantages of RWD are regular incomplete information and potential confounding by indication. Nevertheless, both these problems can be addressed by modern statistical methods such as multiple imputation and propensity score analysis which have been

discussed previously. Furthermore, since RWD are not collected merely for research purposes, they often require rigid cleaning and harmonization[32].

Table 1. Types of clinical data and characteristics.

	Real-world data	Registry	Clinical trial
Type of data	Routinely collected healthcare data	Prospectively collected from a homogeneous group of patients	Data from patients assigned to one or more interventions
Population	Broad	Restricted by participation	Restricted eligibility criteria
Sample size	Large	Moderate to large	Often relatively small
Data presence	Unstructured, often missing data	Structured, occasional missing data	Often highly structured and complete
Generalizability	High	Restricted by patient selection	Often highly restricted by patient selection

Adapted from: *Knevel R, Liao KP. Ann Rheum Dis 2022;0:1–6. doi:10.1136/annrheumdis-2022-222626*

Personalised medicine and treat-to-target in JIA

Well-conducted clinical epidemiological research can provide evidence and tools for personalised JIA treatment. Examples of personalised medicine presented in this thesis are home-monitoring for disease activity (Chapter 12), autoimmune thyroid disease screening in patients with positive family history (Chapter 7), and the prediction models for uveitis (Chapters 5 & 6) and a diagnosis of JIA (Chapter 2).

Treat-to-target is an increasingly used personalised medicine approach in the management of several chronic diseases, including RA and JIA[33]. This strategy involves setting a treatment target such as clinical remission and adjusting individual treatment based on prospectively collected validated and standardised assessment tools in order to reach and maintain the target[34]. Studies have demonstrated treatment-to-target to be effective and feasible for treating disease activity in a range of rheumatic diseases including JIA[35–39] and current treatment guidelines for JIA also recommend using assessment tools such as the clinical Juvenile Arthritis Disease Activity Score (cJADAS) to guide individual treatment decisions[40,41]. The rationale behind a treat-to-target strategy for treating JIA is that a multiplicity of treatment goals such as controlling signs and symptoms, preventing structural damage and avoiding comorbid conditions and drug toxicity can be achieved by focusing on validated assessment tools[35]. However, there are also limitations to treat-to-target. These involve time, subjective scoring of assessment tools, non-compliance in scoring assessment tools, and costs associated with treatment and frequent quantitative assessment[42,43]. For example, there is evidence that there is large variation between physicians in scoring the physician global assessment of disease activity (PGA)[44,45], which is a component of multiple disease activity measures such as the American College of Rheumatology (ACR) paediatric response, JADAS, and ACR criteria for inactive disease[46].

Also, patient-reported global health as captured in the patient visual analogue scale (VAS) can be completely unrelated to JIA and therefore not always a representative tool for guiding JIA treatment decisions. Furthermore, patients might not be compliant in completing assessment tools for treat-to-target, especially if they are not involved in setting the therapeutic target. The issue of non-compliance in completing assessment tools also arose in the THUIS study (Chapter 12), where a significant proportion of patients had to be reminded to complete their questionnaire for remote monitoring of disease activity, which might be a burden in regular care.

Current treatment for JIA is largely based on a step-up and trial and error approach, in which one or more drugs are used to treat arthritis and if unsuccessful, replaced by others. However, nowadays various research efforts are ongoing to move from a trial and error approach to a data-driven approach in which JIA patients will be prescribed their individual best first-line treatment based on clinical and laboratory information such as biomarkers. Examples of such efforts are the North American Start Time Optimization of Biologics in Polyarticular JIA (STOP-JIA) study[47], UK CLUSTER consortium[48] and Canada-Netherlands Personalized Medicine Network in Childhood Arthritis and Rheumatic diseases (UCAN CAN-DU)[49]. Data-driven treatment has the potential to save time and money, but more importantly, adult RA research has shown that treatment outcomes are worse in patients who have switched biological therapy more often[50]. It is unknown for an individual patient at the moment to predict which drug would work best. A recent study demonstrated that non-systemic JIA patients who were initially treated with TNF inhibitors showed a larger improvement in disease activity after six months and longer drug continuation than patients who were treated with non-TNF inhibitor biologicals[51]. So far, studies have indicated younger age, male sex, non-systemic arthritis, shorter disease duration, better function as indicated by the Childhood Health Assessment Questionnaire (CHAQ) and fewer affected joints to be associated with a good response to anti-TNF agents[52–56]. There is however also a debate whether a window of opportunity of treatment exists in JIA[57]. Indeed, studies have reported that early combination therapy of synthetic and biologic disease-modifying antirheumatic drugs (DMARDs), i.e. an early step-down approach, was associated with a higher likelihood of achieving inactive disease in polyarticular JIA than a classical step-up or synthetic DMARD approach[11,58–60]. The effectiveness of a step-down approach compared to the effectiveness of a step-up approach is currently also being studied in the international randomised controlled STARS trial[57].

The same principle of using predictions from clinical epidemiological studies to inform better initial treatment decisions could also be applied to predicting a disease course or the chances of successfully stopping, tapering or switching therapy. Currently, roughly a quarter of JIA patients starting a biologic switches to a second biologic and studies have reported a wide variety of switching patterns and treatment trajectories, with

approximately 50% of the patients not responding to a second biologic[51,61–66]. A multicentre trial has demonstrated that high-sensitivity C-reactive protein and S100A12 are promising biomarkers to predict successful therapy withdrawal[67]. Another study reported that none of the 22 included patients with low levels of myeloid-related protein (MRP)8/14 experienced a flare within 12 months after stopping MTX therapy[68]. Regarding disease course, an 18-year population-based follow-up study in the era of biologic DMARDs reported that 33% of JIA patients achieve long-term clinical remission, which was most often observed in persistent oligoarthritis and systemic arthritis, and least often in ERA[69]. In addition, a number of promising (and externally validated) tools for predicting disease severity and long-term remission in JIA have already been published, with predictors of poor outcome being high disease activity, a longer time from disease onset to the start of treatment, ankle or wrist involvement and poor PROMs[70–72]. Although results are promising, the effects of using these tools on outcomes in clinical practice should ideally be studied in intervention studies.

Importance of the patient perspective in JIA care and research

Most treat-to-target strategies are predominantly focused on disease activity, but many JIA patients in clinical remission suffer from persisting pain and fatigue[35]. This was also observed in Chapter 10 of this thesis where I investigated PROMs following ADA and ETN therapy. Since PROMs cover a broader range of patient health than merely disease activity, clinicians should consider these in guiding treatment decisions, further facilitating a personalised medicine approach to the care of JIA. A consensus conference of the Pediatric Rheumatology Care and Outcomes Improvement Network (PR-COIN) identified the importance of involving patients and their caregivers already at the beginning stage of (defining a treatment target for) a treat-to-target approach[73]. As an example, it could be that some patients and families prefer a step-up approach over a step-down approach and are willing to settle for a lower chance of success if they can use less medication with potential side effects. Shared decision making between clinicians, patients and their caregivers can potentially improve clinical outcomes, for instance by better adherence to medication[34]. Personalised medicine tools, such as model predictions could also be used to inform patients and parents with the aim of informed shared decision making.

In this thesis, I presented that PROMs can be used by paediatric rheumatologists for home-monitoring disease activity (Chapter 12) and predicting a diagnosis of JIA instead of CMPS (Chapter 2). It was described in an editorial that predictions from the latter article can potentially also be used by general paediatricians in order to identify and prioritise children with possible JIA for prompt referral to paediatric rheumatology, especially in settings with a shortage of paediatric rheumatologists[74]. In order to increase face validity and construct validity for home-monitoring, the JAMAR could be further improved by distinguishing between painful and swollen joints. This should help assessors of home-

monitoring results in distinguishing between inflammatory and non-inflammatory pain. In the future, the JAMAR and other PRO tools could also be improved with computer adaptive testing, which is a technology that determines which questions a patient has to answer based on previous provided answers such that questionnaires can be shortened without losing patient-reported information. Computer adaptive testing has already been studied in JIA for the Patient-Reported Outcomes Measurement Information System (PROMIS) measures[75]. A new disease activity score based on parent-centred outcome measures, the parent JADAS, is currently under development and preliminary results have indicated excellent discriminative and predictive ability[76]. The parent JADAS could therefore be a reliable tool for remote disease monitoring.

Patient involvement is not only important in the care of JIA, but also in research. Since patients are the end-users of scientific research together with clinicians, they can greatly contribute to setting research priorities and improving the impact of research on clinical practice, for example through patient organizations such as the European Network for Children with Arthritis (ENCA) and the European Reference Network on immunodeficiency, auto-inflammatory and autoimmune diseases (ERN-RITA; www.ern-rita.org). Some rheumatology journals already include a patient and public involvement statement for each submission. As an example, a method for collaborative research agenda setting by Dutch JIA patients, caregivers and clinicians has been developed by the James Lind Alliance[77]. This effort subsequently identified that top research priorities in JIA are the treatment and mechanisms of persisting pain and fatigue when there is no more arthritis[78]. Surprisingly, the JAMAR which is often used in the clinic as well as in research does not have an item about fatigue, and it is currently being researched how this can be added.

FUTURE PERSPECTIVES

Collaboration in JIA research

Since JIA is rare and its related outcomes even more so, there is strength in (international) collaboration. In this thesis, I collaborated with other departments such as ophthalmology and paediatric gastroenterology, and international centres and registries. By using the Pharmachild data from JIA patients treated in PRINTO centres from 31 countries in the world, it was possible to provide the most comprehensive overview of the prevalence and associated factors of familial autoimmune disease (Chapter 3). Following a grant from FOREUM Foundation for Research in Rheumatology, it was possible to describe the occurrence of four key comorbidities in three international registries, the largest sample of JIA patients so far, indicating regional differences and similarities (Chapter 4). Moreover, data from collaborating centres can be used to externally validate clinical prediction

models, as presented in Chapter 6 of this thesis. External validation of prediction models is especially important for realizing predictions that are generalizable to patients different from the development data, for instance based on ethnicity. By collaboration, not only prediction tools can be validated across registries, but also other study items such as newly developed PROMs. For successful collaboration, it is important to agree in advance upon which data to collect and how on a consistent basis in order to further facilitate validation of research findings and data harmonization. Preferably, raw data of patients with informed consent should be exchanged between collaborators in order to be able to perform in-depth analyses such as individual participant data (IPD) meta-analyses, rather than merely descriptive statistics. This is also in line with the FAIR principles for Findable, Accessible, Interoperable and Reusable data[79]. If patients do not provide consent for exchanging their data, remote cooperation is still possible by exchanging data analysis scripts, as was done for validating and recalibrating the prediction model for uveitis in Chapter 6. Future ERN registries will be built on this federated principle avoiding exchange of health data.

Challenges of big data

Given the current technological possibilities, we are living in the era of big data and real-world evidence. In order to put the large amounts of healthcare data to research and ultimately improved patient care, it is important for medical centres to have a stable and automated data storage infrastructure. For performing more advanced statistical methods, it is also important that data is being stored with sufficient detail. For instance, in order to perform time-varying drug therapy analyses, as described in Chapter 9 of this thesis, it is important that start and stop dates of medication are stored in a structured and easily accessible way. Another major topic for the use of big data from real-world settings for research purposes, is patient privacy and informed consent. When researchers want to study RWD of a large group of patients, it is often not practical to retrospectively collect study-specific informed consents. In such cases, only data from patients with informed consent for a broad range of research questions can be used. For instance, it was not possible to use retrospective data from a number of patients due to a lack of overarching informed consents in the studies presented in Chapters 2 and 9 of this thesis. This could potentially lead to selection bias in the resulting sample of patients who did give consent. In fact, bias in RWD can be related to the way informed consent is collected[25]. Therefore, in the ideal world, academic centres should work with broad informed consents for the use of anonymous routine healthcare data for research purposes. In this system, all (new) patients are asked for consent and whether or not they agree to sharing their anonymous data with third parties (i.e. a multicentre registry or collaborating research centres). Additional study-specific informed consent can be collected in case researchers want to study an intervention or collect biobank material. For this system, researchers should be able to work with anonymous data only and should not have to gather additional data

from electronic health records. In the Netherlands, some centres already have such a system of broad informed consents in place and the Wilhelmina Children's Hospital is currently working on this. Federated registries do not collect health data and are thus in line with the General Data Protection Regulation (GDPR). The EULAR has already published a number of points to consider when making use of big data in rheumatic diseases, addressing privacy, ethical and legal principals[80].

Vaccine safety and efficacy in JIA

According to recent European Alliance of Associations for Rheumatology (EULAR) recommendations, non-live vaccines are effective and save in paediatric patients with autoimmune inflammatory rheumatic diseases such as JIA, meaning they do not aggravate disease activity or cause serious adverse events[81]. This includes patients who are receiving immunomodulatory or immunosuppressive treatment, except for high-dose glucocorticoids and B-cell depleting therapies such as rituximab. The guidelines recommend administration of vaccines from national immunization programs, vaccines advised for travel and seasonal influenza vaccines, and yearly assessment of vaccine antibody levels by treating specialists. This is especially important since immunosuppressive treatment for arthritis poses an increased risk of severe infections, especially with the varicella zoster virus (VZV) or influenza virus[82]. The most recent EULAR and ACR recommendations for immunization in JIA recommend against using live-attenuated vaccines such as the yellow fever and Bacillus Calmette-Guérin (BCG) vaccine in patients who are receiving immunosuppressive treatment, due to the risk of infection with the attenuated pathogen[83]. The EULAR recommendations, however, make an exception for the measles-mumps-rubella (MMR) booster and VZV vaccine under specific conditions[81]. A study of retrospective data from 13 paediatric rheumatology centres from ten countries around the world confirmed safety of the measles-mumps-rubella-varicella booster vaccine in children with JIA and other rheumatic diseases[84]. In addition, a multicentre RCT of 137 JIA patients demonstrated immunogenicity of the MMR booster vaccine without any effect on disease activity[85]. The efficacy of the VZV vaccine was also observed in Chapter 4 of this thesis, with the lowest VZV infection rates in German JIA patients who receive the VZV vaccine as part of the national immunisation program. Nonetheless, some studies have indicated that immunosuppressive drugs such as anti-TNF agents result in a reduced immunogenicity of vaccines in children with JIA[81]. This was also observed for the MenACWY vaccine in Chapter 11 of this thesis. A cross-sectional study furthermore reported lower antibody concentrations and seroprotection rates against mumps, rubella, diphtheria and tetanus in JIA patients compared to healthy controls[86]. Therefore, more (prospective) data should be collected on safety, immunogenicity and efficacy of vaccines in JIA patients. As there is a need for large and representative data, these should ideally be collected via initiatives of international collaboration, such as the Paediatric Rheumatology European Society (PReS) vaccination study group. In Chapter 11, an extra booster vaccine

for MenACWY was recommended one year after the first vaccination in JIA and IBD patients treated with anti-TNF agents, and the effects of this booster on immunogenicity over time should be monitored in a follow-up study. Hopefully, such a study will also yield thresholds for IgG antibody concentrations with 100% protective serum bactericidal assays (SBA), as these have not been identified in the current study. With new variants of the SARS-CoV-2 virus emerging, it will be interesting to study immunogenicity and effectiveness of future COVID-19 vaccines in JIA patients, including the effects of drug therapy. Previous studies have reported the current mRNA vaccines for COVID-19 to be immunogenic, safe and effective in children with autoimmune rheumatic diseases[87–93].

Novel drugs for JIA treatment

In the last years, a number of new drugs for treating JIA has become available, for which it will be interesting to study effectiveness and safety in comparison with previous medication. For this, researchers could make use of RWD and statistical methods to adjust for confounding by indication, as presented in Chapter 10 of this thesis where I compared the TNF-inhibitors ADA and ETN. Biologic DMARDs are costly drugs, especially when still on patent. When their patent is expired, biosimilars that contain a version of the same active substance can lower the price and thereby increase therapeutic options for JIA patients, especially in low-income countries. Since 2016, more than ten biosimilars with different administration routes have been approved for ETN and ADA[94]. This has indeed led to significant cost reductions in the treatment of rheumatic diseases, and some countries even require the use of approved biosimilars[95]. In order to have a biosimilar approved, the developer has to demonstrate similar safety and efficacy to the bio-originator in a RCT in just a single indication. After this, results are extrapolated to all other indications of the bio-originator, which often includes the paediatric age group[95,96]. For this reason, there is a need for long-term surveillance of efficacy and type, severity and frequency of side-effects of biosimilars used in JIA. Few studies are available, but results so far have demonstrated similar efficacy and adverse event rates in JIA patients starting a biosimilar compared to JIA patients starting a bio-originator, and similar outcomes after switching from bio-originator to biosimilar[97–100]. However, two studies reported more reactions/burning sensations at the injection site with biosimilars, which is probably related to the type of conservatives (acids) used[97,99]. Another group of relatively new drugs used in the treatment of JIA and other rheumatic diseases are Janus kinase (JAK) inhibitors, which belong to the class of targeted synthetic DMARDs. These drugs inhibit the activity of one or more JAK proteins which stimulate the production of pro-inflammatory cytokines. Evidence from adult RA patients has shown that JAK inhibitors are more effective than MTX in the early stages of arthritis, and at least as effective with similar toxicity compared to biologicals in patients who failed conventional synthetic DMARDs[101,102]. A phase 3 randomised controlled withdrawal trial (RCWT) provided the first evidence of the efficacy of orafl tofacitinib for polyarticular course JIA[103], and subsequently in 2020 it was the first

JAK inhibitor to be approved for treating JIA. Currently, at least four more trials on the efficacy and safety of tofacitinib and baricitinib in (other subtypes of) JIA are ongoing[104,105]. Additional treatment options for JIA are important for children who do not adequately respond to other treatments or might want to avoid injections. For the future, it will be important to confirm efficacy and assess the long-term safety profile of JAK inhibitors in JIA from RWD or international registries. Especially since patents will expire in the coming years and their costs for production are considerably lower compared to biologicals[105].

Proper methodology in prediction research

In order to make an impact on clinical practice, sound methodology of future prognostic and diagnostic prediction research in JIA is of utmost importance. For this, researchers should adhere to the TRIPOD guidelines for transparent reporting of multivariable prediction models for individual prognosis or diagnosis[106]. Furthermore, clinical prediction models should always be validated based on discrimination and calibration before being used in the clinic, preferably in an external independent cohort. This is to make sure that a prediction model also performs well in different patients than those from the development cohort. As described in Chapters 5 and 6 of this thesis, where I presented prediction models for uveitis in JIA, model predictions in patients from other settings than the development cohort can also be improved by adjusting for optimism and model recalibration. It should be mentioned that there is in general no correct procedure for developing a clinical prediction model. In contrast to classical statistics where it is discouraged to perform multiple testing due to the risk of increasing the type 1 error probability[107], it is acceptable in prediction research to develop multiple models with different predictors and algorithms and validate their predictive performance. This is because in prediction research, interest is not in statistical associations expressed as *P*-values, but merely finding an optimal model in which the predicted values are closest to the observed values. Measures used to assess the performance of a prediction model include the C statistic for discrimination, slope and intercept of a calibration plot, Brier score for overall accuracy and R^2 score for the amount of explained variance[108]. Prediction models should also be user-friendly in order to be useful in the busy clinic. Examples of user-friendly tools for obtaining predicted probabilities are diagrams, risk scores or app-based or web-based risk calculators[109]. Moreover, instead of developing new prediction models for the same clinical endpoints, existing prediction models should ideally be updated with new data. The former approach wastes prior information and unnecessarily increases the number of available prediction models for the same endpoint, making it difficult to decide which model to apply in practice[110]. Updated prediction models also result in better predictions across different patients, whereas newly fitted models might again suffer from overfitting.

Studying the impact of personalised medicine efforts

More progress should be made in demonstrating the long-term (cost-)effectiveness of personalised medicine approaches such as prediction models and remote monitoring in paediatric rheumatology. Ideally, after developing, validating and updating a prediction model, its impact on health outcomes and patient and physician behaviour and management in the clinic should be studied. This can be done in a cluster RCT where groups of patients (e.g. of different physicians or hospitals) are randomised into current practice or prediction model-based practice, which could be merely assistive or directive (i.e. to start a certain treatment above a predefined predicted probability). Examples of model impact measures for clinical usefulness are the net reclassification index (NRI), which measures the improvement in correct treatment decisions gained by using one model versus another, and decision curve analysis, which quantifies the net number of true positive treatment decisions gained by using a model compared to no model over a range of thresholds[108]. Unfortunately, model impact research is not often performed[111]. Nevertheless, evidence on (cost-)effectiveness of personalised medicine approaches are necessary for successful implementation into the current clinical practice for JIA. As for the THUIS study (Chapter 12), in case final results are positive, a logical next step will be to demonstrate cost-effectiveness of skipping a hospital visit using home-monitoring of disease activity, since periodic home-delivery of medication comes with notable costs for the hospital.

Novel trial designs

The most common clinical trial designs used to study JIA are parallel RCTs with placebo or an active comparator such as MTX or NSAIDs, and RCWTs[96,112]. A major limitation of the former design is that some participants will be exposed to placebo only, leading to a reduced willingness for participation and possible ethical concerns from institutional review boards. This is less of a problem in RCWTs, where all participants are treated with a study drug for a defined period of time, only after which responders are randomised to either continue treatment or to placebo. Still, a RCWT has considerable limitations, including a possible carry-over effect in the placebo phase, limited safety and efficacy data (of non-responders) and a bias of treatment effect towards the responders[96]. Out of the mentioned trial designs, parallel RCTs with an active comparator or head-to-head trials should lead to the least ethical obligations, especially since there is currently no strong evidence as to whether or not new drugs such as JAK inhibitors and biosimilars perform differently than established JIA treatments (i.e. the principle of equipoise[2]). Nevertheless, head-to-head trials often require a large sample size for demonstrating a significant effect size[96]. Such studies could therefore also be performed using novel adaptive trial designs. These trials allow for changes in sample size, end-points, or treatment over time based on interim analyses with the aim of identifying the best treatment in the shortest possible time without undermining validity[113]. This could result in fewer participants and possible

prevention of adverse events in case of early evidence for efficacy or futility. A limitation of the adaptive trial design is its challenging statistical analysis, which has to take into account an increased type 1 error as a result of multiple interim analyses. Currently, a multicentre head-to-head RCT with an adaptive trial design is being carried out for comparing the clinical effectiveness and safety of ADA and baricitinib in children with JIA-associated uveitis or chronic ANA-positive uveitis[114]. An overview of the relative strengths and weaknesses of the mentioned trial designs is provided in Table 2.

Table 2. Overview of selected trial designs for studying JIA therapy.

Trial design	Advantages	Disadvantages
Parallel RCT with placebo	Precise effect size Straightforward	Exposure to placebo Low generalisability
Parallel RCT with active comparator	Comparison of effectiveness No exposure to placebo	Large sample size required Less priority to compare drugs of similar classes
Randomised controlled withdrawal trial	All participants get active drug Reduced time on placebo	Bias towards responders Possible carry-over effect in placebo phase
Adaptive trial	Flexible and efficient Prevention of adverse events	Challenging statistical analysis Risk of operational bias if interim analyses are not blinded

Adapted from: *Balevic SJ, Becker ML, Cohen-Wolkowiez M, Schanberg LE. Paediatr Drugs 2017;19(5):379-389. doi:10.1007/s40272-017-0244-2*

Improved JIA classification

The current globally accepted International League of Associations for Rheumatology (ILAR) classification system of JIA was proposed in 2001 by consensus based on expert opinions of paediatric rheumatologists and not formally validated[115]. There is however evidence that some ILAR categories such as rheumatoid factor (RF)-negative polyarthritis and psoriatic arthritis represent heterogeneous conditions and may be better defined[116]. Therefore, there is a need for more homogeneous, evidence-based and validated categories of JIA, which could lead to novel therapeutic targets and treatment strategies. During an international nominal group technique consensus conference held in 2018, six new chronic disorders were proposed that fall under the historical term JIA: (1) systemic JIA, (2) RF-positive JIA, (3) enthesitis/spondylitis-related JIA, (4) early-onset antinuclear antibody (ANA)-positive JIA, (5) other JIA and (6) unclassified JIA[117]. These provisional Paediatric Rheumatology International Trials Organisation (PRINTO) classification criteria are based on clinical and routine laboratory measures and will be validated in at least 1000 new-onset JIA patients[117]. A limitation of both the ILAR and PRINTO classification criteria is that no drugs have been registered for the residual groups (i.e. undifferentiated arthritis and unclassified arthritis, respectively), and that these groups are often not included in RCTs[118]. The UCAN CAN-DU study also aims to develop a new clinical and biology-based taxonomy for JIA. Future JIA care and research is therefore likely to be

based on a set of more homogeneous classifications, which could potentially lead to improved drug therapies, treatment guidelines and predictions of disease course. Better defined JIA categories could also reduce the current differences in classification between childhood-onset and adult-onset arthritis[119], thereby facilitating future collaboration between paediatric and adult rheumatologists in patient care and research. Further improvements in JIA categories might be supported by genetic profiling. For instance, it has been reported that RF-positive polyarticular JIA is genetically more similar to adult RA than to other JIA categories[120]. Further improvements could also be made by identifying biological phenotypes using big data and unsupervised machine learning[119,121], but this strategy is largely influenced by the choice of input data.

To conclude, the studies presented in this thesis are a proper reflection of the various ways in which clinical epidemiology can contribute to better care for JIA patients. This thesis provides practical prediction tools for diagnosis and development of uveitis, comprehensive overviews of comorbidities and familial autoimmune diseases including associated factors, valid estimates of treatment and vaccination effects, and a protocol for studying home-monitoring of disease activity. I demonstrated the usefulness of various study designs in answering different questions in the care of JIA, and how advanced analyses can deal with frequently occurring problems of missing data, dependent measurements, time-varying exposure, model overfitting and confounding by indication. I furthermore discussed the (combined) potential of machine learning, RWD, personalised medicine and PROMs in JIA care and research. The chronic nature of JIA, allowing for long-term prospective data-collection, and continuous developments in drug therapy, vaccination, patient involvement and international collaboration, provide a solid foundation for a future of impactful "clinical epidemiological studies for improving patient care in JIA".

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CHAPTER 14

14

Appendices

LIST OF ABBREVIATIONS

ACR:	American College of Rheumatology
AD:	autoimmune disease
ADA:	adalimumab
AE:	adverse event
AITD:	autoimmune thyroid disease
ANA:	antinuclear antibodies
bDMARD:	biological disease-modifying antirheumatic drug
CD:	Crohn's disease
CI:	confidence interval
CHAQ:	Childhood Health Assessment Questionnaire
cJADAS:	clinical Juvenile Arthritis Disease Activity Score
CMPS:	chronic musculoskeletal pain syndrome
CRP:	C-reactive protein
csDMARD:	conventional synthetic disease-modifying antirheumatic drug
ENCA:	European Network for Children with Arthritis
EQ-5D-Y-5L:	EuroQol five-dimensional 'youth' questionnaire with five levels
ERA:	enthesitis-related arthritis
ERN-RITA:	European Reference Network on immunodeficiency, auto-inflammatory and autoimmune diseases
ESR:	erythrocyte sedimentation rate
ETN:	etanercept
EULAR:	European Alliance of Associations for Rheumatology
GD:	Graves' disease
HLA:	human leukocyte antigen
HT:	Hashimoto's thyroiditis
IBD:	inflammatory bowel disease
IC:	indeterminate colitis
IDDM:	insulin-dependent diabetes mellitus
IFX:	infliximab
ILAR:	International League of Associations for Rheumatology
IQR:	interquartile range
JADAS:	Juvenile Arthritis Disease Activity Score
JAFS:	Juvenile Arthritis Functionality Scale
JAK:	Janus kinase
JAMAR:	Juvenile Arthritis Multidimensional Assessment Report
JIA:	juvenile idiopathic arthritis
JIA-U:	juvenile idiopathic arthritis-associated uveitis
JQL:	paediatric rheumatology quality of life scale

LASSO:	least absolute shrinkage and selection operator
LEF:	leflunomide
MAS:	macrophage activation syndrome
MenACWY:	meningococcal ACWY
MTX:	methotrexate
n:	number
NSAID:	non-steroidal anti-inflammatory drugs
oJIA:	oligoarticular juvenile idiopathic arthritis
PGA:	physician global assessment of disease activity
pJIA:	polyarticular juvenile idiopathic arthritis
PReS:	Paediatric Rheumatology European Society
PRINTO:	Paediatric Rheumatology International Trials Organisation
PROM:	patient-reported outcome measure
PS:	propensity score
psJIA:	psoriatic juvenile idiopathic arthritis
RA:	rheumatoid arthritis
RCT:	randomised controlled trial
RF:	rheumatoid factor
RWD:	real-world data
SBA:	serum bactericidal assay
sJIA:	systemic juvenile idiopathic arthritis
SLE:	systemic lupus erythematosus
SSZ:	sulfasalazine
TB:	tuberculosis
THUIS:	testing an increased visit interval scheme using web-based self-evaluation
TRIPOD:	transparent reporting of a multivariable prediction model for individual prognosis or diagnosis
tsDMARD:	targeted synthetic disease-modifying antirheumatic drug
UC:	ulcerative colitis
uJIA:	undifferentiated juvenile idiopathic arthritis
UMCU:	University Medical Centre Utrecht
VAS:	visual analogue scale
VZV:	varicella zoster virus

NEDERLANDSE SAMENVATTING

Jeugdreuma of juveniele idiopathische artritis (JIA) is een verzamelnaam voor verschillende ziekten gekenmerkt door één of meerdere chronisch ontstoken gewrichten vóór het zestiende levensjaar met onbekende oorzaak. In Europa heeft tussen de 16 en 150 per 100.000 kinderen JIA, en daarmee is het de meest voorkomende reumatische aandoening op de kinderleeftijd. De behandeling van JIA heeft als primaire doel om ziekteactiviteit te verlagen en bestaat uit non-steroidal anti-inflammatory drugs (NSAIDs), intra-articulaire en systemische corticosteroïden, synthetische disease-modifying antirheumatic drugs (DMARDs) en/of biologicals. Met name door de beschikbaarheid van de laatste groep medicijnen, is het voor de meerderheid van de JIA patiënten realistisch om inactieve ziekte te bereiken. De ziekte is niettemin een belangrijke oorzaak van (blijvende) invaliditeit en kan doorgaan op de volwassen leeftijd.

In de studies uit dit proefschrift heb ik verscheidene traditionele en geavanceerde epidemiologische methoden gebruikt om relevante vragen aangaande de behandeling van kinderen met JIA te beantwoorden. De onderzoeksvragen uit dit proefschrift hebben betrekking op de diagnose, comorbiditeiten en behandeling van JIA.

Diagnose

In **hoofdstuk 2** concludeerde ik dat de Juvenile Arthritis Multidimensional Assessment Report (JAMAR) goed onderscheid kan maken tussen een diagnose van JIA en chronisch musculoskeletaal pijnsyndroom in kinderen met bijbehorende symptomen. In dit hoofdstuk presenteer ik verder een gevalideerd predictiemodel waarmee kinderartsen de kans kunnen berekenen op een diagnose van JIA in plaats van chronisch musculoskeletaal pijnsyndroom op basis van de antwoorden uit een JAMAR vragenlijst van de patiënt. Aangezien JIA en chronische pijn de meest voorkomende diagnoses binnen de kinderreumatologie zijn en deze alleen kunnen worden gedifferentieerd middels lichamelijk onderzoek door ervaren kinderreumatologen, kan dit predictiemodel van toegevoegde waarde zijn, vooral voor ziekenhuizen met weinig beschikbare kinderreumatologen.

In **hoofdstuk 3** gaf ik een uitgebreid overzicht van de prevalentie van verschillende auto-immuunziekten bij ouders van kinderen met JIA uit het internationale Pharmachild register. De meest voorkomende familiaire auto-immuunziekten waren psoriasis, auto-immuun schildklierziekte, reumatoïde artritis en de ziekte van Bechterew. Kinderreumatologen zouden deze ziekten dus niet over het hoofd moeten zien tijdens het afnemen van de familieanamnese bij een mogelijke nieuwe JIA patiënt. De prevalentie van verscheidene auto-immuunziekten was hoger in ouders van JIA patiënten in vergelijking met prevalentie cijfers in de gezonde populatie zoals gerapporteerd in de wetenschappelijke literatuur.

Dit impliceert dat de aanwezigheid van auto-immuunziekten in de familie een risicofactor is voor het ontwikkelen van JIA. Een positieve familieanamnese was geassocieerd met het JIA subtype maar niet de ernst of het verloop van de ziekte.

Comorbiditeit

In **hoofdstuk 4** rapporteerde ik de incidentie van macrofaagactiveringssyndroom, tuberculose, waterpokken, gordelroos en uveïtis tijdens het gebruik van methotrexaat (MTX) en biologicals in drie van de grootste JIA registers wereldwijd: de Britse JIA Biologic Registers (BCRD/BSPAR-ETN), de Duitse BiKeR en JuMBO biologic registers en het internationale Pharmachild register. Waterpokken/gordelroos kwam minder vaak voor in de Duitse registers vanwege een hogere vaccinatiegraad. Deze studie demonstreerde de mogelijkheden voor internationale samenwerking bij het bestuderen van relatief zeldzame ziekten en ziekte-uitkomsten, maar toonde ook uitdagingen aan voor het succesvol harmoniseren van data uit verschillende registers.

In **hoofdstuk 5** presenteerde ik een klinisch predictiemodel voor zowel acute als chronische uveïtis bij JIA patiënten, zodat behandelaars individuele voorspelde kansen kunnen verkrijgen in plaats van subjectieve risicotermen uit oogheelkundige screening richtlijnen. Deze voorspelde kansen kunnen worden gebruikt om te helpen bij het bepalen van de frequentie voor screening, het soort medicatie en het informeren van patiënten en ouders/verzorgers. Dit was de eerste studie waarin een klinisch toepasbaar predictiemodel voor JIA-geassocieerde uveïtis is gerapporteerd.

In **hoofdstuk 6** ontwikkelde en valideerde ik een klinisch predictiemodel voor het ontstaan van chronische uveïtis bij verschillende ziekteduren van JIA. Dit was de eerste studie waarin een extern gevalideerd predictiemodel voor JIA-geassocieerde uveïtis is gepresenteerd. In het artikel worden ook aanbevelingen gegeven voor gebruik van het predictiemodel in de klinische praktijk, welke zullen worden besproken in de Multinational Interdisciplinary Working Group for Uveitis in Childhood (MIWGUC).

In **hoofdstuk 7** bestudeerde ik de prevalentie en voorspellende factoren voor auto-immuun schildklierziekte in kinderen met JIA. Ik concludeerde dat de sterkst voorspellende factor voor auto-immuun schildklierziekte een positieve familieanamnese is. Deze studie geeft daarom aanleiding tot de suggestie dat artsen screening op schildklieraandoeningen moeten overwegen bij patiënten met een positieve familieanamnese, welke is gebaseerd op standaard bloedonderzoek.

In **hoofdstuk 8** rapporteerde ik dat de incidentie van inflammatory bowel disease (IBD) verhoogd is in JIA patiënten die etanercept (ETN) gebruiken, onafhankelijk van combinatie therapie met MTX. IBD was verder geassocieerd met enthesitis-gerelateerde artritis (ERA)

en een positieve familieanamnese voor auto-immuunziekten. Hierdoor heeft behandeling met adalimumab (ADA) mogelijk de voorkeur boven ETN in deze groep JIA patiënten.

Behandeling

In **hoofdstuk 9** beschreef ik een gematchte case-control studie naar het effect van MTX op het ontstaan van de uveïtis in biological-naïeve JIA patiënten. MTX was geassocieerd met een bijna drie keer lagere hazard voor uveïtis ontwikkeling in een gecorrigeerde survivalanalyse met tijdsafhankelijke variabele. Er was geen statistisch significant verschil tussen een lage en standaard MTX dosering. De helft van de patiënten die uveïtis ontwikkelden na het stoppen van MTX therapie, ontwikkelden dit binnen één jaar. Vanwege deze resultaten wordt in het artikel voorgesteld om MTX (in lage dosering) snel te starten bij JIA patiënten met een hoog risico op het ontwikkelen van uveïtis en om frequent te screenen op uveïtis kort na het stoppen van MTX.

In **hoofdstuk 10** maakte ik gebruik van real-world data en propensity score analyses om een valide vergelijking te maken van de effecten van ADA en ETN op verschillende klinische uitkomsten in JIA. Beide medicijnen verbeterden ziekteactiviteit in vergelijkbare mate maar de data suggereerden een iets sterkere verbetering van patiënt-gerapporteerd welzijn voor ETN ten opzichte van ADA, alhoewel niet statistisch significant. Grotere studies zijn nodig om dit effect te bevestigen maar een daadwerkelijk verschillend effect zou veroorzaakt kunnen worden door injectiepijn als gevolg van een citraatbuffer in ADA, welke inmiddels uit het medicijn is verwijderd. In deze studie zagen wij dat ziekteactiviteit gescoord door de arts niet altijd correleert met welzijn gescoord door de patiënt, wat aangeeft dat patiënt-gerapporteerde uitkomsten altijd moeten worden meegenomen in de behandeling van JIA.

In **hoofdstuk 11** rapporteerde ik de resultaten van een prospectieve cohort studie naar de veiligheid en immunogeniciteit van het meningokokken ACWY (MenACWY-)vaccin in JIA en IBD patiënten op de lange termijn. Het MenACWY-vaccin veroorzaakte geen serieuze bijwerkingen of een verhoogde ziekteactiviteit. IgG antilichaam concentraties tegen alle vier de serogroepen waren lager in patiënten die tumornecrosefactor (TNF)-α-remmers gebruikten ten opzichte van patiënten die dit niet gebruikten en gezonde controles van dezelfde leeftijd. Het percentage patiënten dat TNF-α-remmers gebruikte met protectieve antilichaam titers tegen serogroep W één jaar na vaccinatie was slechts 76%. Aangezien dit percentage waarschijnlijk verder zal dalen over de tijd, wordt in het artikel geadviseerd om alle patiënten met TNF-α-remmers een booster vaccinatie aan te bieden na één jaar.

In **hoofdstuk 12** presenteerde ik het studieprotocol en interim-resultaten van de THUIS studie. Het doel van deze studie is om aan te tonen dat JIA patiënten met inactieve ziekte veilig een driemaandelijkse controle bij de kinderreumatoloog kunnen overslaan middels

het thuismonitoren van ziekteactiviteit met online vragenlijsten. Op 17 oktober 2022 waren er 76 deelnemers geïncludeerd, waarvan 72% een online vragenlijst voor thuismonitoring had ingevuld. Veertien procent van de deelnemers was opgevolgd na zes maanden en het overslaan van één driemaandelijkse controle. In 9% van de studiedeelnemers werd een opvlamming van de artritis geconstateerd. Dit percentage is niet hoger in vergelijking met historische data van patiënten met inactieve ziekte uit het Wilhelmina Kinderziekenhuis. Verder gaven alle opgevolgde deelnemers aan in de toekomst vaker gebruik te willen maken van thuismonitoren.

DANKWOORD

In dit hoofdstuk richt ik graag een dankwoord aan een aantal personen voor hun bijdrage aan de totstandkoming van dit proefschrift.

Om te beginnen, dank ik alle jeugdreuma patiënten uit binnen- en buitenland voor hun deelname aan onze onderzoeken. In gesprek met de patiënten van het WKZ ervoer ik vaak de goede wil om bij te dragen aan een nog betere zorg voor kinderen met jeugdreuma in de toekomst. Dankzij jullie bereidheid gaat die er zeker komen.

Beste Nico, ik prijs mij gelukkig met een deskundige en vriendelijke promotor zoals jij. Ik ben onder de indruk van wat jij hebt neergezet aan zorg en onderzoek op het gebied van jeugdreuma in het WKZ en internationaal, waarvan ik ook dankbaar gebruik heb mogen maken. Bedankt ook dat je mij hebt betrokken bij jouw vaccinatiestudies, iets waar ik in de toekomst zeker profijt van ga hebben. Ik wens je veel voorspoed en plezier tijdens je pensioen en werkzaamheden voor ERN-RITA en wij houden contact.

Dan mijn copromotoren en dagelijkse begeleiders, Joost en Sytze. Als ik collega's tijdens mijn promotietraject vertelde wie mijn begeleiders waren, kreeg ik letterlijk altijd als reactie dat ik het goed heb getroffen. Ik heb jullie ervaren als deskundige, laagdrempelig te bereiken en uiterst behulpzame begeleiders. Er was tijdens onze samenwerking altijd ruimte voor humor en persoonlijke zaken, wat zeker niet ten koste ging van de kwaliteit van ons onderzoek. Ook dachten jullie altijd mee aan mijn persoonlijke ontwikkeling, getuige ook jullie goedkeuring voor het volgen van de epidemiologie opleiding en het BKO traject. Voor dit alles wil ik jullie heel erg bedanken. Ik had mij oprecht geen aangenamer promotietraject kunnen voorstellen.

Members of the assessment committee, prof. dr. D.E. Grobbee, prof. dr. L.J. Bont, prof. dr. E.A.M. Sanders, prof. dr. A.V. Ramanan and dr. J.M. van den Berg, thank you for reading and reviewing my dissertation.

Beste leden van mijn begeleidingscommissie, Sanne Nijhof en Geert Frederix, bedankt voor de voortgangsgesprekken tijdens mijn promotietraject. Jullie hebben mij er meermaals op gewezen om ook vooral aandacht te besteden aan een goede balans tussen werk en privé. Jullie tips neem ik zeker mee in de rest van mijn carrière.

Beste collegae van de first floor, bedankt voor alle gezellige koffiemomenten, brainstormsessies, activiteiten buiten het ziekenhuis en de verbondenheid. Ik vond het geweldig om te werken in een omgeving met mede PhD'ers van dezelfde leeftijd uit

verschillende afdelingen van het ziekenhuis. Ik wens jullie allen het allerbeste voor de toekomst op het gebied van onderzoek en kliniek maar bovenal de privésfeer.

I furthermore thank my colleagues from PRINTO, Nicola, Gabriella, Luca and Chiara. Thank you for your past and present work on the Pharmachild registry, and your cooperation on many of the studies that are presented in this thesis. I believe they are a great example of international scientific collaboration within paediatric rheumatology.

Dear Lianne, dear Jens, I enjoyed our collaboration on different studies as part of the FOREUM project. Thank you for all the efforts, especially in trying to remotely execute my scripts in R.

Bedankt Gerrie en Regina voor al jullie hulp bij de THUIS studie. Jullie zijn onmisbaar voor alle patiëntonderzoeken op de afdeling. Bedankt voor de ontspannen en gezellige sfeer die jullie meebrengen en ik wens jullie het beste voor de toekomst.

Dank ook aan Bas, Erika, Annet, Berent, kinderreumatologen van het WKZ, voor hun bijdrage aan de THUIS studie en alle prettige gesprekken. Ik heb de sfeer op de afdeling altijd als erg gemoedelijk en laagdrempelig ervaren, iets wat erg te prijzen valt.

Beste Marc, ik heb genoten van onze samenwerking aan de verschillende vaccinatiestudies op de afdeling. Bedankt voor al je deskundige inbreng en scherpe humor.

Dear Mohamad, it was a pleasure to work and socialise with you. You are a friendly, clever and hardworking person. We had lots of fun during the PReS congress in Prague. I wish you all the best in your working and private life in Israel.

Beste Milou, bedankt voor de prettige en succesvolle samenwerking aan de MenACWY studie(s). Ik bewonder jouw nauwkeurigheid en verstand van zaken en wens je veel succes met jouw opleiding tot medisch microbioloog.

Ook bedank ik alle onderzoeksstudenten met wie ik heb mogen samenwerken tijdens mijn promotieonderzoek: Yasmine, Jade, Roline, Laurie, Martine, Simone, Robin en Görkem. Jullie hebben allen fantastisch werk geleverd en waren prettig in de omgang.

Beste Joke, bedankt voor de prettige samenwerking aan twee van de uveïtis studies in dit proefschrift. Jouw oogheelkundige expertise was essentieel voor het doen van concrete aanbevelingen voor de klinische praktijk.

Bedankt Patricia Bruijning voor de begeleiding tijdens mijn onderzoeksproject voor de epidemiologie opleiding. Door jouw kritische blik verbeterde de methodologie van het onderzoek telkens weer.

Ook dank ik Marjolein Musbach, kwaliteitscoördinator onderzoek. Zonder jouw antwoorden en instructies is het doen van WMO-plichtig onderzoek haast niet te doen met alle strikte regelgeving.

Mijn dank gaat ook uit naar de huidige en voormalige secretaresses van cluster B: Annelies, Astrid, Marit, Kirsten en Yvonne. Bedankt voor jullie snelle en adequate hulp bij o.a. het versturen van brieven naar studiedeelnemers en het inplannen van vergaderingen.

Veel dank ook aan alle MAAZ-en voor hun assistentie op de poli bij de THUIS studie.

Ik bedank graag Ewoud Schuit voor zijn deskundige raad bij het kalibreren en valideren van verschillende soorten predictiemodellen (in R).

Bedankt Pauline Heus voor je hulp en het denken in mogelijkheden voor het behalen van mijn BKO certificaat.

Beste Trijn Israels, bedankt voor de mogelijkheid om extra onderzoekservaring op te doen in het Prinses Máxima Centrum en het doen van een goed woordje als referent tijdens mijn sollicitatie voor dit promotietraject.

Beste familie in Suriname, in het bijzonder Ernest, Monique, Lucien, Wilfred, Deborah en oma Angela, bedankt voor jullie liefde, bemoediging en steun en ik hoop jullie in de toekomst vaker te bezoeken.

Beste familie Van Straalen, welke zo groot is dat zij een eigen familiekrant heeft, in het bijzonder Nico, mijn peetouders Lia en Theo en Anneke, bedankt voor jullie hulp in mijn opvoeding, inspiratie en enthousiasme.

Lieve tantes Silvana en Dina, bedankt voor al jullie liefde, letterlijk vanaf mijn geboorte. Jullie noemen mij allebei jullie zoon, ik heb dus drie moeders!

Dan mijn paranimfen, Martijn en Chevy. Wij hebben samen mooie tijden meegemaakt tijdens werk en studie en ik zie jullie daarbuiten als goede vrienden. Daarnaast delen wij het één en ander zoals het geloof en het getrouwde leven. Wat fijn dat jullie mij bijstaan tijdens en voorafgaand aan mijn verdediging.

Lieve schoonfamilie, Iván, Dalia en Roxana, bedankt voor jullie warmte en gastvrijheid. Al bijna tien jaar voel ik mij welkom en geliefd bij jullie thuis. Ik kijk er naar uit om samen in de toekomst nog vele mooie momenten mee te maken.

Mijn lieve zusjes, Fayollah en Chabeli, het voelt soms onwerkelijk om te zien hoe groot en volwassen jullie zijn geworden. Ik ben ontzettend trots op jullie. Jullie doen het super goed met werk, studie, sport en ons lieve nichtje, Aaliyah.

Lieve pa en ma, ik ben jullie heel dankbaar voor de liefdevolle opvoeding die ik heb genoten. Jullie hebben mij middels hard werken alle kansen gegeven om iets te worden in de maatschappij. Bedankt voor al jullie moeite. Jullie zijn een voorbeeld voor mij.

Lieve Andrea, mijn vrouw. Ik noem jou altijd mijn maatje, omdat je dat ook echt bent. Samen met jou is werkelijk alles leuk, en in mindere tijden sta jij altijd voor mij klaar. Ik ben trots op ons. Ik hou van je.

Als laatste bedank ik de Heiland en Verlosser, Jezus Christus. Here, bedankt voor Uw onvoorwaardelijke liefde, kracht, wijsheid en genade. Aan U alle eer.

CURRICULUM VITAE

Joeri William van Straalen was born on 30 January, 1995 in Hoorn, the Netherlands. After completing secondary education and the International Baccalaureate (IB) diploma programme, he went on to study Biomedical Sciences at VU University Amsterdam. After obtaining his BSc degree with elective courses in public health and epidemiology, he completed the MSc program in Health Sciences from VU University Amsterdam with a specialization in International Public Health. As part of his MSc program, he performed a study on predictors for mortality in tuberculosis patients in Suriname, South America. Following graduation, he worked as a teaching assistant in research methods at the Athena Institute of VU University Amsterdam, and later as a research assistant at both the VU University department of Epidemiology and Biostatistics and Princess Máxima Centre in Utrecht. In April 2019, he started his PhD in Clinical Epidemiology at the department of Paediatric Immunology and Rheumatology of the University Medical Centre Utrecht, with a focus on patient care in juvenile idiopathic arthritis. During his PhD training, he obtained a Postgraduate MSc degree in Epidemiology and University Teaching Qualification (BKO) from Utrecht University. He is a registered epidemiologist at the Netherlands Epidemiology Society (VvE) and currently works in the field of infectious disease control at the Public Health Service (GGD) Flevoland in Almere, the Netherlands. Joeri lives together with his wife Andrea in Amsterdam.

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*contributed equally

Not in this thesis

Hamad Saied M, van der Griend L, **van Straalen JW**, Wulffraat NM, Vastert S, Jansen MHA. The protective effect of COVID-19 vaccines on developing multisystem inflammatory syndrome in children (MIS-C): a systematic literature review and meta-analysis. Pediatr Rheumatol Online J. 2023 Aug 7;21(1):80. doi: 10.1186/s12969-023-00848-1.

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measles-mumps-rubella booster vaccination in children with juvenile idiopathic arthritis. Vaccine. 2023 Jul 27:S0264-410X(23)00883-6. doi: 10.1016/j.vaccine.2023.07.052.

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*contributed equally

PHD PORTFOLIO

Name: Joeri van Straalen
PhD period: 1 April, 2019 – 31 March, 2023
PhD supervisors: Prof Dr Nico Wulffraat, Dr Joost Swart, Dr Sytze de Roock

PhD training	Year	Workload
MSc Epidemiology Postgraduate courses		
Introduction to Epidemiology	2019	3 ECTS
Introduction to Statistics and SPSS	2019	1.5 ECTS
Study Design	2019	3 ECTS
Classical Methods in Data Analysis	2019	6 ECTS
Clinical Epidemiology	2019	1.5 ECTS
Clinical Trials and Drug Risk Assessment	2019	1.5 ECTS
Modern Methods in Data Analysis	2020	4.5 ECTS
Research Ethics and Society	2020	1 ECTS
Prognostic Research	2020	1.5 ECTS
Advanced Topics in Causal Research: Confounding and Effect Modification	2020	1.5 ECTS
Systematic Reviews in Intervention Research	2020	1.5 ECTS
Generalized Linear Models	2020	1.5 ECTS
Mixed Models	2020	1.5 ECTS
Survival Analysis	2020	1.5 ECTS
Missing Data	2020	1.5 ECTS
Epidemiology of Infectious Diseases	2020	1.5 ECTS
Mathematical Modelling of Infectious Diseases	2020	3 ECTS
Machine Learning: Application in Medicine	2020	1.5 ECTS
Advanced Diagnostic Research	2021	1.5 ECTS
Research Project	2021	56 ECTS
Presentation and Writing Research Proposal	2021	2 ECTS
BKO leergang modules		
Didactiek en onderwijs ontwerpen	2021	0.1 FTE
Blended learning	2021	0.1 FTE
Activerende werkvormen	2021	0.1 FTE
Onderwijs in kleine groepen (deel 1)	2021	0.1 FTE
Begeleiden van individuele studenten	2022	0.1 FTE
Beoordelen van individuele studenten	2022	0.1 FTE
Presenteren en videoreflectie	2022	0.1 FTE
Onderwijs in kleine groepen (deel 2)	2022	0.1 FTE
Toetsing	2022	0.1 FTE
Ontwerpen van onderwijs en presentaties	2022	0.1 FTE

Online GCP-WMO training modules		
Basics	2021	1.5 hrs
Opzet	2021	1.5 hrs
Voorbereiding	2021	1.5 hrs
Indiening	2021	1.5 hrs
Start onderzoek	2021	1.5 hrs
Uitvoer	2021	1.5 hrs
Afronden en archiveren	2021	1.5 hrs
Teaching		
Lectures (3)	2022	9 DBU
Workgroups (16)	2020 – 2022	122 DBU
Supervisor research students (7)	2019 – 2022	245 DBU
Congresses attended		
PReS e-congress & Young Investigator Meeting: poster & oral presentation	2020	10 CME
PReS e-congress & Young Investigator Meeting: poster presentation	2021	14 CME
International Uveitis Study Group symposium, Utrecht, the Netherlands: oral presentation	2022	17 CME
PReS congress & Young Investigator Meeting, Prague, Czech Republic: poster & oral presentation (3rd prize category clinical science)	2022	19 CME
CARRA annual scientific meeting, New Orleans, USA: oral presentation	2023	0.6 FTE