Student thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Clinical and Molecular Medicine

Mads Lillehammer Paulsen and Ludvik Stuve Frøhoel

Sex differences in juvenile idiopathic arthritis (JIA) with respect to disease characteristics and disease outcome

Data based on the Norwegian JIA study (NorJIA)

Student thesis in Medicine
Supervisor: Marite Rygg, MD, Professor, and paediatrician with competence in Paediatric Rheumatology and local principal investigator (PI) for the Nordic JIA study.
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Collaborators

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Co-supervisor: Pål Richard Romundstad, Professor, ISM, expert in Epidemiology, contributes with advice in epidemiology and medical statistics.

Collaborator: Anette Lundestad, MD PhD candidate in the NorJIA project, responsible for the NorJIA database.

Abstract

Background: Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease among children and is an umbrella term which includes eight different categories of the disease.

Aims: We aimed to describe phenotypic sex differences and disease outcome according to sex in a Norwegian JIA cohort assessed twice during a 2-year period.

Methods: We used data from a Norwegian multicentre, observational study, NorJIA, that included 228 children between 4-16 years of age diagnosed with JIA and a control group of 224 children without the disease. Inclusion criteria were participation in the NorJIA study at both study visits. The children were assessed twice over the course of two years with clinical examination, blood samples, and patient-reported outcome measures. We looked for sex differences both at the baseline visit and the second visit. Girls and boys were analysed separately according to demographics, clinical and biochemical characteristics, outcome variables, and treatment. Differences in continuous variables were analysed with a two-sample t-test with unequal variances, and for categorical variables we used two-sampled proportion tests.

Results: We included 208 children, 126 girls and 82 boys. Mean age of the girls was 11.5 (SD 3.2) years and the boys were 12.7 (SD 2.9) (% point difference -1.2 (95% CI -2.0, -0.3)) years at visit 1. A similar sex difference was found for disease onset with mean onset age for girls 5.7 (SD 4.1) and for boys 7.4 (SD 3.9) (% point difference -1.7 (95% CI -2.8, -0.6)). More girls than boys were ANA positive, while the proportion of uveitis was more similar between the sexes. Distinctly more girls than boys had extended oligoarticular JIA while boys had more enthesitis-related JIA, with a % point difference at visit 2 of 11.8 (95% CI 3.8, 19.8) and -15.2 (95% CI -24.8, -5.5), respectively. Girls tended to have poorer outcome with more active disease and especially poorer patient-reported outcome, such as pain (% point difference 28.6 (15.2, 41.9) and physical disability (% point difference 20.4 (8.7, 32.2)). More boys than girls had never been treated with disease modifying antirheumatic drugs (DMARDs) while more girls had been treated only with synthetic DMARDs. The proportions treated with biologic DMARDs were similar.

Conclusion: This study highlights several sex differences in JIA, some of which have been seen in other studies. Less known is the apparent female predominance in the extended oligoarthritis category and the uneven sex distribution in the use of synthetic disease modifying anti-rheumatic drugs. Our results need to be confirmed in larger studies.

Sammendrag

Bakgrunn: Juvenil idiopatisk artritt (JIA) er den vanligste revmatiske sykdommen blant barn og er et paraplybegrep som omfatter åtte sykdomskategorier.

Mål: Vårt mål var å beskrive kjønnsforskjeller innenfor både fenotype og utfall av sykdommen i en norsk kohort av pasienter med JIA som ble undersøkt to ganger i løpet av en periode på to år.

Metode: Vi brukte data fra en norsk multisenter, observasjonsstudie, NorJIA, som inkluderte 228 barn mellom 4-16 år diagnostisert med JIA, og en kontrollgruppe på 224 barn uten sykdommen. Inklusjonkriteriene var oppmøte til begge studievisitter i NorJIA. Barna ble undersøkt to ganger i løpet av to år med klinisk undersøkelse, blodprøver, og pasientrapporterte utfallsmål. Vi lette etter kjønnsforskjeller ved både første og andre studievisitt. Jenter og gutter ble analysert separat med tanke på demografi, kliniske og biokjemiske karakteristika, utfallsvariabler og behandling. Forskjeller i kontinuerlige variabler ble analysert ved hjelp av to-utvalgs t-test, mens for kategoriske variabler brukte vi en proporsjonstest.

Resultater: Vi inkluderte 208 barn, hvorav 126 jenter og 82 gutter. Gjennomsnittlig alder ved første visitt var 11.5 (SD 3.2) år for jentene, og 12.7 (SD 2.9) (prosentpoeng forskjell -1.2 (95% CI -2.0, -0.3)) år for guttene. En lignende kjønnsforskjell ble funnet for sykdomsdebut med gjennomsnittlig debutalder for jenter på 5.7 (SD 4.1) år, og for gutter 7.4 (SD 3.9) år (prosentpoeng forskjell -1.7 (95% CI -2.8, -0.6)). Flere jenter enn gutter var positive for ANA, mens andelen med uveitt mellom kjønnene var mer lik. Betraktelig flere jenter enn gutter hadde utbredt oligoartikulær JIA, mens guttene hadde mer entesitt-relatert JIA, henholdsvis med en forskjell på 11.8 (95% CI 3.8, 19.8) og -15.2 (95% CI -24.8, -5.5) prosentpoeng ved andre visitt. Jenter hadde en tendens til å ha dårligere utfall av sykdommen i form av høyere sykdomsaktivitet, spesielt ved pasientrapporterte utfallsmål som smerte (prosentpoeng forskjell 28.6 (15.2, 41.9)) og fysisk funksjonsnivå (prosentpoeng forskjell 20.4 (8.7, 32.2)). Flere gutter enn jenter hadde aldri brukt sykdomsmodifiserende antirevmatiske legemidler (DMARDs), mens flere jenter hadde blitt behandlet med kun syntetiske DMARDs. Andelen som var behandlet med biologiske DMARDs var nokså lik.

Konklusjon: Denne studien finner flere kjønnsforskjeller ved JIA, hvorav enkelte også har blitt funnet i andre studier. Mindre kjent er den tilsynelatende overvekten av jenter i kategorien med utbredt oligoartritt og den ujevne kjønnsfordelingen i bruk av syntetiske sykdomsmodifiserende antirevmatiske legemidler. Resultatene våre må bekreftes i større studier.

Abbreviations

ACR	American College of Rheumatology
ANA	Antinuclear antibodies
BMI	Body Mass Index
CHAQ	Childhood Health Assessment Questionnaire
CHQ phys	Child Health Questionnaire (physical summary score)
CHQ psyc	Child Health Questionnaire (psychosocial summary score)
CI	Confidence interval
CRP	C-reactive Protein
bDMARDs	Biologic disease-modifying antirheumatic drugs
sDMARDs	Synthetic disease-modifying antirheumatic drugs
ERA	Enthesitis-related arthritis
ESR	Erythrocyte sedimentation rate
GDPR	General data protection regulation
HEp-2 cell	Human epithelial cells
HLA-B27	Human leukocyte antigen B27
ILAR	International League of Associations for Rheumatology
IQR	Interquartile range
JADAS	Juvenile arthritis disease activity score
JIA	Juvenile idiopathic arthritis
NorJIA	The Norwegian juvenile idiopathic arthritis study
NSAIDs	Non-steroid anti-inflammatory drugs
PatGA	The patient's/parents' global assessment of disease impact on wellbeing
PhysGA	The physician's global assessment of disease activity
PROMs	Patient-reported outcome measures
RF	Rheumatoid factor
SD	Standard deviation
SUN	Standardization of Uveitis Nomenclature
TNFα	Tumor necrosis factor alpha
VAS	Visual analog scale
Z-score	Standard deviation score

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Introduction

Juvenile idiopathic arthritis (JIA) is a chronic disease with onset before the age of 16. With approximately 150 newly diagnosed children each year, it is the most common rheumatic disease in children in Norway, as is also true internationally[1,2]. However, the incidence is shown to be especially high in the Nordic countries[3]. JIA is an umbrella term, and the diagnosis is based on the International League of Associations for Rheumatology (ILAR) classification criteria with further subgrouping into eight categories; systemic arthritis, oligoarthritis (persistent or extended), polyarthritis with positive or negative rheumatoid factor (RF), psoriatic arthritis, enthesitis-related arthritis (ERA), and undifferentiated arthritis[4]. JIA is clinically characterized by swollen joints, contractures, morning stiffness, pain, and limping gait. The child may also have extraarticular manifestations, such as fever, rash, and uveitis, depending on the category of JIA[2]. The outcomes are highly variable. Many patients experience fluctuating symptoms, and some achieve complete remission either off or on treatment, while others progress to a more chronic persistent course, with ongoing or recurrent active disease into adulthood[5]. Common medications used to treat children with JIA include non-steroidal anti-inflammatory drugs (NSAIDs) and intraarticular corticosteroids, or synthetic and/or biologic disease-modifying antirheumatic drugs (sDMARDs and bDMARDs). Several different sDMARDs and bDMARDs exist, but some are far more often used than others. Among the most used sDMARDs is methotrexate. The most used bDMARDs are the TNFα-inhibitors, such as etanercept and adalimumab. The etiology of the disease is currently unknown, although both genetic predisposition and environmental factors seem to be involved in the development of the condition[2,6].

The disease generally affects more girls than boys with a ratio of sometimes described as high as 3-6.6:1, but the ratio varies depending on the JIA category[6]. In contrast, ERA more often affects boys than girls[7]. A similar association between axial rheumatic disease and males are also seen in adult rheumatic conditions, while problems from peripheral joints tend to affect females more. The sex differences also depend on the ethnic race of the child, as oligoarthritis is more common among girls in Europe and North America, but more common among boys in Asia[6]. In Asian populations, ERA constitutes a significantly higher proportion of JIA patients compared to that of Caucasian children[7]. Most autoimmune childhood diseases affect boys and girls equally, while women are more prone to autoimmunity than men in adulthood. JIA, however, differs because of the gender-dependent distribution during

childhood. This could indicate that autoimmunity is regulated by factors other than sex hormones, which is known to play a key role in the function of immune cells[6]. Uveitis is a well-known extraarticular manifestation in 20-30% of children with JIA in Europe and is reported to affect girls more often than boys. Less is known about sex differences for other clinical characteristics and disease outcomes[6].

The purpose of our study was to describe sex differences in the cohort of children with JIA included in the Norwegian JIA study (NorJIA) which have been assessed twice during a 2-year period. We investigated whether there were sex differences in demographics, clinical characteristics, and outcomes at the baseline visit and at the follow-up two years later. Our main goal was to investigate if there are unknown differences between the sexes that can complement our current understanding of the underlying mechanisms of the disease or disease categories.

Materials and methods

Study design

The NorJIA study (https://norjia.com) is a prospective, multicenter, observational study which spanned over 5 years, from 2015 to 2020. It included 228 children aged 4-16 years with diagnosed JIA, attending university clinics in Bergen, Tromsø, and Trondheim. These clinics had regional responsibility for the diagnosis and follow-up of all children with rheumatic diseases within their catchment area. The study also included a control group of 224 children with no rheumatic diseases, although this material will not be explored in our thesis. The inclusion criteria were children diagnosed with JIA according to the ILAR criteria, aged between 4-16 years at inclusion, with informed consent from parents or legal guardians (from now only referred to as parents). Apart from absence of consent, there were no other exclusion criteria. The study design of this thesis will be a longitudinal study, comparing data from the baseline examination with the 2-year follow-up data. Additional inclusion criterion in our study was participation at both visit 1 and 2.

Data collection

The participating children with JIA were examined by experienced pediatric rheumatologists at the university hospitals in Bergen, Tromsø, and Trondheim, at visit 1 and two years later at visit 2. In addition, the child (if 9 years or older) or the parents (of children less than 9 years old) filled out several patient-reported outcome measures (PROMS) in the form of validated questionnaires. Information about the highest fulfilled parental education level was reported by the parents, or the participating child if old enough to come alone to the study visit. The participants spent approximately two days on the data collection process for each study visit.

Relevant data from the two study visits included age, sex, body mass index (BMI), onset age, duration of disease, JIA category according to the ILAR classification criteria[4], disease activity status according to the Wallace criteria[8,9], general joint status evaluated by the physician, uveitis, the physician's assessment of disease activity, blood test results, and medication (past and present). Anti-nuclear antibodies (ANA), rheumatoid factor (RF), and human leukocyte antigen B-27 (HLA-B27) were measured around the time of disease onset, while C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured at the study visits. ANA were measured with indirect immunofluorescence with human epithelial cells (HEp-2 cells), and RF were tested twice at least 3 months apart. Height and

weight were measured by experienced pediatric rheumatologists at both study visits. The parents or the child, if 9 years or older, filled out the Childhood Health Assessment Questionnaire (CHAQ) and a self-reported visual analogue scale (VAS) for pain and general wellbeing, as well as reporting duration of morning stiffness.

Measures

Demographics

Parental education levels were divided into 4 groups: Primary and middle school (7 to 10 years of education), high school (11 to 13 or 14 years), university education less than 5 years, and university education more than 5 years. The last two levels were grouped together as higher education. Body mass index (BMI) was calculated using weight (in kilograms) divided by height (in meters) squared. BMI Z-score was estimated using participant mean BMI minus mean BMI for the Norwegian reference population[10], divided by BMI standard deviation (SD) of the reference population.

Clinical characteristics and outcome

The physician's global assessment of disease activity (PhysGA), the patient's or parents' global assessment of disease impact on wellbeing (PatGA), and disease-related pain during the last week were all reported using a 21-numbered circle VAS ranging from 1-10[11]. PhysGA was reported by the physician where 0 = no activity and 10 = maximum activity, while PatGA (0 = very well and 10 = very poor), disease-related pain (0 = no pain and 10 = very severe pain), and morning stiffness (in minutes) were reported by the child, or the parents if the child was under 9 years old.

The Juvenile Arthritis Disease Activity Score based on 71 joints (JADAS71, hereafter referred to as JADAS) is a validated disease activity composite score including four measures; the PhysGA (range 0-10), the PatGA (range 0-10), erythrocyte sedimentation rate (ESR) (normalized to a 0-10 scale), and active joint count assessed in 71 joints (range 0-71) with a total score from 0-101 (0 = no activity, 101 = maximum activity)[12,13].

Uveitis was evaluated according to the Standardization of Uveitis Nomenclature (SUN), defining no active uveitis as < 1 cell in field size 1mm by a 1mm slit beam[14].

Accumulated joints were defined as the total number of active joints (past or present) since disease onset. A joint with active arthritis was defined as a joint with swelling not due to bony enlargement, or limitation of movement accompanied by motion pain or tenderness if

no swelling was present, as defined by The American College of Rheumatology (ACR)[8]. Inactive disease and remission on/off medication was defined according to the modified Wallace criteria endorsed by the American College of Rheumatology[8,9]. The criteria for inactive disease (on or off medication) includes no joints with active arthritis, no active uveitis, no rash, fever or serositis, no splenomegaly or general lymphadenopathy due to JIA, normal ESR and/or CRP (both must be normal if both are tested) unless explained by another condition, no morning stiffness >15 minutes, and PhysGA indicating no active disease. Remission on medication is achieved when the criteria for inactive disease are maintained for at least 6 months, while remission off medication is achieved when the patient maintains inactive disease criteria for at least 12 months after discontinuation of all antirheumatic, anti-inflammatory, and anti-uveitis medications.

Treatment

Past and present treatment at each study visit were divided into 3 groups, based on the use of DMARDs. These groups were 1) no DMARDs, 2) synthetic DMARDs only (sDMARDs), and 3) biologic DMARDs (bDMARDs) with or without sDMARDs. sDMARDs included methotrexate, hydroxychloroquine, cyclosporine, and mycophenolate mofetil. bDMARDs included infliximab, adalimumab, etanercept, certolizumab, golimumab, abatacept, tocilizumab, and rituximab. The three treatment categories were used both for ongoing treatment at the study visit and for treatment ever used since onset (including ongoing medication). Data about other treatments, including NSAIDs, intraarticular steroid injections, and systemic steroids, were also registered, but not used in this study.

Statistical analysis

Continuous data such as age, disease duration, and BMI Z-score, were expressed as mean with either standard deviation (SD) or 95% confidence interval (CI). Most of our data consists of categorical variables, which have been estimated in absolute frequencies and percentages (%).

All variables were assessed for each sex separately and then compared to investigate differences between girls and boys. Differences in continuous variables were analysed with a two-sample t-test with unequal variances, and for categorical variables we used two-sampled proportion tests.

The data were prepared and organized with Microsoft Excel, which was also used for simple analyses and overall summarizing. Statistical analyses were carried out using STATA version 17 (STATA Corp., College Station, Texas, USA). Graphs and figures were created with STATA.

Ethics

The NorJIA study is approved by The Ethics Committee, Helse Vest (REK no 2012/542). The study is registered on ClinicalTrials.gov with Identifier: NCT03904459 (1). Access to data material for this study has been granted by the NorJIA research group, and personal data is collected, managed, and stored according to the General Data Protection Regulation (GDPR). For participants under 16 years old, the parents have given a signed consent with written information. The participating children have been informed about the study by researchers and the parents.

Results

In the NorJIA study, 360 children with JIA were invited to participate, and 228 accepted, giving a response rate of 63.3% (Figure 1). The response rate was 68.4% in Trondheim, 67.1% in Tromsø, and 56.1% in Bergen. Among the 228 participants, 11 boys and 9 girls failed to attend visit 2. These were excluded from this study. The final study included 208 participants, 126 girls (60.1%) and 82 boys.

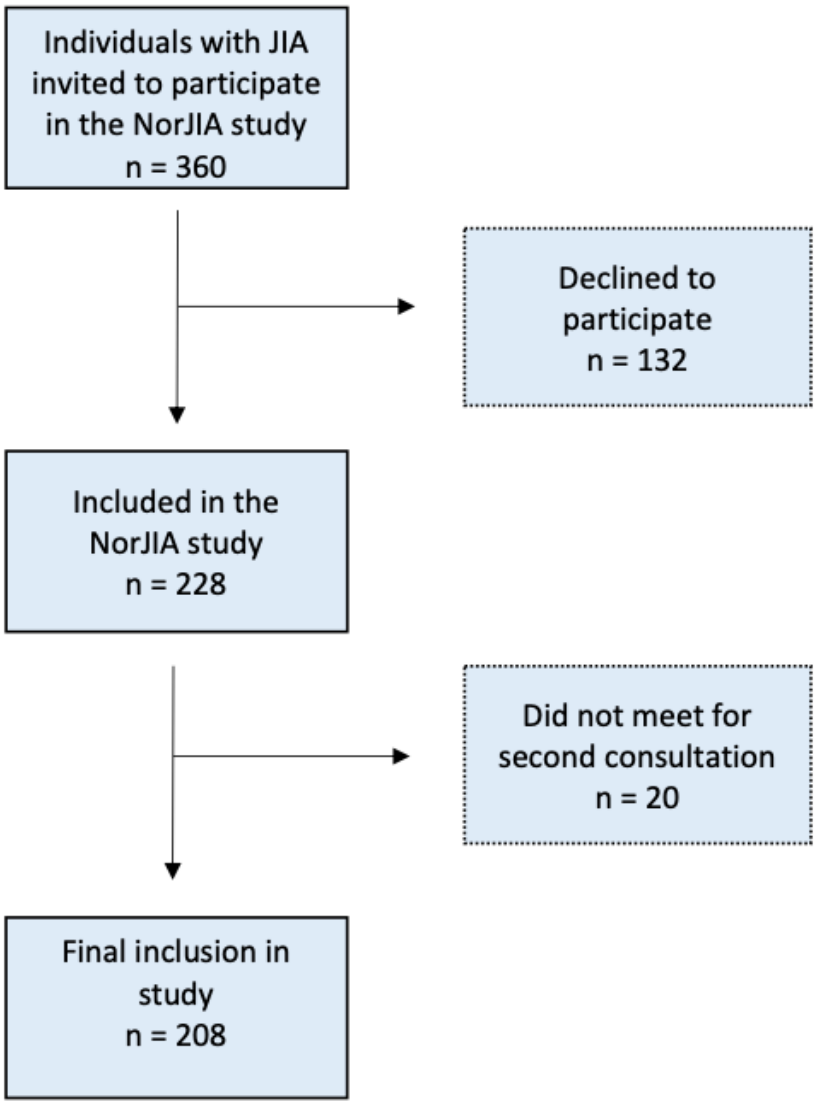

Figure 1: Final inclusion of patients with juvenile idiopathic arthritis (JIA) in the study.

Demographic characteristics

Among the 208 participants included in this study, mean age was 12.0 and 14.0 years at visit 1 and 2, respectively with girls slightly younger than boys, mean difference -1.2 years (95% CI -2.0, -0.3) at visit 1 (Table 1). The mean BMI Z-score was slightly higher in girls at both visits compared to a Norwegian reference population, while the boys kept closer to the reference population at both visits. Mean difference in BMI Z-score between girls and boys increased to 0.4 (95% CI 0.1, 0.7) at visit 2.

Table 1: Demographic characteristics of the participants with juvenile idiopathic arthritis in the study

	Total (n=208) Values	**Girls** (n=126) Values	**Boys** (n=82) Values	**Difference[a] (95% CI)**
Age visit 1 (years), mean (SD)	12.0 (3.1)	11.5 (3.2)	12.7 (2.9)	-1.2 (-2.0, -0.3)
Age visit 2 (years), mean (SD)	14.0 (3.1)	13.5 (3.2)	14.7 (2.9)	-1.1 (-2.0, -0.3)
Parental higher education[b]				
Fathers, n (%)	81 (39.9)	49 (39.8)	32 (40.0)	-0.2 (-13.9, 13.6)
Mothers, n (%)	129 (63.2)	79 (64.2)	50 (61.7)	2.5 (-11.1, 16.1)
BMI Z-score[c]				
Visit 1, mean (95% CI)	0.2 (1.1)	0.3 (1.2)	0.0 (1.0)	0.3 (0.0, 0.6)
Visit 2, mean (95% CI)	0.3 (1.1)	0.4 (1.2)	0.1 (1.0)	0.4 (0.1, 0.7)

IQR = Interquartile range, referred to as 1st-3rd interquartile, CI = confidence interval, SD = Standard deviation, BMI = Body mass index
[a]Difference with 95% CI estimated either by two-sample t-test with unequal variances (age difference) or by proportion test (% point difference)
[b]Education levels were divided into 4: Primary and middle school (7 to 10 years of education), high school (11 to 13 or 14 years), university education less than 5 years, and university education more than 5 years; the last two levels were grouped together as higher education. Missing information fathers, n=5 (2 boys, 3 girls), missing information mothers, n=4 (1 boy, 3 girls)
[c]BMI Z-score was calculated as (participant's BMI – mean BMI for reference population) / BMI SD of reference population. Sources for Norwegian reference population data: The Bergen growth study https://www.vekststudien.no/en/. Missing information BMI Z-score visit 2, n=1 (1 girl).

Clinical characteristics

The mean age of disease onset was 5.7 years in girls and 7.4 years in boys, with a difference of 1.7 years (95% CI -2.8, -0.6) (Table 2). The median age of disease onset was 3.7 years (IQR 2.1-10.0) for girls and 8.1 (IQR 4.4-10.9) for boys (results not shown). Girls showed a peak in onset age at a low age around 2-3 years, while boys showed a steady increase in onset age throughout childhood (Figure 2). The onset age in both groups seemed to decline in late adolescence.

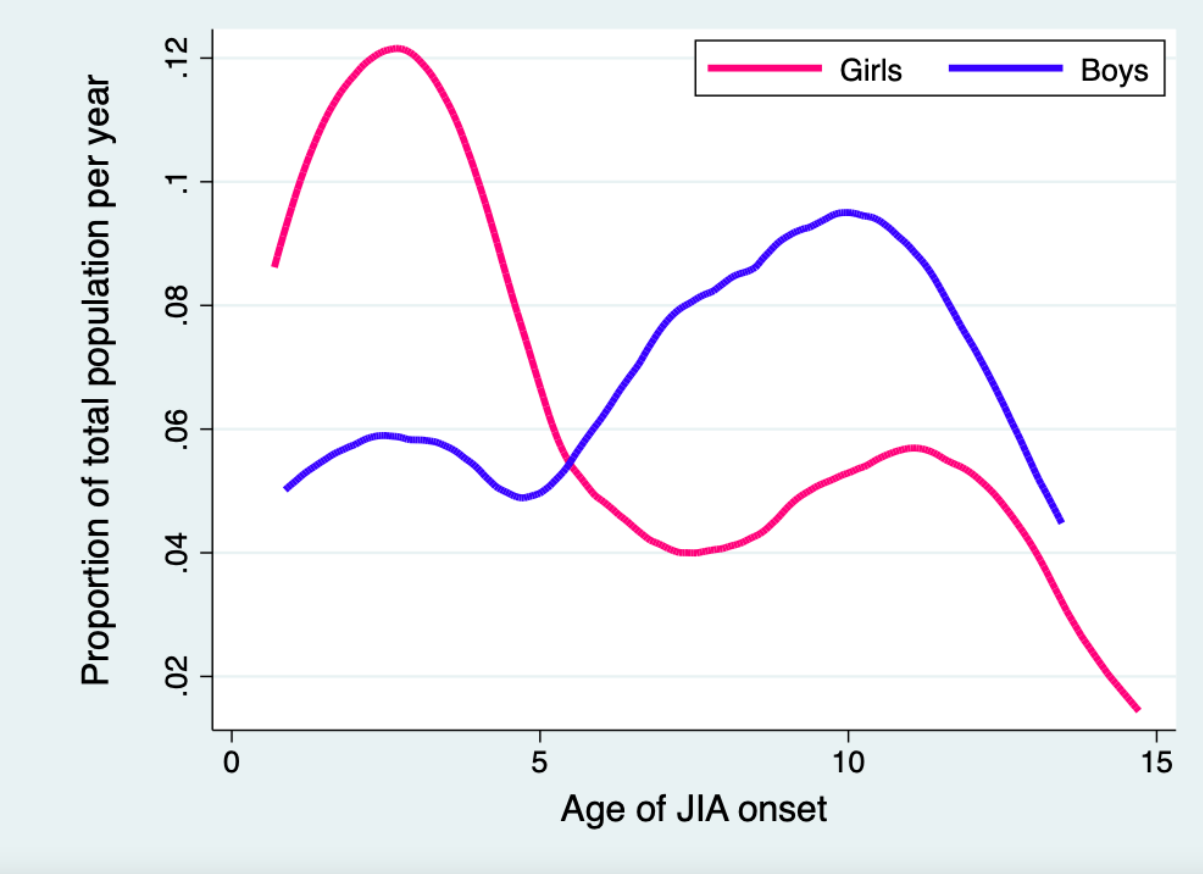

Figure 2: Age distribution of onset for girls and boys with juvenile idiopathic arthritis (JIA) in the study (Kernel density plot)

Disease duration tended to be slightly longer in girls, mean difference 0.6 years (95% CI -0.4, 1.7). More girls were ANA positive (41.9%) compared to boys (19.5%), mean % point difference 22.4 (95% CI 10.1, 34.7). Uveitis had developed in 18.4% of the girls and 15.8% of the boys at visit 2 (% point difference 2.6 (95% CI -8.4, 13.6). A distinct sex difference was seen in two JIA categories at both visits with girls dominating in the extended oligoarthritis category, % point difference 11.8 (95% CI 3.7, 19.9) at visit 2 (Table 2 and Figure 3). On the contrary, less girls than boys were found in the ERA category (5.6% versus 20.7%, % point difference -15.2 (-25.0, -5.4) at visit 2.

Table 2: Clinical and biochemical characteristics of the participants with juvenile idiopathic arthritis in the study

	Total (n=208) Values	**Girls** (n=126) Values	**Boys** (n=82) Values	**Difference[a] % points** (95% CI)
Age at onset (years), mean (SD)	6.3 (4.1)	5.7 (4.1)	7.4 (3.9)	-1.7 (-2.8, -0.6)
Disease duration visit 1 (years), mean (SD)	5.7 (3.7)	5.9 (3.6)	5.3 (3.9)	0.6 (-0.5, 1.7)
Disease duration visit 2 (years), mean (SD)	7.7 (3.7)	7.9 (3.6)	7.3 (3.9)	0.6 (-0.4, 1.7)
ANA positive, n (%)[b]	68 (33.0)	52 (41.9)	16 (19.5)	22.4 (10.2, 34.6)
HLA B27 positive, n (%)	59 (28.4)	32 (25.4)	27 (32.9)	-7.5 (-20.2, 5.2)
RF positive, n (%)	5 (2.4)	4 (3.2)	1 (1.2)	2.0 (-1.9, 5.8)
Uveitis[c], n (%)				
Visit 1	28 (13.5)	19 (15.1)	9 (11.1)	4.0 (-5.3, 13.2)
Visit 2	33 (17.4)	21 (18.4)	12 (15.8)	2.6 (-8.2, 13.5)
JIA category[d] visit 1, n (%)				
Oligoarthritis persistent	70 (33.7)	42 (33.3)	28 (34.2)	-0.8 (-14.0, 12.3)
Oligoarthritis extended	22 (10.6)	20 (15.9)	2 (2.4)	13.4 (6.2, 20.6)
Polyarthritis RF negative	48 (23.1)	32 (25.4)	16 (19.5)	5.9 (-5.6, 17.4)
Polyarthritis RF positive	3 (1.4)	3 (2.4)	0 (0.0)	2.4 (-0.3, 5.0)
Psoriatic arthritis	8 (3.9)	5 (4.0)	3 (3.7)	0.3 (-5.0, 5.6)
Enthesitis-related arthritis	22 (10.6)	6 (4.8)	16 (19.5)	-14.7 (-24.1, -5.4)
Systemic arthritis	7 (3.4)	2 (1.6)	5 (6.1)	-4.5 (-10.1, 1.1)
Undifferentiated arthritis	28 (13.5)	16 (12.7)	12 (14.6)	-1.9 (-11.5, 7.7)
JIA category[d] visit 2, n (%)				
Oligoarthritis, persistent	65 (31.3)	40 (31.7)	25 (30.5)	1.2 (-11.6, 14.1)
Oligoarthritis, extended	25 (12.0)	21 (16.7)	4 (4.9)	11.8 (3.8, 19.8)
Polyarthritis, RF negative	46 (22.1)	30 (23.8)	16 (19.5)	4.3 (-7.0, 15.7)
Polyarthritis, RF positive	3 (1.4)	3 (2.4)	0 (0.0)	2.4 (-0.3, 5.0)
Psoriatic arthritis	10 (4.8)	7 (5.6)	3 (3.7)	1.9 (-3.8, 7.6)
Enthesitis-related arthritis	24 (11.5)	7 (5.6)	17 (20.7)	-15.2 (-24.8, -5.5)
Systemic arthritis	7 (3.4)	2 (1.6)	5 (6.1)	-4.5 (-10.1, 1.1)
Undifferentiated arthritis	28 (13.5)	16 (12.7)	12 (14.6)	-1.9 (-11.5, 7.7)

IQR = Interquartile range, referred to as 1st-3rd interquartile, CI = confidence interval, SD = standard deviation, ANA = anti-nuclear antibody, analysed using HEP-2 cells, ANA positive defined as 2 positive tests at least 3 months apart, HLA-B27 = Human leukocyte antigen B27, RF = rheumatoid factor, RF positive defined as 2 positive tests analysed at least 3 months apart, JIA = juvenile idiopathic arthritis

[a]Difference and 95% CI estimated either by two-sample t-test with unequal variances (age difference) or by proportion test (% point difference)

[b]Missing observations, n=2 (2 girls)

[c]Number of children that had developed uveitis from onset until last observation before/at study visit. Missing observations at visit 1, n= 1 (1 boy), missing observations at visit 2, n= 18 (6 boys, 12 girls).

[d]JIA category defined according to the International League of Associations for Rheumatology (ILAR) classification criteria.

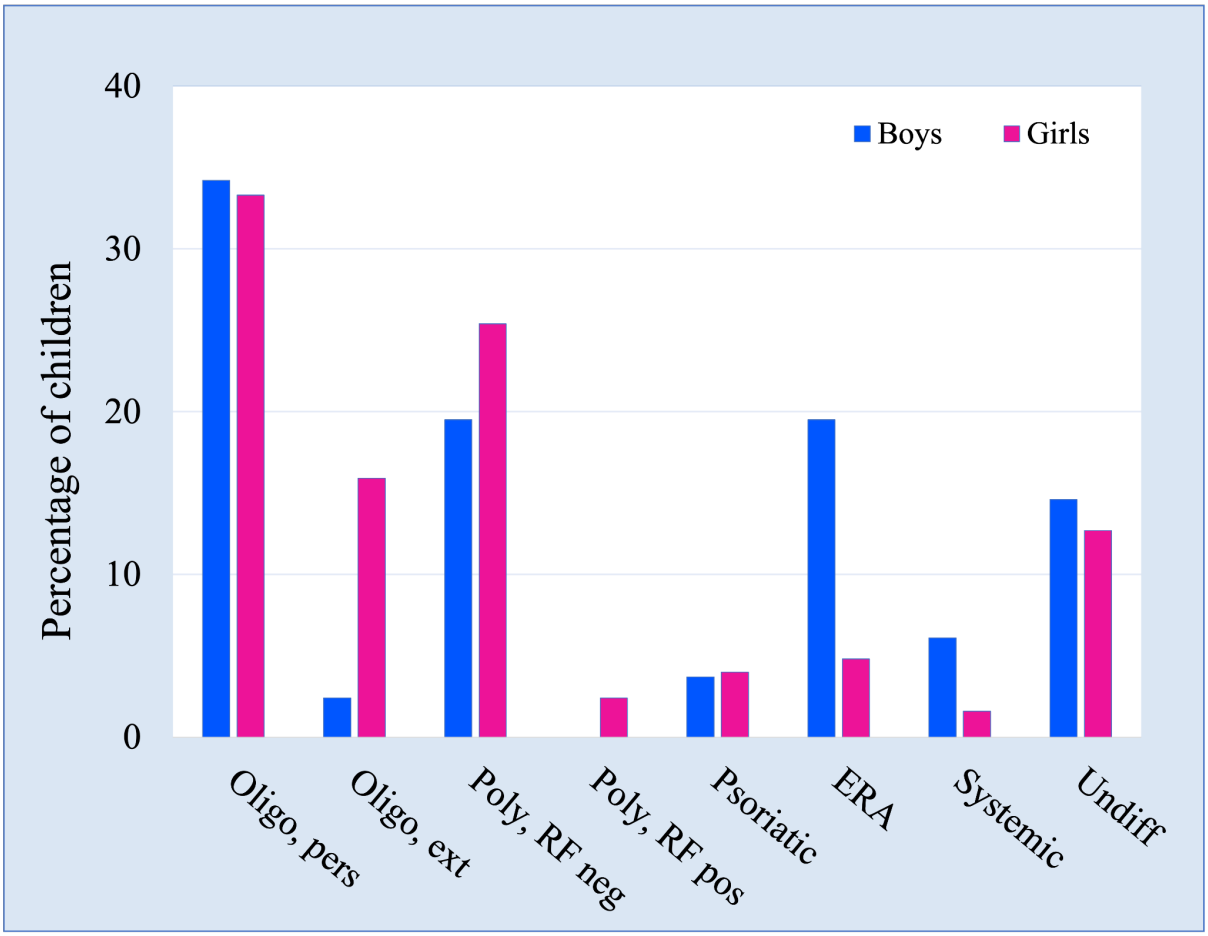

Figure 3: Distribution of categories of juvenile idiopathic arthritis in boys and girls in the study at visit 1. *Oligo, pers = persistent oligoarthritis; Oligo, ext = extended oligoarthritis; Poly, RF neg = polyarthritis rheumatoid factor (RF) negative; Poly, RF pos = Polyarthritis RF positive; Psoriatic = psoriatic arthritis; ERA = enthesitis-related arthritis; Systemic = systemic arthritis; Undiff = undifferentiated arthritis.*

Outcome

Some sex differences in outcomes were seen at both visits both in disease status, number of accumulated active joints, and patient-reported outcome measures (PROMs). However, the confidence intervals are wide, and the results must be interpreted with caution. More girls tended to be in active disease than boys at visit 1, percent point difference 7.1 (95% CI -6.5, 20.6) and the difference increased to 11.6 (95% CI -13.1, 24.6) at the second visit. Similarly, boys tended to be more likely to have achieved remission off medication than girls at the first visit, with sex difference further increasing by the second visit, percent point difference -7.5 (95% CI -17.2, 2.1) and -13.8 (95% CI -25.2, -2.3), respectively. Also, girls tended to have higher number of accumulated active joints than boys, and the difference increased between the two visits. When comparing PROMs, overall, girls tended to report more pain, more physical disability (CHAQ >0, CHQ physical >40), and more negative disease impact on well-being (PatGA >0) than boys, and the sex differences increased from the first to the second visit, most obvious for pain and impaired physical health (CHQ physical <40) with a percent difference of 28.6 (95% CI 15.2, 41.9), and 20.4 (95% CI 8.7, 32.2), respectively. However, no substantial sex difference was seen in mental health reports.

Table 3: Sex differences in outcome variables among study participants with juvenile idiopathic arthritis at two study visits two years apart

	N	**Total** n=208 n (%)	**Girls** n=126 n (%)	**Boys** n=82 n (%)	**Difference**[a] % points (95% CI)
Visit 1					
Disease status[b]					
Active	208	85 (40.9)	55 (43.6)	30 (36.6)	7.1 (-6.5, 20.6)
Inactive	208	97 (46.6)	59 (46.8)	38 (46.3)	0.5 (-13.4, 14.4)
Remission off medication	208	26 (12.5)	12 (9.5)	14 (17.1)	-7.5 (-17.2, 2.1)
Accumulated joints[c] ≥5	208	106 (51.0)	69 (54.8)	37 (45.1)	9.6 (-4.2, 23.5)
Patients with active joints[d]	208	50 (24.0)	34 (27.0)	16 (19.5)	7.5 (-4.1, 19.0)
ESR ≥20	206	8 (3.9)	3 (2.4)	5 (6.2)	-3.8 (-9.7, 2.1)
CRP ≥5	205	10 (4.9)	4 (3.2)	6 (7.5)	-4.3 (-10.8, 2.2)
PhysGA >0	208	75 (36.1)	48 (38.1)	27 (33.0)	5.2 (-8.1, 18.4)
JADAS ≥1	203	135 (66.5)	86 (70.5)	49 (60.5)	10.0 (-3.4, 23.4)
PatGA >0	203	148 (72.9)	94 (77.0)	54 (66.7)	10.4 (-2.3, 23.1)
VAS pain >0	203	125 (61.6)	80 (65.6)	45 (55.6)	10.0 (-3.7, 23.7)
CHAQ >0	202	116 (57.4)	78 (63.9)	38 (47.5)	16.4 (2.6, 30.3)
CHQ physical <40	200	47 (23.5)	28 (23.1)	19 (24.0)	0.9 (-12.9, 11.1)
CHQ psychosocial <40	200	17 (8.5)	7 (5.8)	10 (12.7)	-6.9 (-15.3, 1.6)
Visit 2					
Disease status[b]					
Active	208	73 (35.1)	50 (39.7)	23 (28.0)	11.6 (-13.1, 24.6)
Inactive	208	94 (45.2)	58 (46.0)	36 (43.9)	2.1 (-11.7, 16.0)
Remission off medication	208	41 (19.7)	18 (14.3)	23 (28.0)	-13.8 (-25.2, -2.3)
Accumulated joints[c] ≥5	208	110 (52.9)	72 (57.1)	38 (46.3)	10.8 (-3.0, 24.6)
Patients with active joints[d]	208	30 (14.4)	22 (17.5)	8 (9.8)	7.7 (-1.5, 16.9)
ESR ≥20	207	4 (1.9)	3 (2.4)	1 (1.2)	1.2 (-2.4, 4.8)
CRP ≥5	208	10 (4.8)	9 (7.1)	1 (1.2)	5.9 (0.8, 11.0)
PhysGA >0	203	54 (26.6)	38 (31.4)	16 (19.5)	11.9 (0.0, 23.8)
JADAS ≥1	193	121 (62.7)	74 (66.1)	47 (58.0)	8.0 (-5.8, 21.9)
PatGA >0	197	130 (66.0)	82 (70.7)	48 (59.3)	11.4 (-2.1, 24.9)
VAS pain >0	197	128 (65.0)	89 (76.7)	39 (48.1)	28.6 (15.2, 41.9)
CHAQ >0	197	97 (49.2)	65 (56.0)	32 (39.5)	16.5 (2.6, 30.5)
CHQ physical <40	188	49 (26.1)	38 (34.5)	11 (14.1)	20.4 (8.7, 32.2)
CHQ psychosocial <40	188	19 (10.1)	11 (10.0)	8 (10.2)	-0.2 (-9.0, 8.5)

CI = confidence *interval*, SD = *standard deviation*, ESR =*Erythrocyte sedimentation rate*, CRP = *C-reactive protein*, PhysGA = *physician's global assessment of disease activity measured on a 21-point visual analogue scale (VAS) (0 = inactive, 10 = maximal disease activity)*, JADAS = *juvenile arthritis disease activity score with 71 joints (0 = inactive, 101 = maximal activity)*, PatGA = *patient's/parent's global assessment of disease impact on wellbeing measured on a 21-point VAS (0 = inactive, 10 = maximal disease impact), VAS pain = pain*

intensity during the last week reported by the patient/parent on a 21-point VAS (0 = no pain, 10 = maximal pain).
[a]Percent point difference with 95% CI estimated by proportion test
[b]According to Wallace et al.[8]: Active = flare or continuous active disease. Inactive = inactive disease on medication < 6 months or off medication < 12 months, or remission on medication (inactive disease on medication for more than 6 months). Remission off medication = inactive disease off medication for ≥ 12 months
[c]Total number of affected joints from disease onset to study visit
[d]Number of patients with active inflammation in any joint judged by the physician at the study visit

Treatment

More boys than girls had never received any DMARDs at visit 1, 28.1% versus 18.3%, respectively, percent point difference -9.8 (95% CI -21.6, 2.0) (Table 4). The sex difference was stable over the next two years, even if a few more had started DMARD treatment at visit 2. More girls had received only synthetic DMARDs at the two visits compared to boys. The difference in percentage points was 12.8 (95% CI -0.3, 25.9) at visit 1, but reduced to 8.1 (95% CI -4.4, 20.7) at visit 2. In contrast, about half of the participants had received biological DMARDS, slightly increasing from visit 1 to visit 2, with no sex differences.

Table 4: Treatment in juvenile idiopathic arthritis (JIA) according to sex

	Total n=208 n (%)	**Girls** n=126 n (%)	**Boys** n=82 n (%)	**Difference[a]** % points (95% CI)
Visit 1				
No DMARDs ever	46 (22.1)	23 (18.3)	23 (28.1)	-9.8 (-21.6, 2.0)
No DMARDs ongoing	68 (32.7)	37 (29.4)	31 (36.6)	-8.4 (-20.3, 5.9)
Only sDMARDs[b] ever	77 (37.0)	53 (42.1)	24 (29.3)	12.8 (-0.3, 25.9)
Only sDMARDs[b] ongoing	58 (27.9)	41 (32.5)	17 (21.9)	10.6 (-1.5, 22.7)
bDMARDs[c] ever	85 (40.9)	50 (39.7)	35 (42.7)	-3.0 (-16.7, 10.7)
bDMARDs[c] ongoing	82 (39.4)	48 (38.1)	34 (41.5)	-3.4 (-17.0, 10.2)
Visit 2				
No DMARDs ever	36 (17.3)	17 (13.5)	19 (23.2)	-9.7 (-20.6, 1.2)
No DMARDs ongoing	74 (35.6)	41 (32.5)	33 (40.2)	-7.7 (-29.6, 5.7)
Only sDMARDs[b] ever	66 (31.7)	44 (34.9)	22 (26.8)	8.1 (-4.6, 20.7)
Only sDMARDs[b] ongoing	39 (18.8)	25 (19.8)	14 (17.1)	2.8 (-7.9, 13.5)
bDMARDs[c] ever	106 (51.0)	65 (51.6)	41 (50.0)	1.6 (-12.3, 15.5)
bDMARDs[c] ongoing	95 (45.7)	60 (46.8)	35 (42.7)	4.1 (-9.7, 17.9)

CI = confidence intervals, DMARDs = disease-modifying antirheumatic drugs, sDMARDs = synthetic DMARDs, including methotrexate, hydroxychloroquine, cyclosporine, mycophenolate mofetil, bDMARDs = biologic DMARDs, including etanercept, infliximab, adalimumab, tocilizumab, abatacept, certolizumab, golimumab, rituximab, ever = treatment ever used from disease onset to the study visit (including ongoing treatment at the visit), ongoing = ongoing treatment at the study visit
[a]Percent point difference with 95% CI estimated by proportion test
[b]Participants who have only used or are using sDMARDs, not bDMARDs.
[c]Participants who have used or are using bDMARDs, with or without sDMARDs.

Discussion

Summary

The results from this study indicate that, on average, JIA onset age is earlier in girls than in boys. Girls also showed a peak in onset at early age (around 3 years old), while boys showed a steady increase in onset with age. A higher number of girls developed oligoarticular extended disease, whereas more boys had enthesitis-related arthritis. In addition, the number of ANA positive girls were twice as high as in boys, while the difference in uveitis was minor. More girls tended to have long-lasting active disease, while more boys achieved and maintained remission off medication. Furthermore, patient-reported outcome was more negative among girls, with more pain, more physical disability, and negative disease impact on their daily lives compared to boys. More boys had never used any DMARDs, while more girls had used synthetic DMARDs alone. However, the proportion of boys and girls who had used biologic DMARDs was similar.

Strength and limitations

With the prevalence of patients suffering from JIA in mind, the sample size of this study may be considered large. Such a group of patients studied in terms of a moderately rare disease have the potential of uncovering representative results according to the study goals. Patients were recruited from the university hospitals of three different major cities of Norway. The university hospitals of all these cities are responsible for patients from the whole region surrounding the city. This means that children with JIA from the districts are referred to these hospitals to receive specialized health care. The hospitals are placed at very different geographic locations, in the northern, western, and central parts of Norway. As a result, our patients represented children from very different parts of Norway. All participants had multiple aspects of their disease assessed at two occasions separated by two years. Assessments were performed with validated measurements, including biochemical, clinical, and composite measures taking both the physician's and parent/patient's experience into account. This gives potential for uncovering how the disease changes over time within the same patient. Although some categories are rarer than others, the study included participants from all disease categories. As such, the patients of our study represent a large portion of the Norwegian JIA population and the entire spectrum of patients with JIA.

Although the study is large in terms of disease prevalence, any study that consists of 208 patients is still a small sample by scientific standards. A small sample size may threaten the statistical reliability of the results. The latter can be exemplified by the wide confidence intervals of some differences found in our analyses. Another challenge with a small study group is that the consequence of patients dropping out of the study between visits impact the findings at the second visit, thus making interpretation of temporal changes uncertain. As seen in the results from PROMs, this is exactly what has happened between the first and second visit of our study. Although the study is probably representative of the Norwegian population, it includes few participants of non-Caucasian descent, and the result may thus not be representative of JIA cohorts from other regions in the world. Another challenge to be acknowledged is the possibility of selection bias in the study group. It is known that the outpatient clinics are visited more frequently by patients with more severe disease status compared to patients with a milder disease course. Thus, it would be natural to assume that a larger number of patients with more severe disease would be invited to participate. Additionally, more severely affected patients would perhaps be more interested in participating in the study hoping to gain from a more extensive examination, while less affected patients would be less inclined to spend two days of examination at the hospital.

Our study represents a wide variety of Norwegian children with JIA as well as the progression of their disease course. The reliability of our finding can still be deemed uncertain, especially considering the small sample size and some missing values in certain variables. In conclusion, we advise to interpret our results with caution, and to be careful in extrapolating the findings to non-Caucasian populations.

Comparison to literature

This study found that the onset of juvenile idiopathic arthritis in girls has a peak at an early age, while boys exhibit a steady increase in onset age. These findings are consistent with a Nordic study conducted in 2003, which also reported a peak in onset among girls under 3 years old and no peak among boys[15]. Additionally, the Nordic study observed a corresponding peak in ANA positive girls at a young age, indicating its possible contribution to the onset of the disease. A Swedish study from 2019 similarly showed a peak in onset age among girls at 2 years of age, whereas boys had a less prominent peak at 12 years of age[16]. A Danish study published in 2021 identified two peaks in onset age for girls, one at age 0-5

years and the other at 12-15 years, while boys had no such peak[17]. Some previous American studies also examined the age of disease onset among boys and girls with JIA. One study from 1975 found that girls exhibited a peak in onset at 1-3 years old, while boys had a bimodal peak at 2 years and later at 9 years of age[18]. Another American study from 1983 reported that girls had a peak incidence at 0-4 years old while boys had a peak at 10-15 years old, similar to the Swedish study[19].

The prevalence of JIA is known to vary by sex, with boys generally more likely to develop enthesitis-related arthritis (ERA) and girls more likely to develop oligoarthritis[6,7,20-24]. However, few studies have examined sex differences in extended oligoarthritis JIA, specifically. Data from a Canadian study published in 2007 with a total of 65.8% female participants found that 88.9% of the study population with extended oligoarthritis were girls[25]. A Spanish study published in 2010 including 52 male and 93 female participants with JIA found that 7 of the 8 participants with extended JIA were girls[26]. These results are consistent with the results in our study. Other studies suggest that sex differences in extended oligoarthritis are modest. A Swedish study published in 2019 with a total of 66.5% female participants found that 69.6% of the participants with extended oligoarthritis were girls, leading to a negligible sex difference[16]. Similarly, an Estonian study published in 2007 including 76 male and 86 female participants with JIA, found that 10 out of 17 participants with extended oligoarthritis were girls[27]. This results in 9.2% of boys and 11.6% of girls in the extended oligoarthritis group. However, the design of these studies are quite different, and cross-sectional or retrospective designs with unknown selection bias and loss to follow-up, making comparison with our study difficult.
We did not find any studies examining the sex ratios of positive ANA in JIA. However, data from existing studies suggest a female preponderance, though mostly in samples with a higher proportion of girls[28,29]. The presence of ANA and female sex have been associated with a large and homogenous group of children with early onset oligoarthritis and high risk of uveitis, and some studies have proposed a new classification for this subgroup of JIA[30-32]. Although we did not find any significant sex difference in uveitis prevalence, our results support that ANA positivity and female sex may be linked and be important factors to consider in the classification and management of JIA.

We found that girls with JIA tended to have more active disease than boys measured in several outcome dimensions, both physician-reported, as composite measures, and especially

patient-reported outcomes, such as pain, physical disability, and disease impact on well-being. Several studies describe outcome in JIA, but few have focused specifically on sex differences. Mixed effects regression analyses have shown associations between female sex, disease categories, and PhysGA to more pain, poorer quality of life, and poorer function[33]. Whether these differences are due to real differences in disease outcome or gender-specific differences in perception of disease effects, are not clear. Sex and gender differences in patient-reported outcome in a spectrum of conditions have shown that women and men report their physical symptoms, health-related quality of life, and psychosocial burden differently[34], and this must be held in mind when evaluation the sex differences in PROMs in this study.

Interpretations

The reason more girls were affected by extended oligoarthritis in this study is unclear, and research regarding the sex distribution of the two oligoarticular categories is limited. Two possible explanations may be suggested; either persistent oligoarticular and extended oligoarticular JIA are two different diseases with different genetic background and with female preponderance in the latter category, or the two oligoarticular categories are more similar, but female sex are more vulnerable to develop into a more extended and severe form of JIA, while the boys stay in the persistent group with a higher chance of achieving a long-lasting remission off medication. A study from 2018 found that the transcriptome of fibroblast-like synoviocytes were indistinguishable when comparing polyarticular and extended-to-be oligoarticular arthritis[35]. This suggests that the genetics in persistent and extended oligoarthritis may be different, while polyarticular and extended oligoarticular may have a similar genetic background. Our study found a predominance of girls in the extended oligoarthritis group, but equal distribution in persistent oligoarthritis, which may partially be explained if the two categories are fundamentally more different than first anticipated. According to our results, boys in general tend to be less likely to have used or currently use DMARDs and less likely to have used or currently use synthetic DMARDs as monotherapy. Previously most children with JIA were started on sDMARDs as a second-line treatment after failing NSAIDs and/or intraarticular steroids. Nowadays, sDMARDs as monotherapy are mostly used in oligoarticular and especially extended oligoarticular JIA, while children with more severe disease categories like polyarticular JIA are started directly on combination therapy with sDMARDs and bDMARDs. As more girls than boys developed extended oligoarticular JIA, this may explain why more girls were treated with sDMARDs as monotherapy. Some categories of JIA are less sensitive to sDMARDs, among them we find

ERA, in particular. Based on the well-known higher prevalence of boys in the ERA group, our interpretation is that boys in need of a DMARD, more often were treated immediately with bDMARDs, skipping the usual first step of only sDMARDs.

Conclusion

In conclusion, results from this study highlights several sex differences in JIA. Most notably are the peak in young onset age among girls, the high proportion of ANA positive girls, the male preponderance in ERA and the female preponderance in extended oligoarthritis, as well as a larger proportion of girls using sDMARDs, but equal sex distribution of bDMARDs use. Also, a trend towards higher disease burden in outcome in girls compared to boys, is noticed. While several studies have shown similar results regarding onset age and more boys having ERA, studies examining the other key points are limited. The underlying reason for the results in this study is unclear, but it may be associated with both biological and environmental factors. The estimates from this study are uncertain, and therefore, it is crucial to validate the results in larger-scale studies conducted in different countries or regions.

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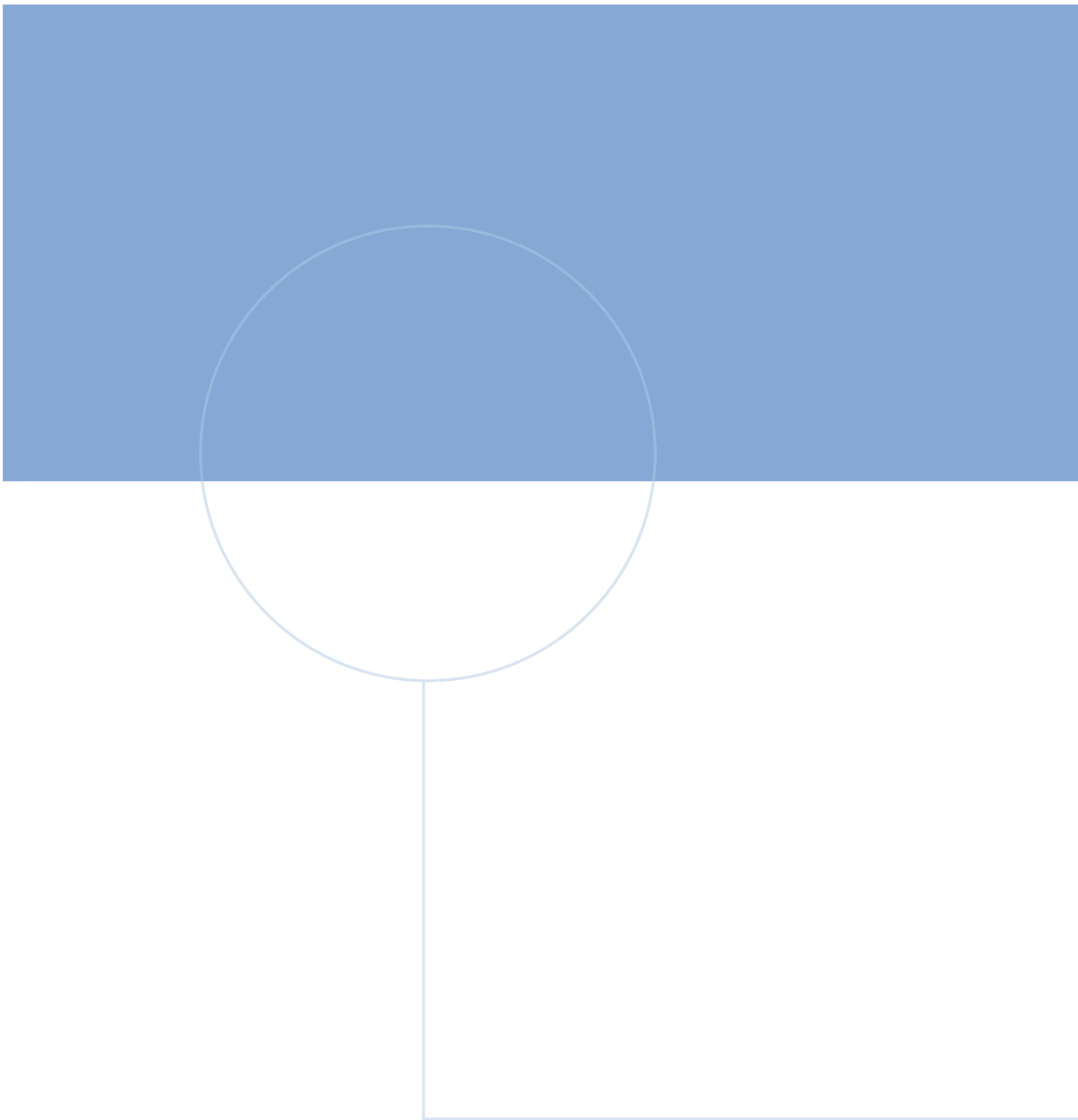

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