Student thesis

NTNU
Norwegian University of Science and Technology
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Department of Clinical and Molecular Medicine

Marie Ellinor Sæterdal and Ingrid Bråten Støen

Growth and puberty in a Norwegian juvenile idiopathic arthritis (JIA) cohort

Results from the NorJIA study

Student thesis in Medicine, programme of professional study
Supervisor: Marite Rygg
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Collaborators

Supervisor: Marite Rygg, MD, Professor, and pediatrician with competence in Paediatric Rheumatology and local principal investigator (PI) for the Nordic JIA study
Co-supervisor: Pål Richard Romundstad, Professor, ISM, expert in Epidemiology, contributes with advice in epidemiology and medical statistics.
Collaborator: Anette Lundestad, MD PhD in the NorJIA project, responsible for the NorJIA database, and Petur Benedikt Juliusson, professor, Department of Clinical Science, University of Bergen, Department of Health Registry Research and Development, Norwegian Institute of Public Health, and Department of Paediatrics, Haukeland University Hospital, Bergen.

Abstract

Background: Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease that affects children in numerous ways (1, 2). Growth may be impaired because of ongoing inflammation, nutritional impairment, or treatment with systemic corticosteroids (2). Treatment aims to relieve disease symptoms and potentially induce remission as early as possible, to prevent damage and facilitate normal development. Our study investigates height, BMI, and pubertal onset in a Norwegian cohort of children with JIA, compared to a sex- and age-matched control group and to Norwegian reference data.

Methods: This study is based on data from the prospective, multicenter, observational study NorJIA, including 228 children with JIA and 224 controls (3). Inclusion criteria were participation in the NorJIA study and available height for both study visits, two years apart. Height and BMI z-scores were calculated based on Norwegian reference data (4). Height z-scores, parent-adjusted height z-scores, BMI z-scores, and ages for pubertal onset and menarche for participants with JIA were compared to the controls. Height and BMI z-scores were also compared between subgroups of JIA based om age at onset, disease duration, disease activity, and treatment status.

Results: We used data from 207/228 children with JIA and 182/224 controls from the NorJIA cohort. Boys and girls were studied separately. In sub-analyses of parent-adjusted height z-scores, 205 children with JIA and 74 controls were included. Both sexes displayed lower height z-scores in children with JIA compared to controls and Norwegian references, but the differences were small, and the 95% confidence intervals included zero. Girls with JIA had lower height z-scores related to unfavorable disease characteristics and use of disease modifying anti-rheumatic drugs (DMARDs). Boys did not show the same pattern of height z-scores related to disease severity. The results remained generally unchanged after adjustment for parental height. BMI z-scores were higher in girls with JIA than the female controls and the Norwegian references, but with no clear pattern related to disease severity. Mean BMI z-score for boys with JIA were similar to the Norwegian references, while controls of both sexes had a slightly higher mean BMI z-score than the references. Age at pubertal onset and menarche did not differ between JIA and controls, nor compared to reference data from a large population-based health study, The Trøndelag Health Study (5, 6).

Conclusion: The observed differences in mean height z-scores between groups are small, and the sample size of the more severe forms of JIA makes it difficult to draw conclusions. Still, there is reason to believe that patients with severe forms of JIA, especially girls, may still experience some degree of growth impairment.

Sammendrag

Bakgrunn: Juvenil idiopatisk artritt (JIA) er en kronisk inflammatorisk sykdom med en heterogen pasientgruppe som affiseres på mange områder (1, 2). Vekst kan bli påvirket av pågående inflammasjon, påvirket kosthold og bruk av systemiske kortikosteroider. Målet med behandlingen er effektiv symptomlindring og å oppnå remisjon så tidlig som mulig slik at barna unngår varige skader og normal utvikling ikke forstyrres (2). Studien vår undersøker høyde, kroppsmasseindeks (KMI) og pubertetsstart i en norsk kohort av barn med JIA sammenlignet med en kjønns- og alderstilpasset kontrollgruppe og med norske referansedata.

Metoder: Denne studien er basert på data fra en prospektiv multisenter observasjonsstudie, NorJIA, som inkluderer 228 barn med JIA og 224 kontroller (3). Inklusjonskriterier var deltagelse i NorJIA-studien og tilgjengelige høydedata fra begge studievisitter, gjennomført med to års intervall. Høyde og KMI ble omregnet til z-skårer basert på norske referansedata (4). Høyde z-skår, foreldrejustert høyde z-skår, KMI z-skår og alder for pubertetsstart og menarke ble sammenlignet mellom gruppen med JIA og kontrollene. Høyde og KMI z-skårer ble også sammenlignet mellom subgrupper av JIA, basert på alder ved sykdomsdebut, varighet av sykdom, sykdomsaktivitet og behandlingsstatus.

Resultater: Vi inkluderte data fra 207/228 barn med JIA og 182/224 kontroller fra NorJIA-studien. I subanalyser for foreldrejustert høyde z-skårer benyttet vi data fra 205 deltakere med JIA og 74 kontroller. Resultatene for begge kjønn viste lavere høyde z-skårer blant barna med JIA sammenlignet med kontrollene og norske referansedata, men forskjellene var små og 95% konfidensintervallene inneholdt null. Blant jentene observerte vi lavere høyde z-skårer relatert til alvorlig sykdomsforløp og bruk av sykdomsmodifiserende antirevmatisk medisin (DMARDs). Guttene viste ikke samme mønster for høyde z-skårer relatert til alvorlighetsgrad av sykdom. Justering for foreldrehøyde førte ikke til noen vesentlig endring av resultatene. Gjennomsnittlig KMI z-skår var høyere blant jentene med JIA enn de kvinnelige kontrollene og norske referansedata, men viste ikke noe tydelig mønster relatert til alvorlighetsgrad av sykdom. Gjennomsnittlig KMI z-skår for guttene med JIA var tilsvarende norske referansedata, mens kontroller av begge kjønn viste en høyere gjennomsnittlig KMI z-skår enn norske referansedata. Median alder for pubertetsstart og menarke var lik for JIA og kontrollene, og også lik referansedata fra den store helseundersøkelsen i Trøndelag, HUNT4 (5, 6).

Konklusjon: De observerte forskjellene i gjennomsnittlig høyde z-skår mellom gruppene er små, og det begrensede utvalget gjør det vanskelig å trekke konklusjoner. Det kan likevel se ut som pasienter, og spesielt jenter, med alvorlige former for JIA fremdeles fortsatt risikerer å oppleve noe veksthemming.

Acknowledgements

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Abbreviations

ACR	American College of Rheumatology
ANA	Anti-nuclear antibody
B1-B5	Tanner breast stage 1-5
bDMARD	Biological disease modifying antirheumatic drug
BMI	Body mass index
CHQ P50	Child Health Questionnaire, parent version 50
CI	Confidence interval
CRP	C-reactive protein
DMARD	Disease-modifying antirheumatic drug
ESR	Erythrocyte sedimentation rate
G1-G5	Tanner genital stage 1-5
HLA-B27	Human leucocyte antigen B27
ILAR	International League of Associations for Rheumatology
IQR	Interquartile range
JADAS	Juvenile arthritis disease activity score
JIA	Juvenile idiopathic arthritis
N	Number
NSAIDs	Non-steroidal anti-inflammatory drugs
PatGA	Patients' global assessment for overall well-being
PH1-PH5	Tanner pubic hair stage 1-5
PhysGA	Physicians' global assessment of disease activity
RF	Rheumatoid factor
SD	Standard deviation
sDMARD	Synthetic disease modifying antirheumatic drug
TNF	Tumor necrosis factor
VAS	Visual analogue scale
WHO	World Health Organization
Z-score	Standard deviation score

Table of Contents

Introduction

Juvenile idiopathic arthritis (JIA) is the joint term for a heterogenous group of conditions which all involve chronic arthritis of unknown aetiology in children (1). Chronic arthritis is defined by the International League of Associations for Rheumatology (ILAR) as "swelling within a joint, or limitations in the range of joint movement with joint pain or tenderness, which persists for at least 6 weeks, is observed by a physician and is not due to primarily mechanical disorders or to other identifiable causes." (2). Furthermore, ILAR defines JIA as idiopathic arthritis with disease onset before the age of 16 years. JIA is divided into eight phenotypically different categories, persistent oligoarthritis representing the most benign type (2).

The incidence rate of JIA is high in the Nordic countries, with an incidence rate of 23 per 100 000 per year in northern and central Norway (7, 8). In comparison, the incidence rate in England is estimated to be 5.61 per 100 000 per year (9) and in Minnesota, the United States, the incidence is 10.3 per 100 000 per year (10). The pathophysiology is unknown but is thought to be related to both genetic and environmental factors, which results in a clinically heterogeneous patient group with different disease manifestations (7, 8). In addition to various degrees of joint inflammation, symptoms may include extraarticular manifestations such as chronic uveitis and skin lesions (1).

Treatment of JIA aims to relieve symptoms and achieve remission in as many patients as possible, with minimal adverse effects. Treatment options have increased tremendously during the last decades, and especially since the early 2000s with the introduction of biologic disease-modifying antirheumatic drugs (bDMARDs), resulting in better symptom relief and improved general health (11). As treatment has improved in the biologic era, there is reason to investigate to what extent children with JIA still experience reduction in quality of life, including pain, fatigue or psychosocial stress, physical disabilities, ongoing disease activity or permanent damage to joints, reduced skeletal health, and disturbance of growth and puberty compared to peers.

The consequences of JIA vary between patients and patient groups (1), and may be assessed differently by the patient, parents, and physician (12). Physician-reported outcomes include results of a medical examination, including joint count with number of affected joints, and detection of uveitis, results of blood tests, like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and the physician's global assessment of disease activity (13).

Patient-reported outcomes include pain, global assessment of well-being, and quality of life (13, 14). Composite measures, to assess multiple aspects of disease with one measure, are also established. A validated tool commonly used to score disease activity is The Juvenile Arthritis Disease Activity Score (JADAS)(14, 15). Definitions of inactive disease and clinical remission were suggested by Wallace et al. in 2004 (16) and endorsed by The American College of Rheumatology in 2011 (ACR) (17). Long-term consequences of chronic arthritis include articular damage, bone mass deficit/osteoporosis, eye complications with reduced vision/blindness, chronic pain, and fatigue. Growth impairment and delayed puberty are also known long-term consequences of JIA (18, 19).

Disturbances in growth and pubertal development in patients with JIA may result from a combination of systemic inflammation, nutritional impairment, and treatment with systemic corticosteroids for longer periods (20, 21). This is also seen in other chronic inflammatory conditions, as hormonal activity is influenced by inflammation (22). Growth and puberty are closely linked, so it is difficult to conclude what are the decisive factors. A prepubertal onset of disease may delay the pubertal growth spurt, with the possibility for catch-up growth later (20, 23). Due to other more effective drugs, longer periods of treatment with systemic corticosteroids are less common today. Thus, it is expected that growth disturbances will be less prominent in the future, but few studies have looked at this in detail in the "biologic era" (20, 23-25).

This thesis investigated growth and pubertal onset in children and adolescents with JIA. We specifically examined whether the mean height of Norwegian children with JIA was reduced compared to Norwegian reference data and to an age- and sex-matched control group. In sub-analyses, the parents' heights were adjusted for in both the JIA and the control group. Due to the large variations in disease characteristics within the JIA group, height was also compared between different subgroups of JIA. We investigated subgroups characterized with more severe outcomes, and thus possibly with higher risk of growth impairment, such as young age at disease onset, longer disease duration, more severe disease categories, ongoing active disease, and medication status. Because of the association between puberty and growth in adolescents, we also investigated if pubertal onset was delayed in Norwegian children with JIA compared to the age- and sex-matched control group.

Materials and methods

Study design

The NorJIA study is a prospective, multicentre, observational study (3)(clinical trials NCT03904459). The study includes 228 children with JIA recruited from university clinics in Bergen, Tromsø, and Trondheim. Inclusion criteria for participants with JIA were a JIA diagnosis according to the ILAR criteria and age between 4 and 16 years at visit 1, with parents' or legal guardians' (hereafter only referred to as parents) informed consent. There were no exclusion criteria. A control group of 224 children without JIA were recruited from seven Public Dental Service (PDS) clinics and matched (1:1) according to sex, age, and centre site. Two study visits were carried out with an interval of 2 years. Collection of data took place between March 25th, 2015, and June 20th, 2020.

The study design of this thesis is a longitudinal study using anthropometric and pubertal data from both study visits. The inclusion criteria were participation in the NorJIA study and available height, and weight registered at both study visits. The additional inclusion criterion for our sub-analyses was registration of both parents' height. In the analyses of pubertal development, all children from the NorJIA study with available pubertal data were included.

Data collection

Participating children with JIA and their parents were submitted to broad questioning as well as thorough anthropometric, clinical, laboratory, radiological, and oral examinations at visit 1 and at visit 2 two years later (26). The children with JIA spent approximately two days on the data collection process for each study visit. Controls spent about half a day for each study visit. Data collection for both participants with JIA and controls included age, sex, ethnicity, parents' level of education, height, weight, and an oral examination, as well as the parent-reported Child Health Questionnaire, Parent version 50 (CHQ P50, hereafter named CHQ). Additionally, the following data collected from the participants with JIA was used in our study: Date of disease onset, JIA category according to the ILAR classification, past and present use of medication, number of joints with active inflammation or limited range of motion at the study visit, and total number of affected joints since disease onset. Human leucocyte antigen B-27 (HLA-B27), rheumatoid factor (RF), and anti-nuclear antibodies

(ANA) were measured close to the time of disease onset, while erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were analysed at the study visits.

Height and weight measures were performed by experienced paediatric rheumatologists at each study visit for the participants with JIA, and by experienced dentists or dental hygienists at the oral examination for the controls. Height was mainly measured with wall-mounted stadiometers, however for some of the controls in Bergen a portable laser height meter was used for measuring. Parental height was mainly self-reported. Pubertal data was registered at each visit for participants with JIA. For controls from Tromsø and Trondheim consenting to an extended study visit, pubertal data was reported at visit 2, in addition to blood tests and imaging measures. Pubertal data was mainly self-reported and categorized with the use of illustrations of sexual maturity rates (Tanner stages) in both JIA and control participants (27, 28)(Supplemental figure 1).

Measures

Demographic and socioeconomic characteristics

Ethnicity was dichotomized into Caucasian and Non-Caucasian. Parents' education was specified at the four following levels: 7-10 years of education (primary and middle school), 11 to 13 or 14 years (high school), less than 5 years of university education, and more than 5 years of university education. The last two levels were merged and referred to as Higher education.

Height and weight measures

Standardization of height according to sex and age (in months) was estimated based on references from the Norwegian growth study (4) and expressed as z-scores by one of our collaborators and responsible for the Norwegian growth study (P. B Juliusson), since the background data for the Norwegian reference study are not publicly available. The height z-scores were calculated as participants' height minus the mean height for the reference population, divided by height standard deviation of the reference population. Parent-adjusted height z-score was calculated as the difference between z-score for height of the children and target height z-score based on parental height (4). Low height z-score and low parent-

adjusted height z-score was defined as height z-score or parent-adjusted height z-score < -0.5. Reduced growth tempo or height deflection was defined as delta height z-score (height z-score at visit 2 – height z-score at visit 1) < -0.25 per year (29).

Body mass index (BMI) was calculated as weight (kg) divided by height (meters) squared with adjustments for age and sex (iso-BMI grouping) according to The International Obesity Task Force recommendations (30). Due to a low number of participants in the outermost iso-BMI categories, several categories were combined. Mild, moderate, and severe underweight were combined in the category underweight, and obesity and severe obesity were combined in the category obesity. BMI z-scores were calculated by one of our collaborators (P.B. Juliusson) as the participant's BMI minus the mean BMI for the Norwegian reference population, divided by BMI standard deviation of the reference population (4, 30).

Outcome measures

To evaluate both the patient's and physician's understanding of disease activity, composite measures were applied. The Juvenile Arthritis Disease Activity Score based on 71 joints (JADAS71, hereafter referred to as JADAS) was calculated based on ESR, the physician's global assessment of disease activity (PhysGA), the patient's global assessment of the disease's impact on overall well-being (PatGA), and number of joints with active arthritis assessed in 71 joints, giving a score from 0-101, where >1 is defined as active disease (14, 15). The PhysGA was reported by the physician on a 21-numbered circle visual analogue scale (VAS) from 0-10 where 0 equals "no activity" and 10 equals "high activity" (13). PatGA was reported by the patient/parent on a 21-numbered circle VAS from 0-10, where 0 represents "no influence at all" and 10 "severely influenced" (13, 14). Patient-/parent-reported disease-related pain was measured on a 21-numbered circle VAS, where 0 equals "no pain at all" and 10 equals "very severe pain" (13). For children under the age of 9, parents filled out the VAS scale for pain and PatGA on behalf of their child.

Inactive disease and remission were determined using the Wallace criteria (16), revised and endorsed by The American College of Rheumatology (ACR) (17). Wallace et al. defined preliminary criteria for inactive disease, with two types of clinical remission criteria in 2004. Clinical remission on medication defined as maintained inactive disease on medication for a minimum of 6 continuous months, and clinical remission off medication defined as maintained inactive disease without medication for a minimum of 12 continuous months. In

2011, a revised set of criteria defining inactive disease were endorsed by ACR (17). The criteria include no active arthritis, no fever, rash, serositis, splenomegaly or general lymphadenopathy due to JIA, no active uveitis, no morning stiffness > 15 minutes, and normal ESR and/or CRP unless otherwise explained by other conditions (17).

For children of all ages, both with JIA and controls, parents filled out the CHQ. The questionnaire was used to measure general functioning and quality of life. The CHQ includes 50 non-disease-specific questions about topics such as general health, physical functioning, physical pain, mental health, as well as the impact on both the patient's parents and family in general. The answers were compiled into a summarized score with a scale from 1 to 100, where a higher score indicates a higher level of functioning and quality of life comparable to norm scores (50 +/- 10) from the general U.S. population (31). The responses were used to calculate a Physical Summary Score (PhS) and Psychosocial summary Score (PsS), also with norm scores (50 +/- 10) (31).

Puberty measures

Collection of pubertal data was done according to the Tanner methods for sexual maturity (27, 28). For girls, sexual maturity was specified according to breast (B1-B5) and pubic hair (PH1-PH5) maturation, and for boys according to genitals (combined score for testis and penis) (G1-G5), and pubic hair (PH1-PH5). Female participants specified dates for B2, PH2 and menarche, and male participants specified dates for G2 and PH2. Pubertal onset was defined as date of B2 in females or G2 in males. Pubertal onset age was calculated from date of birth (DOB) to the date of female B2 / male G2. Age of menarche was calculated from DOB to the date of menarche. Delayed pubertal onset was defined as age at B2 ≥13 years or age at G2 ≥14 years (32). Delayed menarche was defined as age of menarche ≥15 years (32). Delayed puberty was defined as a delay in either pubertal onset or menarche.

To calculate the percentage of participants with delayed pubertal onset, two groups were included: Participants with available dates for Tanner stage B2 (or PH2) for girls and G2 (or PH2) for boys, and participants with the age limit for delayed puberty reached but not the Tanner stadium for pubertal onset. To ensure an adequate number of included participants, the inclusion criteria based on height and weight data from both visits were not applied here.

Treatment measures

Three groups of medications were assessed: DMARDs divided into synthetic DMARDs (sDMARDs) and biologic DMARDs (bDMARDs), and systemic corticosteroids. sDMARDs included methotrexate, hydroxychloroquine, cyclosporine, and mycophenolate mofetil. bDMARDs included five tumour necrosis factor (TNF) inhibitors (infliximab, adalimumab, etanercept, certolizumab, and golimumab), and in addition abatacept, tocilizumab, and rituximab.

The participants with JIA were stratified into three groups based on DMARDs ever used, meaning used at any time from disease onset to study visit, and three groups based on ongoing DMARDs at the time of the study visit. Treatment ever used was divided into participants that had never used any DMARDs, participants that had only used sDMARDs (never bDMARDs), and participants that had ever used bDMARDs. Similarly, ongoing treatment was defined as no DMARDs ongoing, only sDMARDs ongoing, and bDMARDs ongoing. Participants were also grouped based on whether they had ever received systemic corticosteroids or not.

Statistical analysis

To describe the clinical characteristics and disease activity of the cohort, we have estimated the mean with standard deviation (SD), mean with 95% confidence interval (CI), or median with 1st-3rd interquartile ranges (IQR) for continuous variables, and absolute frequencies and percentages (%) for categorical variables.

Mean z-scores for height and BMI in the JIA group were compared to the control group, for boys and girls separately. The mean z-scores of the JIA group and the control group were then analysed using a two-sample t-test with unequal variances. To further assess the association between the height z-score for children with JIA, and disease-specific outcome variables, the JIA group was subdivided according to disease-specific outcome variables and categorized as follows; Age at disease onset (< 6 years, ≥ 6 years old), disease duration (< 5 years, ≥ 5 years), disease status (Remission off medication, Inactive disease with or without medication or remission on medication, Active disease), past and present medication status (no DMARDs, sDMARDs, bDMARDs), and JADAS (≤1 = Inactive disease, >1 = Active disease).

Crude linear regression analyses were applied to compare height z-scores and BMI z-scores between the subgroups of JIA according to disease categories, disease status and medication status. In sensitivity analyses, linear regression analyses were adjusted for age at disease onset and disease duration.

Median age for pubertal onset and menarche was estimated in the group with JIA and the group of controls using survival analyses. The median survival time is the time at which half of the participants have arrived at an event, in this case pubertal onset or menarche. The method of survival analysis was applied to take into account the participants that had not yet reached pubertal onset within the time of data collection (right censoring), and therefore expected to increase the median age of pubertal or menarcheal onset with a longer follow-up. Log-rank tests were performed to evaluate whether there were differences between the groups.

Data was processed, categorized, and prepared using Excel, as well as simple analysis such as mean and overall summarizing. Statistical analyses were carried out using STATA version 17, software (STATA Corp., College Station, Texas, USA).

Ethics

The NorJIA study was approved by The Ethics Committee, Helse Vest (REK no 2012/542). The study is registered on ClinicalTrials.gov with Identifier: NCT03904459. (33). Data access for this study was granted by the NorJIA research group, and storage of data has been in alignment with General Data Protection Regulation (GDPR). For participants under the age of 16, parents have signed a written informed consent form. Parents and researchers have informed the children about the study.

Results

In total, 360 children with JIA were invited to participate in the NorJIA study and 228 accepted the invitation, resulting in a 63% response rate (Figure 1). For our study, 207 participants fulfilled the inclusion criteria of height and weight registered at both visits. Missing parental height for two participants resulted in 205 participants for our sub-analyses on parent-adjusted height.

For the control group, 294 children without JIA were invited, and 70 declined to participate. Thus, 224 controls were included in the NorJIA study, with a 76% response rate. After exclusion of 42 individuals lacking height or weight data, the final study group included 182 controls. In the sub-analyses on parent-adjusted height, 74 controls with both parents' height available were included.

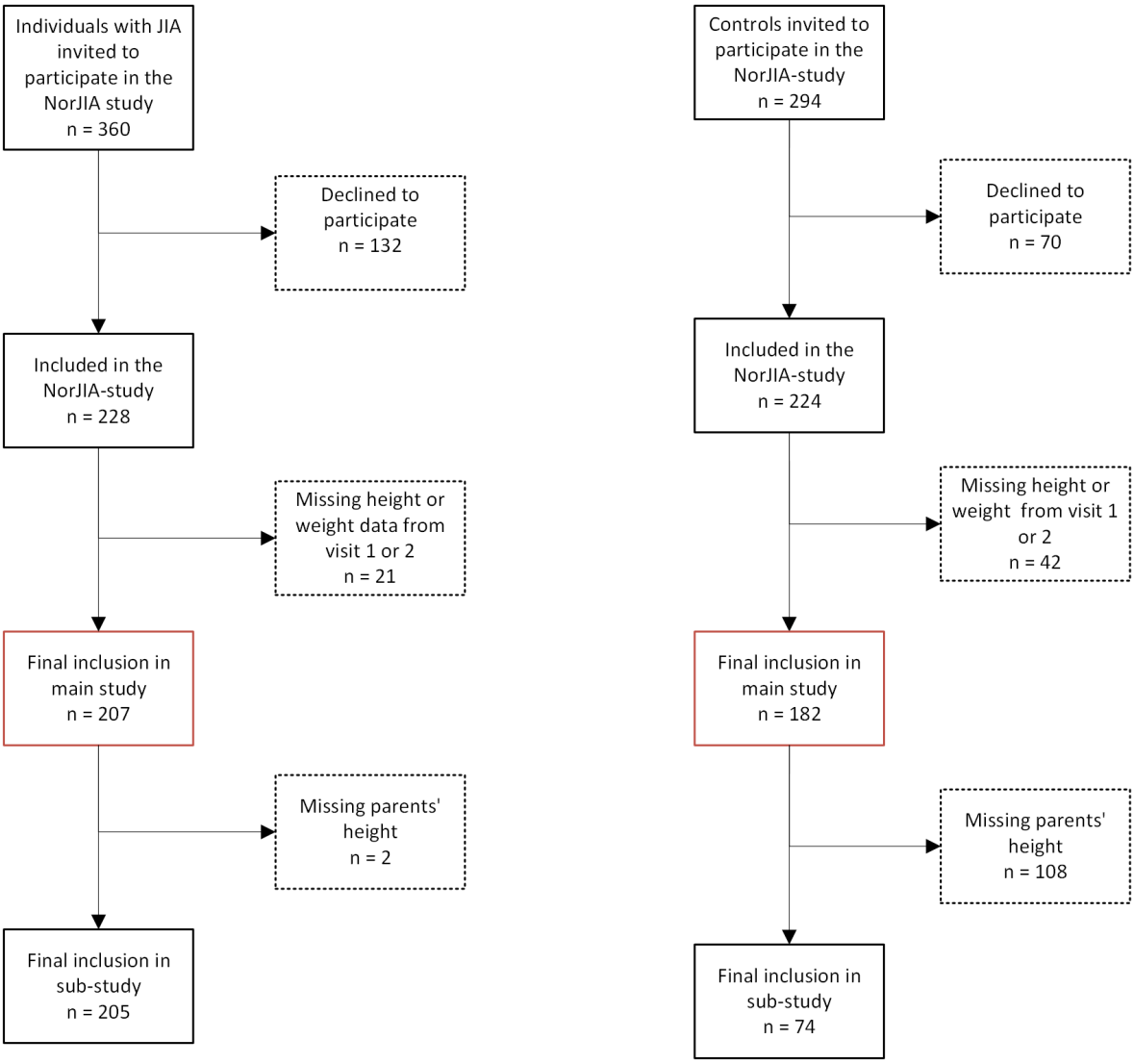


Figure 1 Flow chart of children with juvenile idiopathic arthritis (JIA) and controls in the study

Demographic and socio-economic characteristics

Both the JIA and the control group had an overweight of female participants, with 60.4% and 59.9% girls, respectively (Table 1). Caucasian ethnicity and age at the study visits were also comparable in both groups. The median age at visit 1 was 12.6 for participants with JIA and 12.4 for controls. Mothers and fathers with higher education constituted 63.5% and 40.1%, respectively, in the group of children with JIA, and 70.5% and 61.7% in the control group. The mean CHQ physical summary score was lower for participants with JIA compared to controls (46.1 versus 56.0 at visit 1 and 46.3 versus 55.4 at visit 2) with a difference of approximately one standard deviation at both visits. For psychosocial CHQ summary score, the results were more similar in the two groups.

Among the children with JIA that declined to participate, 58% were girls. Their mean age was 10.5, while the mean age for those who participated in the NorJIA study was 12.0 at visit 1. The 21 children with JIA that were excluded from our study due to missing height or weight data, consisted of 48% girls, with a median age of 13.4 years at visit 1. Of the 42 controls excluded, 57% were female, and their median age was 13.5 years at visit 1. In the sub-analyses, the controls with missing parental height had a median age of 12.5 years at visit 1 and consisted of 54% girls.

Table 1 Demographic and socio-economic characteristics of the study population

	JIA		CONTROLS	
	N	**Values**	**N**	**Values**
Females, n (%)	207	125 (60.4)	182	109 (59.9)
Caucasian ethnicity[a], n (%)	207	202 (97.6)	80	78 (97.5)
Parent w/higher education[b], n (%)				
Mother	203	129 (63.5)	173	122 (70.5)
Father	202	81 (40.1)	175	108 (61.7)
Age, median years (IQR)				
Visit 1	207	12.6 (9.5-14.6)	182	12.4 (9.7-14.8)
Visit 2	207	14.6 (11.4-16.5)	182	14.5 (11.7-16.9)
CHQ[c] summary score physical				
Visit 1 mean (SD)	199	46.1 ± 10.3	169	56.0 ± 3.9
Visit 2 mean (SD)	187	46.3 ± 10.1	169	55.4 ± 6.9
CHQ[c] summary score mental				
Visit 1 mean (SD)	199	53.0 ± 7.9	169	55.6 ± 5.9
Visit 2 mean (SD)	187	52.3 ± 9.0	169	54.5 ± 6.9

JIA = Juvenile idiopathic arthritis, N = Number, IQR = Interquartile range, CHQ = Child Health Questionnaire, SD = Standard deviation.
[a] Ethnicity was divided into two groups: Caucasian and Non-Caucasian according to self-report.
[b] Parent education was divided into 4 levels: 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 parents with higher education.
[c] The parent-reported Child Health Questionnaire (CHQ P50) summarizes general functioning and quality of life on a scale from 1 to 100, where a higher score indicates a higher level of functioning and quality of life comparable to norm scores (50 +/- 10) from the general U.S. population. The responses are used to calculate a Physical Summary Score (PhS) and Psychosocial summary Score (PsS) (26), also with norm scores (50 +/- 10).

Clinical characteristics for the participants with juvenile idiopathic arthritis

Median age at disease onset for girls with JIA was 3.7 years (IQR: 2.2-10.2) and for boys 8.1 years (IQR: 4.4-10.9) (Table 2). Median disease duration was one year longer for girls compared to boys. Of the children with JIA, 33.2% were ANA positive, 28% were HLA-B27 positive, and 2.4% were RF positive. The distribution of JIA categories showed that the full spectrum of disease categories was represented, and 33.8% had persistent oligoarthritis at visit 1, while 31.4% still had persistent oligoarthritis at visit 2.

Active disease with a JADAS score above one was seen in 58.9% at visit 1 and 52.7% at visit 2. According to the Wallace criteria at visit 1, 40.6% had active disease, 46.9% had inactive disease, and 12.6% were in remission off medication. At visit 2, 50.7% of the children had been treated with bDMARDS at some point, and 17.4% had never been treated with any DMARDs. Systemic corticosteroids had been used by 26.1% of the children at visit 2. The proportion of children with physician-reported active disease at the visit (PhysGA above 0) was reduced from 35.7% to 26.6% from visit 1 to visit 2, but the percentage of participants reporting some degree of disease-associated pain (VAS pain >0) increased slightly between the visits.

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

	VISIT 1		VISIT 2	
	N	Values	N	Values
Age at JIA onset, median years (IQR)				
Female	125	3.7 (2.2-10.2)		
Male	82	8.1 (4.4-10.9)		
ANA positive, n (%)	205	68 (33.2)		
HLA-B27 positive, n (%)	207	58 (28.0)		
RF positive, n (%)	207	5 (2.4)		
JIA duration, median years (IQR)				
Female	125	5.0 (3.1-8.5)	125	7.1 (5.2-10.4)
Male	82	4.0 (2.4-7.5)	82	6.2 (4.4-9.5)
JIA category[a], n (%)				
Oligoarticular persistent	207	70 (33.8)	207	65 (31.4)
Oligoarticular extended	207	22 (10.6)	207	25 (12.1)
Polyarticular RF negative	207	48 (23.2)	207	46 (22.2)
Polyarticular RF positive	207	3 (1.4)	207	3 (1.4)
Enthesitis-related arthritis	207	21 (10.1)	207	23 (11.1)
Psoriasis arthritis	207	8 (3.9)	207	10 (4.8)
Systemic	207	7 (3.4)	207	7 (3.4)
Undifferentiated	207	28 (13.5)	207	28 (13.5)
JADAS > 1, n (%)	207	122 (58.9)	207	109 (52.7)
ESR ≥ 20, n (%)	205	8 (3.9)	206	4 (1.9)
CRP ≥ 5, n (%)	204	10 (4.9)	207	9 (4.3)
Children with active joints > 0, n (%)	207	49 (23.7)	207	30 (14.5)
Disease status[b], n (%)				
Remission off medication	207	26 (12.6)	207	41 (19.8)
Inactive	207	97 (46.9)	207	93 (44.9)
Active	207	84 (40.6)	207	73 (35.3)
No DMARDs ever, n (%)	207	46 (22.2)	207	36 (17.4)
Only sDMARDs[c] ever n (%)	207	77 (37.2)	207	66 (31.9)
bDMARDs[d] ever n (%)	207	84 (40.6)	207	105 (50.7)
No DMARDs ongoing, n (%)	207	68 (32.9)	207	74 (35.7)
Only sDMARDs[c] ongoing, n (%)	207	58 (28.0)	207	39 (18.8)
bDMARDs[d] ongoing, n (%)	207	81 (39.1)	207	94 (45.4)
Systemic corticosteroids ever, n (%)	207	46 (22.2)	207	54 (26.1)
PhysGA[f] > 0, n (%)	207	74 (35.7)	203	54 (26.6)
VAS pain[e] > 0, n (%)	207	129 (62.3)	196	127 (64.8)

N = Number, ANA = Anti-nuclear antibody, analysed using HEP-2 cells, 2 positive test at least 3 months apart, HLA-B27 = Human leukocyte antigen B27, RF = Rheumatoid factor, 2 positive tests analysed at least 3 months apart, JIA = Juvenile idiopathic arthritis, IQR = Interquartile range, JADAS = The Juvenile Arthritis Disease Activity Score, ESR = Erythrocyte sedimentation rate, CRP = C-reactive protein, DMARDs = Disease modifying anti-rheumatic drugs, VAS = visual analogue scale, PhysGA = Physician's global assessment of disease activity.

[a] JIA category = defined according to the International League of Associations for Rheumatology classification criteria.
[b] Disease status according to Wallace et al.; Remission off medication = inactive disease off medication for more than 12 months, Inactive disease = inactive disease on medication for less than six months or off medication for less than twelve months, or remission on medication (inactive disease on medication for more than six months), Active disease = continued activity since onset or flare (one or more episodes of clinical significant worsening with a change from inactive to active disease, requiring a change in medication).
[c] sDMARD = synthetic DMARD (methotrexate, hydroxychloroquine, cyclosporine, mycophenolate mofetil).
[d] bDMARD = biologic DMARD (etanercept, infliximab, adalimumab, tocilizumab, abatacept, certolizumab, golimumab, rituximab).
[e] PhysGA = Physician's global assessment of disease activity measured on a 21-numbered circle visual analogue scale from 0 to 10 (0 = No activity, > 0 = activity).
[f] VAS pain = Disease-related pain reported by the patient/parent on a 21-numbered circle visual analogue scale from 0 to 10 (0 = no pain, > 0 = pain).

Height in JIA and controls

Compared to the Norwegian reference data, the children with JIA had slightly lower height z-scores and the control group had higher height z-scores (Table 3). The difference between JIA and controls were slightly larger in girls than in boys and marginally larger at visit 2 with a difference in mean height z-score between JIA and controls of -0.4 (95% CI: -0.6, -0.1) and -0.3 (95% CI: -0.6, 0.0) in girls and boys, respectively. The results did not change substantially after adjustment for parental height. In the first visit, 39.2% of the girls with JIA had a low height z-score (< -0.5), compared to 26.6% of the girls in the control group (percentage points difference 12.6 (95% CI 0.7, 24.5)), with comparable results in boys. Adjusting for parental height gave similar results. The trends from visit 1 were also found in visit 2. The proportion of children with reduced growth tempo during the 2-year study (height deflection) were similar in girls with JIA and controls, while slightly more boys with JIA, 17.1%, showed height deflection, compared to 11.0% of the male controls (percentage point difference 8.1 (95% CI -4.7, 17.0)).

Table 3 Height in children with juvenile idiopathic arthritis and controls

	JIA		CONTROLS		DIFFERENCE[a]
	N	Values	N	Values	Values
Height z-score[b], mean (95 % ci)					
Female, visit 1	125	-0.2 (-0.5, 0.2)	109	0.2 (-0.2, 0.5)	-0.3 (-0.6, 0.0)
Female, visit 2	125	-0.1 (-0.4, 0.3)	109	0.3 (-0.1, 0.6)	-0.4 (-0.6, -0.1)
Male, visit 1	82	-0.1 (-0.5, 0.3)	73	0.1 (-0.3, 0.6)	-0.2 (-0.6, 0.1)
Male, visit 2	82	-0.1 (-0.6, 0.3)	73	0.2 (-0.3, 0.6)	-0.3 (-0.6, 0.0)
Parent-adjusted height z-score[c], mean (95 % CI)					
Female, visit 1	125	-0.1 (-0.4, 0.3)	51	0.3 (-0.2, 0.9)	-0.4 (-0.8, -0.1)
Female, visit 2	125	0.0 (-0.3, 0.4)	51	0.3 (-0.2, 0.8)	-0.3 (-0.6, 0.0)
Male, visit 1	80	-0.1 (-0.5, 0.3)	23	0.2 (-0.6, 1.0)	-0.3 (-1.0, 0.3)
Male, visit 2	80	-0.1 (-0.6, 0.3)	23	0.2 (-0.6, 1.0)	-0.3 (-0.9, 0.3)
					Percentage points (95 % CI)
Low height z-score[d], n (%)					
Female, visit 1	125	49 (39.2)	109	29 (26.6)	12.6 (0.7, 24.5)
Female, visit 2	125	45 (36.0)	109	27 (24.8)	11.2 (-0.5, 22.9)
Male, visit 1	82	31 (37.8)	73	20 (27.4)	10.4 (-4.2, 25.1)
Male, visit 2	82	28 (34.1)	73	18 (24.7)	9.5 (-4.8, 23.7)
Low parent-adjusted height z-score[d], n (%)					
Female, visit 1	125	44 (35.2)	51	12 (23.5)	11.7 (-2.7, 26.0)
Female, visit 2	125	41 (32.8)	51	14 (27.5)	5.3 (-9.4, 20.1)
Male, visit 1	80	30 (37.5)	23	3 (13.0)	24.5 (7.1, 41.8)
Male, visit 2	80	22 (27.5)	23	4 (17.4)	10.1 (-8.2, 28.4)
Height deflection[f], n (%)					
Female	125	9 (7.2)	109	10 (9.2)	-2.0 (-9.0, 5.1)
Male	82	14 (17.1)	73	8 (11.0)	6.1 (-4.7, 17.0)

JIA = Juvenile idiopathic arthritis, N = number, z-score = standard deviation score, CI = confidence interval.
[a] Difference calculated by two-sample t-test with unequal variances.
[b] Height z-score calculated as (participant's height – mean height for reference population) / height SD of reference population. Source: Norwegian reference population data: The Bergen growth study https://www.vekststudien.no/en/ (4).
[c] Parent-adjusted height z-score is calculated as the difference between z-score for height of the children and target height z-score based on parental height.
[d] Low height z-score and low parent-adjusted height z-score defined as height z-score < -0.5.
[f] Height deflection defined as delta height z-score < -0.25 per year.

BMI in JIA and controls

For girls with JIA, mean BMI z-scores tended to be higher than both the reference data and the control group at both visits, 0.4 (95% CI: 0.1, 0.8) at visit 2 with a difference between JIA and controls of 0.2 (95% CI: -0.1, 0.5) (Table 4). The boys with JIA had lower BMI z-scores than the controls, while indistinguishable from the Norwegian reference data. Considering the iso-BMI groups, the controls had 80% of participants defined as normal weight, while 72% with JIA were of normal weight. The categories underweight, overweight and obese were all overrepresented in the group with JIA compared to the controls, across both sexes. BMI z-scores followed the same pattern in visit 2 as in visit 1, and so did the distribution of participants within the iso-BMI groups.

Table 4 Body mass index (BMI) in children with juvenile idiopathic arthritis and controls

	JIA		CONTROLS		DIFFERENCE[a]
	N	**Values**	**N**	**Values**	**Values**
BMI z-score[b], mean (95% CI)					
Female, visit 1	125	0.3 (-0.1, 0.6)	109	0.1 (-0.3, 0.5)	0.2 (-0.1, 0.4)
Female, visit 2	125	0.4 (0.1, 0.8)	109	0.2 (-0.2, 0.6)	0.2 (-0.1, 0.5)
Male, visit 1	82	0.0 (-0.3, 0.3)	73	0.2 (-0.2, 0.7)	-0.2 (-0.6, 0.1)
Male, visit 2	82	0.1 (-0.3, 0.4)	73	0.3 (-0.2, 0.7)	-0.2 (-0.5, 0.1)
					Percentage points (95% CI)
Iso-BMI groups[c], n (%)					
Underweight[d], visit 1	207	14 (6.8)	182	8 (4.4)	2.4 (-2.2, 6.9)
Underweight[d], visit 2	207	10 (4.8)	182	7 (3.8)	1.0 (-3.1, 5.0)
Normal weight, visit 1	207	149 (72.0)	182	145 (79.7)	-7.7 (-16.2, 0.8)
Normal weight, visit 2	207	150 (72.5)	182	143 (78.6)	-6.1 (-14.6, 2.4)
Overweight, visit 1	207	35 (16.9)	182	27 (14.8)	2.1 (-5.2, 9.3)
Overweight, visit 2	207	38 (18.4)	182	27 (14.8)	3.5 (-3.9, 10.9)
Obesity[e], visit 1	207	9 (4.3)	182	2 (1.1)	3.2 (0.1, 6.4)
Obesity[e], visit 2	207	9 (4.3)	182	4 (2.7)	1.6 (-2.1, 5.3)

JIA = Juvenile idiopathic arthritis, N = number, z-score = standard deviation score, CI = confidence interval, BMI = Body mass index, iso-BMI = Body Mass Index with adjustments for age and sex.
[a] Difference calculated by two-sample t-test with unequal variances.
[b] BMI z-score 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/ (4).
[c] Iso-BMI groups calculated using the formula: Weight (kilograms) / [height (metres)]2 and subsequently adjusted for age and sex according to The International Obesity Task Force (IOTF) cut-off values to allow for comparison with adult BMI (Juliusson, 2013).
[d] Including mild, moderate and severe underweight
[e] Including severe obesity

Height z-scores for girls with JIA according to disease characteristics

The mean height z-scores differed for different subgroups of girls with JIA, and although the differences were small, they consistently displayed lower z-scores for less favourable subgroups based on disease duration, JIA category, disease status, disease activity and medication (Table 5). Girls with persistent oligoarticular JIA and girls who had never been treated with DMARDs had the highest height z-scores. The largest differences in height z-scores were found between groups based on treatment status. Girls that had never been treated with any DMARDs at visit 2 had a height z-score of 0.6 (95% CI: 0.1, 1.1), and girls that had ever used bDMARDs had a height z-score of -0.4 (95% CI: -0.6, -0.1). Treatment with systemic corticosteroids showed little to no effect on height z-scores. Adjusting for parental height gave very similar results (Supplemental Table 1).

Table 5 Height z-scores in girls with juvenile idiopathic arthritis according to disease characteristics

	VISIT 1		VISIT 2	
	N	**Height z-score**[a] Mean (95% CI)	**N**	**Height z-score**[a] Mean (95% CI)
Total females	125	-0.2 (-0.4, 0.0)	125	-0.1 (-0.3, 0.1)
Age at onset				
≥ 6 years	49	-0.2 (-0.5, 0.1)	49	-0.2 (-0.4, 0.1)
< 6 years	76	-0.1 (-0.4, 0.1)	76	-0.1 (-0.3, 0.2)
Disease duration				
< 5 years	63	-0.1 (-0.4, 0.2)	31	-0.1 (-0.4, 0.3)
≥ 5 years	62	-0.2 (-0.5, 0.1)	94	-0.1 (-0.3, 0.1)
JIA category[b]				
Persistent oligoarthritis	42	0.2 (-0.1, 0.5)	40	0.3 (0.0, 0.5)
Other JIA categories	83	-0.3 (-0.6, -0.1)	85	-0.3 (-0.5, 0.0)
Disease status[c]				
Remission off medication	12	0.1 (-0.3, 0.6)	18	0.6 (0.2, 1.1)
Inactive disease	59	-0.1 (-0.4, 0.2)	57	-0.2 (-0.4, 0.1)
Active disease	54	-0.3 (-0.6, 0.1)	50	-0.3 (-0.6, 0.1)
Disease activity				
JADAS ≤1	47	0.0 (-0.3, 0.2)	54	-0.1 (-0.3, 0.2)
JADAS >1	74	-0.2 (-0.5, 0.1)	71	-0.1 (-0.4, 0.1)
Medication status				
No DMARDs ever	23	0.4 (-0.1, 0.8)	17	0.6 (0.1, 1.1)
Only sDMARDs[d] ever	53	-0.2 (-0.5, 0.1)	44	0.1 (-0.2, 0.3)
bDMARDs[e] ever	49	-0.4 (-0.7, 0.0)	64	-0.4 (-0.6, -0.1)
No DMARDs ongoing	37	0.1 (-0.3, 0.5)	41	0.3 (0.1, 0.6)
Only sDMARDs[d] ongoing	41	-0.2 (-0.5, 0.2)	25	-0.2 (-0.6, 0.2)
bDMARDs[e] ongoing	47	-0.4 (-0.7, 0.0)	59	-0.3 (-0.6, -0.1)
No systemic corticosteroids ever	101	-0.2 (-0.4, 0.0)	97	-0.1 (-0.3, 0.2)
Systemic corticosteroids ever	24	-0.1 (-0.5, 0.4)	28	-0.2 (-0.6, 0.2)

N = Number, z-score = Standard deviation score, CI = Confidence interval, JIA = Juvenile idiopathic arthritis, JADAS = The Juvenile Arthritis Disease Activity Score, DMARDs = Disease modifying anti-rheumatic drugs.

[a] Height z-score calculated as (participant's height – mean height for reference population) / height SD of reference population. Source: Norwegian reference population data: The Bergen growth study https://www.vekststudien.no/en/ (4).

[b] JIA categories defined according to the International League of Associations for Rheumatology classification criteria.

[c] Disease status according to Wallace et al.: Remission off medication = inactive disease off medication for more than 12 months, Inactive disease = inactive disease on medication for less than six months or off medication for less than 12 months, or remission on medication (inactive disease on medication for more than six months), Active disease = continued activity since onset or flare (one or more episodes of clinical significant worsening with a change from inactive to active disease, requiring a change in medication).

[d] sDMARDs = synthetic DMARDs (methotrexate, hydroxychloroquine, cyclosporine, mycophenolate mofetil).

[e] bDMARDs = biologic DMARDs (etanercept, infliximab, adalimumab, tocilizumab, abatacept, certolizumab, golimumab, rituximab).

Height z-scores for boys with JIA according to disease characteristics

In contrast to girls, boys did not show a pattern of lower height z-scores related to less favourable subgroups of JIA (Table 6). Height z-scores differed little between different groups, except maybe in the subgroups based on medication. Boys with no DMARDs ongoing and boys with bDMARDs ongoing both had a height z-score of -0.2 (95% CI: -0.6, 0.1) at visit 2. The boys with only sDMARDs ongoing had a height z-score of 0.5 (95% CI: -0.2, 0.8). As for the girls, treatment with systemic corticosteroids did not seem to have a negative impact on height z-scores. Similarly, the results for parent-adjusted z-scores were comparable to the height z-scores not adjusted for parental height (Supplemental table 2).

In sub-analyses, height z-scores for all the subgroups of girls and boys with JIA were analysed using linear regression with adjustments for age at disease onset and disease duration. The analyses did not show significant impact of age at disease onset or disease duration on height z-scores (results not shown).

Table 6 Height z-scores in boys with juvenile idiopathic arthritis according to disease characteristics

	VISIT 1		VISIT 2	
	N	**Height z-score**[a] Mean (95 % CI)	**N**	**Height z-score**[a] Mean (95 % CI)
Total males	82	-0.1 (-0.3, 0.1)	82	-0.1 (-0.4, 0.1)
Age at onset				
≥ 6 years	55	-0.2 (-0.5, 0.1)	55	-0.2 (-0.5, 0.1)
< 6 years	27	0.1 (-0.3, 0.4)	27	0.0 (-0.3, 0.4)
Disease duration				
< 5 years	50	-0.1 (-0.4, 0.2)	28	-0.1 (-0.4, 0.3)
≥ 5 years	32	-0.1 (-0.5, 0.2)	54	-0.2 (-0.5, 0.1)
JIA category[b]				
Persistent oligoarthritis	28	-0.2 (-0.6, 0.2)	25	-0.1 (-0.5, 0.3)
Other JIA categories	54	-0.1 (-0.3, 0.2)	57	-0.1 (-0.4, 0.1)
Disease status[c]				
Remission off medication	14	-0.3 (-0.7, 0.2)	23	-0.2 (-0.6, 0.2)
Inactive disease	38	0.0 (-0.4, 0.3)	36	-0.1 (-0.5, 0.3)
Active disease	30	-0.1 (-0.5, 0.2)	23	-0.1 (-0.5, 0.3)
Disease activity				
JADAS ≤1	38	-0.1 (-0.4, 0.3)	44	-0.1 (-0.4, 0.2)
JADAS >1	43	-0.1 (-0.5, 0.2)	38	-0.2 (-0.5, 0.2)
Medication status				
No DMARDs ever	23	-0.2 (-0.5, 0.1)	19	-0.3 (-0.7, 0.2)
Only sDMARDs[d] ever	24	0.1 (-0.4, 0.6)	22	0.0 (-0.4, 0.4)
bDMARDs[e] ever	35	-0.2 (-0.6, 0.2)	41	-0.1 (-0.5, 0.2)
No DMARDs ongoing	31	-0.2 (-0.5, 0.1)	33	-0.2 (-0.6, 0.1)
Only sDMARDs[d] ongoing	17	0.3 (-0.3, 0.8)	14	0.5 (-0.2, 0.8)
bDMARDs[e] ongoing	34	-0.3 (-0.6, 0.1)	35	-0.2 (-0.6, 0.1)
No systemic corticosteroids ever	60	-0.3 (-0.5, 0.0)	56	-0.2 (-0.5, 0.1)
Systemic corticosteroids ever	22	0.3 (-0.1, 0.7)	26	0.0 (-0.4, 0.4)

N = Number, z-score = Standard deviation score, CI = Confidence interval, JIA = Juvenile idiopathic arthritis, JADAS = The Juvenile Arthritis Disease Activity Score, DMARDs = Disease modifying anti-rheumatic drugs.

[a] Height z-score calculated as (participant's height – mean height for reference population) / height SD of reference population. Source: Norwegian reference population data: The Bergen growth study https://www.vekststudien.no/en/ (4).

[b] JIA categories defined according to the International League of Associations for Rheumatology classification criteria.

[c] Disease status according to Wallace et al.; Remission off medication = inactive disease off medication for more than 12 months, Inactive disease = inactive disease on medication for less than six months or off medication for less than 12 months, or remission on medication (inactive disease on medication for more than six months), Active disease = continued activity since onset or flare (one or more episodes of clinical significant worsening with a change from inactive to active disease, requiring a change in medication).

[d] sDMARDs = synthetic DMARDs (methotrexate, hydroxychloroquine, cyclosporine, mycophenolate mofetil).

[e] bDMARDs = biologic DMARDs (etanercept, infliximab, adalimumab, tocilizumab, abatacept, certolizumab, golimumab, rituximab).

BMI z-scores for children with JIA according to disease characteristics

The BMI z-scores for girls with JIA were slightly higher than the reference data at both study visits, with inconsistent variations between the subgroups (Table 7). The boys had an overall lower BMI z-score than the girls, but consistent with the Norwegian reference population (Table 8). The lowest BMI z-score for the boys was found for the subgroup with disease onset before 6 years (-0.4 (95% CI -0.7, -0.2) at visit 1 and -0.3 (95% CI (-0.6, 0.0) at visit 2), compared to a BMI z-score of 0.2 (95% CI 0.0, 0.5) for those with disease onset after 6 years of age. Slightly elevated BMI z-scores of 0.3 (95% CI 0.0, 0.6) and 0.4 (95% CI 0.0, 0.8) were found for those that had used bDMARDs ever or ongoing, respectively.

Table 7 Body mass index (BMI) z-scores in girls with juvenile idiopathic arthritis according to disease characteristics

	VISIT 1		VISIT 2	
	N	**BMI z-score[a]** Mean (95% CI)	**N**	**BMI z-score[a]** Mean (95% CI)
Total females	125	0.3 (0.1, 0.5)	125	0.4 (0.2, 0.6)
Age at onset				
≥ 6 years	49	0.4 (0.1, 0.7)	49	0.5 (0.2, 0.8)
< 6 years	76	0.2 (-0.1, 0.5)	76	0.3 (0.0, 0.6)
Disease duration				
< 5 years	63	0.3 (0.1, 0.6)	31	0.6 (0.2, 1.0)
≥ 5 years	62	0.2 (-0.1, 0.5)	94	0.4 (0.1, 0.6)
JIA category[b]				
Persistent oligoarthritis	42	0.2 (-0.1, 0.5)	40	0.4 (0.1, 0.7)
Other JIA categories	83	0.3 (0.0, 0.6)	85	0.4 (0.1, 0.7)
Disease status[c]				
Off medication remission	12	0.4 (-0.3, 1.1)	18	0.2 (-0.3, 0.6)
Inactive disease	59	0.4 (0.1, 0.7)	57	0.4 (0.1, 0.7)
Active disease	54	0.1 (-0.2, 0.5)	50	0.5 (0.1, 0.9)
Disease activity				
JADAS ≤1	47	0.5 (0.2, 0.8)	54	0.4 (0.1, 0.8)
JADAS >1	74	0.1 (-0.2, 0.4)	71	0.4 (0.1, 0.7)
Medication status				
No DMARDs ever	23	0.4 (-0.1, 0.8)	17	0.5 (0.0, 1.0)
Only sDMARDs[d] ever	53	0.2 (-0.1, 0.5)	44	0.2 (-0.1, 0.5)
bDMARDs[e] ever	49	0.4 (0.0, 0.7)	64	0.5 (0.2, 0.9)
No DMARDs ongoing	37	0.3 (-0.1, 0.6)	41	0.4 (0.1, 0.7)
Only sDMARDs[d] ongoing	41	0.2 (-0.1, 0.5)	25	0.3 (-0.2, 0.7)
bDMARDs[e] ongoing	47	0.4 (0.0, 0.8)	59	0.5 (0.1, 0.8)
No systemic corticosteroids ever	101	0.3 (0.1, 0.5)	97	0.5 (0.2, 0.7)
Systemic corticosteroids ever	24	0.2 (-0.4, 0.7)	28	0.3 (-0.3, 0.8)

N = Number, z-score = Standard deviation score, CI = Confidence interval, JIA = Juvenile idiopathic arthritis, JADAS = The Juvenile Arthritis Disease Activity Score, DMARDs = Disease modifying anti-rheumatic drugs.

[a] BMI calculated as Weight (kilograms) / [height (metres)]^2. BMI z-score 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/ (4).

[b] JIA categories defined according to the International League of Associations for Rheumatology classification criteria.

[c] Disease status according to Wallace et al.; Remission off medication = inactive disease off medication for more than 12 months, Inactive disease = inactive disease on medication for less than six months or off medication for less than 12 months, or remission on medication (inactive disease on medication for more than six months), Active disease = continued activity since onset or flare (one or more episodes of clinical significant worsening with a change from inactive to active disease, requiring a change in medication).

[d] sDMARDs = synthetic DMARDs (methotrexate, hydroxychloroquine, cyclosporine, mycophenolate mofetil).

[e] bDMARDs = biologic DMARDs (etanercept, infliximab, adalimumab, tocilizumab, abatacept, certolizumab, golimumab, rituximab).

Table 8 Body mass index (BMI) z-scores in boys with juvenile idiopathic arthritis according to disease characteristics

	VISIT 1		VISIT 2	
	N	**BMI z-score[a]** Mean (95% CI)	**N**	**BMI z-score[a]** Mean (95% CI)
Total males	82	0.0 (-0.2, 0.2)	82	0.1 (-0.2, 0.3)
Age at onset				
≥ 6 years	55	0.2 (-0.1, 0.5)	55	0.2 (0.0, 0.5)
< 6 years	27	-0.4 (-0.7, -0.2)	27	-0.3 (-0.6, 0.0)
Disease duration				
< 5 years	50	0.2 (-0.1, 0.4)	28	0.4 (0.1, 0.7)
≥ 5 years	32	-0.2 (-0.6, 0.1)	54	-0.1 (-0.4, 0.2)
JIA category[b]				
Persistent oligoarthritis	28	-0.1 (-0.4, 0.3)	25	0.0 (-0.4, 0.5)
Other JIA categories	54	0.0 (-0.3, 0.3)	57	0.1 (-0.2, 0.3)
Disease status[c]				
Off medication remission	14	-0.3 (-0.8, 0.2)	23	-0.2 (-0.6, 0.2)
Inactive disease	38	0.1 (-0.2, 0.5)	36	0.3 (-0.1, 0.6)
Active disease	30	-0.1 (-0.4, 0.3)	23	0.0 (-0.4, 0.4)
Disease activity				
JADAS ≤1	38	-0.2 (-0.5, 0.1)	44	0.0 (-0.3, 0.3)
JADAS >1	43	0.2 (-0.2, 0.5)	38	0.2 (-0.2, 0.5)
Medication				
No DMARDs ever	23	-0.3 (-0.7, 0.1)	19	-0.1 (-0.6, 0.3)
Only sDMARDs[d] ever	24	-0.2 (-0.5, 0.2)	22	-0.2 (-0.6, 0.1)
bDMARDs[e] ever	35	0.3 (0.0, 0.7)	41	0.3 (0.0, 0.6)
No DMARDs ongoing	31	-0.3 (-0.7, 0.0)	33	-0.2 (-0.5, 0.1)
Only sDMARDs[d] ongoing	17	-0.1 (-0.5, 0.3)	14	-0.2 (-0.6, 0.3)
bDMARDs[e] ongoing	34	0.3 (0.0, 0.7)	35	0.4 (0.0, 0.8)
No systemic corticosteroids ever	60	-0.1 (-0.4, 0.2)	56	-0.1 (-0.3, 0.2)
Systemic corticosteroids ever	22	0.3 (-0.1, 0.7)	26	0.3 (-0.1, 0.7)

N = Number, BMI = Body mass index, z-score = Standard deviation score, CI = Confidence interval, JIA = Juvenile idiopathic arthritis, JADAS = The Juvenile Arthritis Disease Activity Score, DMARDs = Disease modifying anti-rheumatic drugs.

[a] BMI calculated as Weight (kilograms) / [height (metres)]^2. BMI z-score calculated as (participant's BMI – mean BMI for reference population) / BMI SD of reference population. Source: Norwegian reference population data: The Bergen growth study https://www.vekststudien.no/en/ (4).

[b] JIA categories defined according to the International League of Associations for Rheumatology classification criteria.

[c] Disease status according to Wallace et al.: Remission off medication = inactive disease off medication for more than 12 months, Inactive disease = inactive disease on medication for less than six months or off medication for less than 12 months, or remission on medication (inactive disease on medication for more than six months), Active disease = continued activity since onset or flare (one or more episodes of clinical significant worsening with a change from inactive to active disease, requiring a change in medication).

[d] sDMARDs = synthetic DMARDs (methotrexate, hydroxychloroquine, cyclosporine, mycophenolate mofetil).

[e] bDMARDs = biologic DMARDs (etanercept, infliximab, adalimumab, tocilizumab, abatacept, certolizumab, golimumab, rituximab).

Pubertal onset and menarche

There was little to no difference in median age for pubertal onset between the children with JIA and the controls (Table 9). Median age of menarche was also very similar between girls with JIA and controls, 13.0 (95% CI 12.4, 13.2) versus 12.8 (95% CI 12.3, 13.4) years, respectively. The numbers for delayed pubertal onset and menarche were also similar, but the groups were too small to draw firm comparisons. The results from log-rank tests supported that there was no substantial difference in pubertal onset and menarche between the groups (results not shown).

Table 9 Age of pubertal onset and menarche in children with juvenile idiopathic arthritis and controls

	JIA		CONTROLS	
	N[a]	Values	N[a]	Values
Girls				
Median age pubertal onset[b] (95% CI)	67	11.0 (10.6, 11.3)	50	11.4 (10.9, 12.0)
Median age menarche (95% CI)	109	13.1 (12.4, 13.2)	73	12.8 (12.3, 13.2)
Delayed pubertal onset[c], n (%)	43	3 (7.0)	33	1 (3.0)
Delayed menarche[d], n (%)	69	1 (1.4)	46	0 (0.0)
Boys				
Median age pubertal onset[e] (95% CI)	39	12.5 (12.1, 13.1)	34	12.7 (12.4, 13.5)
Delayed pubertal onset boys[f], n (%)	25	5 (20.0)	25	5 (20.0)

JIA = juvenile idiopathic arthritis, CI = Confidence interval, N = number of participants

[a] The number included all participants with available pubertal data at visit 2. Calculations were based on survival analyses to take into account participants that had not yet reached pubertal onset or menarche within the time of data collection.
[b] Pubertal onset for girls is defined as Tanner stage B2.
[c] Delayed pubertal onset for girls is defined as pubertal onset at age ≥ 13 years.
[d] Delayed menarche is defined as menarche at age ≥ 15 years.
[e] Pubertal onset for boys is defined as Tanner stage G2.
[f] Delayed pubertal onset for boys is defined as pubertal onset at age ≥ 14 years.

Discussion

Summarized main results

The population of children with JIA in this study had a slightly lower mean height z-score compared to the control group and to Norwegian references. However, the difference is small, and the confidence intervals indicate that the results must be interpreted with caution. For subgroups of girls with JIA with more unfavourable disease characteristics, including use of bDMARDs, the mean height z-scores were even lower. For boys, there was no consistent pattern within the chosen subgroups. Treatment with systemic corticosteroids did not show a clear association with height z-scores. The mean BMI z-score for girls with JIA was higher than the Norwegian reference data, while the BMI z-scores for boys were more similar to the references than among females. Both boys and girls in the control group had slightly higher BMI z-scores than the references. We found no clear association between disease characteristics or medication status and BMI z-scores. Nor did we observe a higher frequency of delayed puberty among the children with JIA compared to the controls.

Strengths

Our study is based on two study visits, making it possible to compare growth and disease variables over time. A large study cohort including all JIA categories, distributed over three centres across the country with a broad range of relevant variables, provides representative data for children with JIA in Norway. Validated outcome measures for the JIA group were used to follow international standards. In addition to comparisons between the group with JIA and the controls, both groups were compared to Norwegian reference data which is an additional strength.

Limitations

A possible limitation of our study is that participants with JIA may have had more severe disease than the average patient with JIA, as patients with active disease attend medical appointments more frequently and may also be more prone to accept an invitation to participate in the study than patients with milder disease. The lower mean age of children that declined to participate may be due to the extensive study program. A higher proportion of parents with higher education in the control group could indicate a higher socioeconomic

status in those accepting to participate, which in turn may be related to height. This could explain why our control group is slightly taller than the references. Alternatively, it is possible that Norwegian children today are taller and with a higher BMI than the reference data measured in 2003-2006 (4). The lack of information about duration of treatment, especially information on duration of systemic corticosteroid treatment known to be of importance for height, is a recognizable limitation. Additionally, the study had low power to investigate certain clinical subgroups due to the limited number of participants in several of these groups.

Comparison to literature

Growth in children with JIA has been studied extensively in the past, but the constant development in treatment possibilities profoundly influences the comparison of results. Long periods of treatment with systemic corticosteroids are known to impair growth, but this is more rarely used today in countries with access to modern medicine. Newer studies therefore attempt to investigate the disease's impact on growth independent from treatment.

A French study with data collected between 1966 and 1998 found that children with JIA had a mean height z-score of -2.7 when treated with systemic corticosteroids, but with 70% achieving catch-up growth after discontinuation of the treatment (23). The catch-up growth could either be due to lower disease activity following treatment, or discontinuation of the growth-inhibiting treatment itself. Decreased height z-scores while in active disease, followed by improvement in growth with low disease activity or after remission was obtained, was also found by Saha et al. in a Swedish study from 1999 (34). Concurrent with our results for girls, they found lower height z-scores in children with polyarthritis than in the pauciarticular (or oligoarticular) types of juvenile chronic arthritis (JCA).

Studies from the biologic era suggest that patients with more severe forms of JIA still experience growth impairment. The British Childhood Arthritis Prospective Study (CAPS) showed that 39% of patients with JIA had growth restriction, defined as change in height z-score < -0.5 in the first three years after disease onset (35). They also found large differences between subgroups, the lowest height z-scores belonging to children with systemic JIA and psoriasis arthritis, while oligoarticular JIA had better results. Significant associations were

found between lower height z-scores and more severe disease characteristics, such as higher CHAQ scores, lower BMI, and longer duration of symptoms (35). In the Canadian ReACCh-Out study, 10% of children with systemic JIA, uncontrolled disease and/or long periods of steroid treatment had increased risk of growth impairment, while children with less severe JIA categories had normal growth (36).

Another study from the UK looked specifically at growth after starting treatment with the bDMARD etanercept (37). They observed that mean height z-score improved from -0.75 to -0.45 over the course of two years after treatment initiation. Further improvement was seen in subgroups not simultaneously treated with systemic corticosteroids, possibly supporting the hypothesis that more severe disease predisposes to lower height. A similar improvement was found in a Finnish study by Tynjälä et al. in 2006 (38), describing a 0.45 increase in height z-score after 2 years of therapy with anti-TNF-α in 53 children with JIA with delayed growth at baseline (38).

A Portuguese study from 2020 (39), studying height and sexual maturity in girls with JIA, showed that both BMI and height z-scores were lower, and pubertal onset was later, in girls with JIA than controls. The results were also most pronounced in the subgroups with more unfavourable disease characteristics. Patients with oligoarthritis had a mean height z-score of 0.48 while systemic and polyarthritis had a mean height z-score of -0.64. Compared to our study, they had a lower number of participants (44 girls), and they used different measures for disease activity (Disease Activity Score 28). Girls with polyarticular juvenile idiopathic arthritis were significantly more likely to present with short stature than those with oligoarticular disease. While their results on height z-scores for girls were consistent with ours, their results on BMI and puberty were not. We found no pubertal delay in comparison with controls, but also comparable to a large population-based health study, the adolescent part of The Trøndelag Health Study, The Young-HUNT 3 and 4 Study showing a median age for menarche of 13 years (5, 6).

A student thesis from NTNU from 2020 looked at final height and BMI in patients with JIA, using the same study design and variables as our study (40). The study used data from a Nordic JIA cohort followed for 18 years after inclusion in 1997-2000. Some of the data was

collected at two of the same centres with the same catchment areas (Mid- and North-Norway) as the NorJIA study. Since data collection for the study of adult height took place 10-15 years before commencement of the NorJIA study, the patient groups have gotten different treatment, as bDMARDs have become more available with time. Even though the thesis by Monterotti looked at adult height, the results were comparable to ours for girls with JIA, with the same trends in height z-scores related to disease severity. However, Monterotti found even lower height z-scores for the boys with JIA, opposite to our results. The latter could possibly be explained by the fact that the boys in our study had a shorter disease duration than the girls, and the known fact that boys experience their height spurt (and possibly their most sensitive period for growth impairment) later than girls (40).

Interpretations/clinical relevance

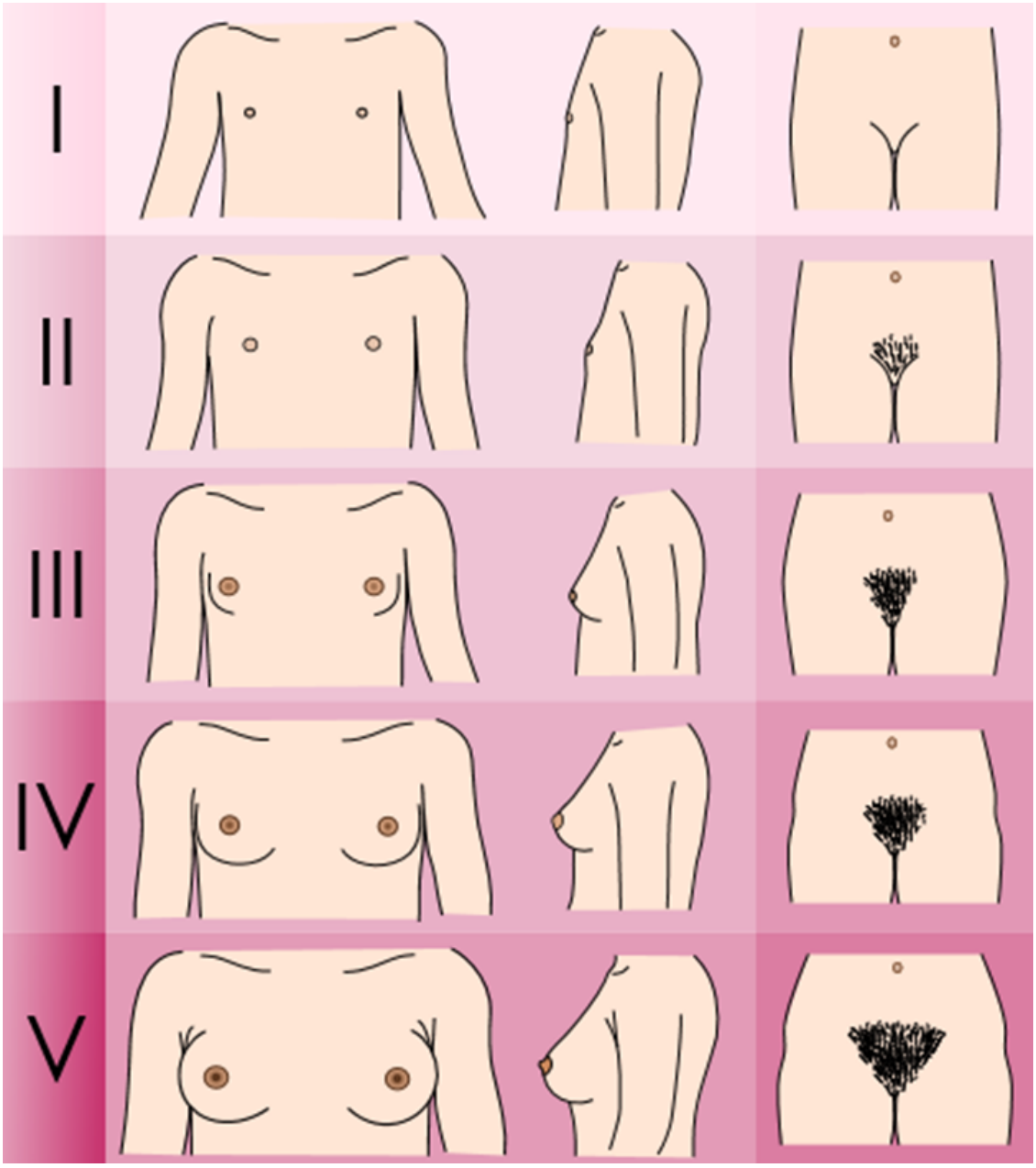
The results from our study show small differences and uncertain associations. This may be partly because of small subgroups, but also because of actual small differences in anthropometric and puberty measures between children with JIA and controls, thanks to the treatments available today. Furthermore, it is worth questioning whether the findings are clinically important. One standard deviation from the mean height constitutes 6 cm for a 13-year-old girl, and 7.5 cm for a 13-year-old boy (4). This roughly translates to our most affected subgroup, girls that had ever been treated with bDMARDs, having a mean height deficit of 2.4 cm at age 13, compared to the Norwegian references.

Nonetheless, aligning with other research on the field, our results imply that severe forms of JIA may still influence growth. It is plausible that girls treated with bDMARDs displaying lower height z-scores is an indirect expression of disease severity, rather than the direct effect of treatment on height. Short periods of treatment with systemic corticosteroids do not seem to lead to growth impairment. There is reason to believe that the treatment periods were short for the 26.1% of children in our study that had been treated with systemic corticosteroids, due to the availability and affordability of bDMARDs for families in Norway. Children with JIA are now given DMARDs at an early stage of the disease, benefiting from the “window of opportunity”, to try to halt the disease early on and minimize adverse effects such as growth impairment.

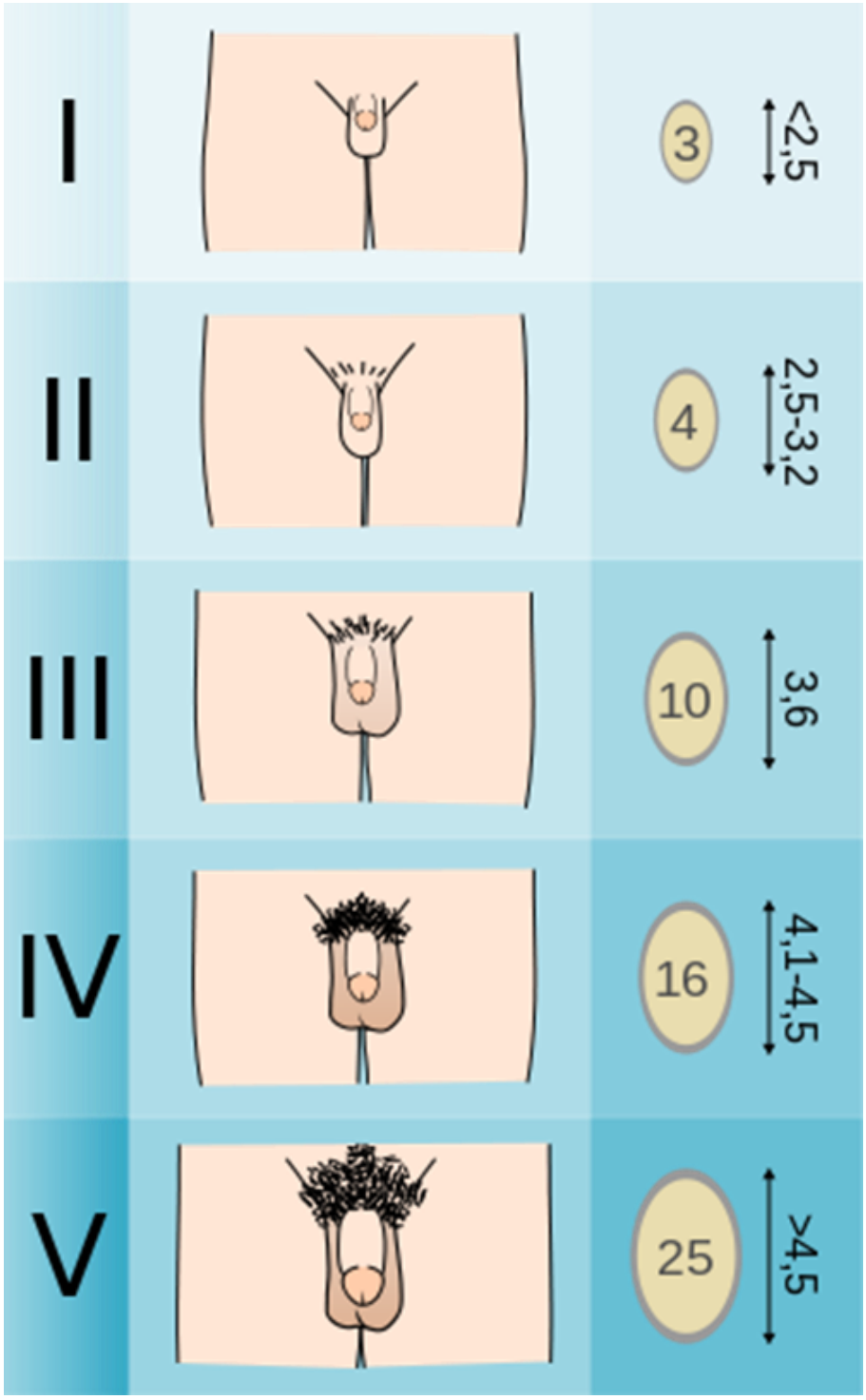
Conclusion

In conclusion, the mean height and BMI z-scores for children with JIA did not differ substantially from the control group or from Norwegian reference data. However, both girls and boys with JIA tended towards lower height z-scores compared to controls, and the girls followed a pattern of lower height z-scores consistently relating to more severe disease characteristics. If children with JIA do in fact experience a loss of height, we suspect that disease activity and JIA category are important factors. The results imply that children with JIA who are treated by current standards may still experience adverse effects of their disease, including growth impairment. Thus, there may still be something to gain from further optimising treatment and initiating treatment as early as possible.

Supplements



Supplemental figure 1 Tanner stages in girls B1-5 and PH1-5. Illustration from the NorJIA study (3)



Supplemental figure 2 Tanner stage in boys G1-5 and PH1-5. Illustration from the NorJIA study (3)

Supplemental table 1 Parent-adjusted height z-scores for girls with juvenile idiopathic arthritis according to disease characteristics

	VISIT 1		VISIT 2	
	N	**Parent adjusted height z-score**[a] Mean (95% CI)	**N**	**Parent adjusted height z-score**[a] Mean (95% CI)
Total females	125	-0.1 (-0.3, 0.1)	125	0.0 (-0.2, 0.2)
Age at onset				
≥ 6 years	49	0.1 (-0.2, 0.4)	49	0.1 (-0.2, 0.3)
< 6 years	76	-0.1 (-0.4, 0.1)	76	0.0 (-0.3, 0.2)
Disease duration				
< 5 years	63	0.0 (-0.2, 0.3)	31	0.1 (-0.2, 0.5)
≥ 5 years	62	-0.2 (-0.4, 0.1)	94	0.0 (-0.2, 0.2)
JIA category[b]				
Persistent oligoarthritis	42	0.2 (-0.2, 0.5)	40	0.3 (-0.1, 0.6)
Other JIA categories	83	-0.2 (-0.4, 0.0)	85	-0.1 (-0.3, 0.1)
Disease status[c]				
Remission off medication	12	0.1 (-0.4, 0.6)	18	0.4 (-0.1, 0.9)
Inactive disease	59	0.0 (-0.3, 0.2)	57	-0.1 (-0.3, 0.2)
Active disease	54	-0.1 (-0.5, 0.2)	50	0.0 (-0.3, 0.3)
Disease activity				
JADAS ≤1	47	0.0 (-0.3, 0.3)	54	0.0 (-0.3, 0.3)
JADAS >1	74	-0.1 (-0.4, 0.2)	71	0.0 (-0.2, 0.3)
Medication status				
No DMARDs ever	23	0.4 (0.0, 0.8)	17	0.6 (0.0, 1.1)
Only sDMARDs[d] ever	53	0.0 (-0.3, 0.3)	44	0.2 (-0.1, 0.5)
bDMARDs[e] ever	49	-0.3 (-0.6, 0.0)	64	-0.2 (-0.5, 0.0)
No DMARDs ongoing	37	0.2 (-0.2, 0.6)	41	0.5 (0.2, 0.8)
Only sDMARDs[d] ongoing	41	0.0 (-0.4, 0.3)	25	-0.1 (-0.5, 0.3)
bDMARDs[e] ongoing	47	-0.3 (-0.6, 0.0)	59	-0.2 (-0.5, 0.0)
No systemic corticosteroids ever	101	-0.1 (-0.3, 0.1)	97	0.1 (-0.1, 0.3)
Systemic corticosteroids ever	24	0.1 (-0.3, 0.5)	28	-0.2 (-0.6, 0.2)

N = Number, z-score = Standard deviation score, CI = Confidence interval, JIA = Juvenile idiopathic arthritis, JADAS = The Juvenile Arthritis Disease Activity Score, DMARDs = Disease modifying anti-rheumatic drugs.

[a] Parent-adjusted height z-score is calculated as the difference between z-score for height of the children and target height z-score based on parental height.

[b] JIA categories defined according to the International League of Associations for Rheumatology classification criteria.

[c] Disease status according to Wallace et al.: Remission off medication = inactive disease off medication for more than 12 months, Inactive disease = inactive disease on medication for less than six months or off medication for less than 12 months, or remission on medication (inactive disease on medication for more than six months), Active disease = continued activity since onset or flare (one or more episodes of clinical significant worsening with a change from inactive to active disease, requiring a change in medication).

[d] sDMARDs = synthetic DMARDs (methotrexate, hydroxychloroquine, cyclosporine, mycophenolate mofetil).

[e] bDMARDs = biologic DMARDs (etanercept, infliximab, adalimumab, tocilizumab, abatacept, certolizumab, golimumab, rituximab).

Supplemental table 2 Parent-adjusted height z-scores for boys with juvenile idiopathic arthritis according to disease characteristics

	VISIT 1		VISIT 2	
	N	**Parent adjusted height z-score[a]** Mean (95% CI)	**N**	**Parent adjusted height z-score[a]** Mean (95% CI)
Total males	80	-0.1 (-0.3, 0.1)	80	-0.1 (-0.4, 0.1)
Age at onset				
≥ 6 years	53	-0.2 (-0.5, 0.1)	53	-0.2 (-0.5, 0.1)
< 6 years	27	0.1 (-0.3, 0.4)	27	0.0 (-0.3, 0.3)
Disease duration				
< 5 years	48	-0.2 (-0.5, 0.2)	27	-0.1 (-0.5, 0.3)
≥ 5 years	32	0.0 (-0.4, 0.4)	53	-0.1 (-0.4, 0.1)
JIA category[b]				
Persistent oligoarthritis	27	-0.1 (-0.6, 0.3)	24	-0.1 (-0.5, 0.3)
Other JIA categories	53	-0.1 (-0.4, 0.2)	56	-0.2 (-0.4, 0.1)
Disease status[c]				
Remission off medication	13	-0.2 (-0.7, 0.3)	22	-0.1 (-0.5, 0.3)
Inactive disease	38	0.0 (-0.3, 0.4)	35	-0.1 (-0.5, 0.3)
Active disease	29	-0.3 (-0.6, 0.1)	23	-0.2 (-0.6, 0.2)
Disease activity				
JADAS ≤1	37	0.1 (-0.3, 0.4)	42	0.0 (-0.3, 0.3)
JADAS >1	42	-0.2 (-0.6, 0.1)	38	-0.3 (-0.6, 0.1)
Medication status				
No DMARDs ever	21	-0.2 (-0.5, 0.1)	18	-0.2 (-0.6, 0.3)
Only sDMARDs[d] ever	24	0.1 (-0.5, 0.6)	22	-0.1 (-0.5, 0.4)
bDMARDs[e] ever	35	-0.2 (-0.6, 0.2)	40	-0.2 (-0.5, 0.2)
No DMARDs ongoing	29	-0.2 (-0.5, 0.2)	32	-0.1(-0.4, 0.2)
Only sDMARDs[d] ongoing	17	0.2 (-0.4, 0.8)	14	0.1 (-0.5, 0.7)
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No systemic corticosteroids ever	58	-0.2 (-0.5, 0.0)	54	-0.2 (-0.4, 0.1)
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[d] sDMARDs = synthetic DMARDs (methotrexate, hydroxychloroquine, cyclosporine, mycophenolate mofetil).
[e] bDMARDs = biologic DMARDs (etanercept, infliximab, adalimumab, tocilizumab, abatacept, certolizumab, golimumab, rituximab).

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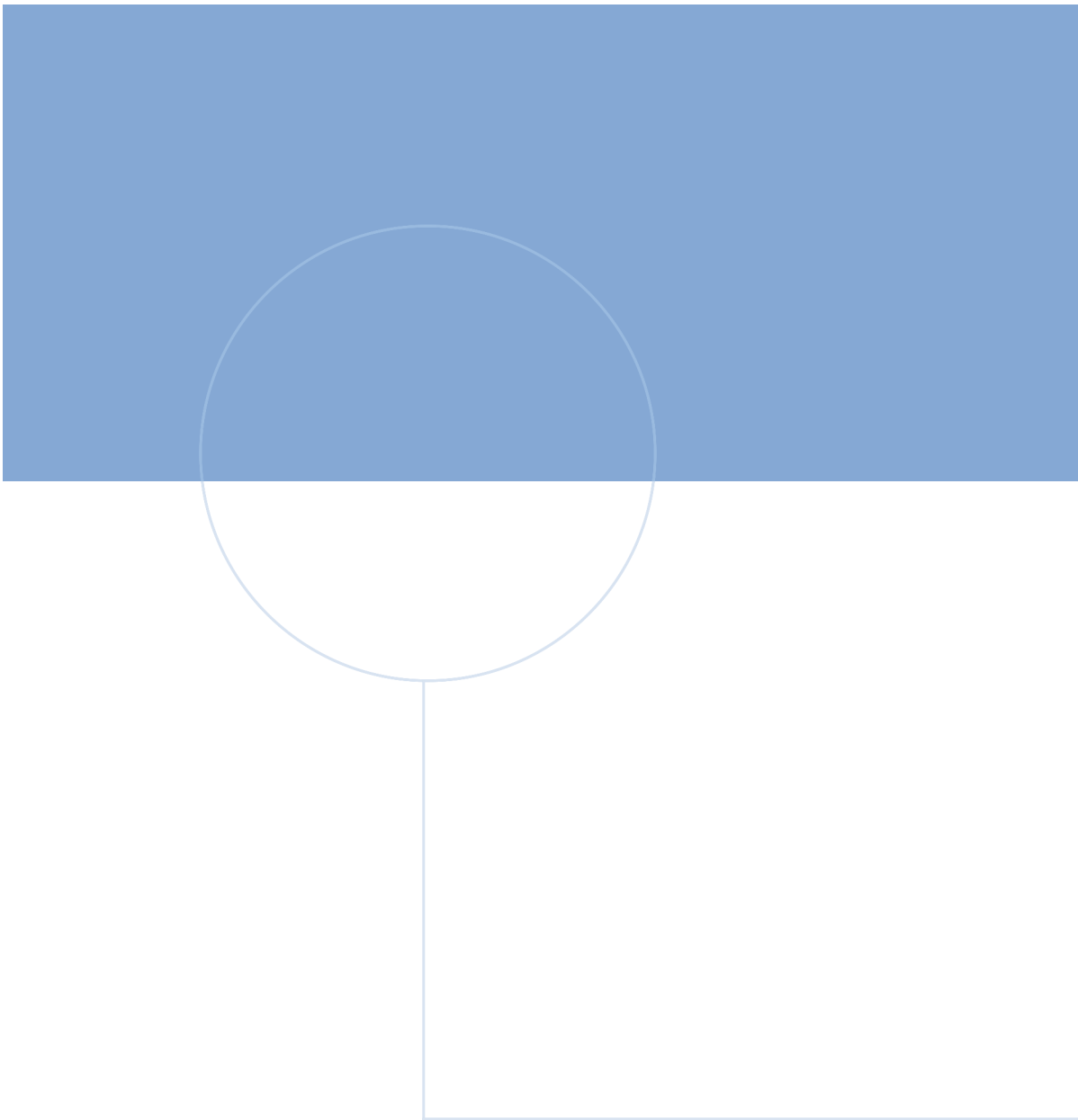

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