Juvenile Chronic Arthritis

From Childhood to Adolescence and Adulthood

Lennart Bertilsson

Center for Bone and Arthritis Research, Department of
Rheumatology and Inflammation Research
Institute of Medicine
Sahlgrenska Academy at University of Gothenburg

UNIVERSITY OF GOTHENBURG

Gothenburg 2014

Juvenile Chronic Arthritis

lennart.bertilsson@gu.se

ISBN 978-91-628-9013-1

Printed in Gothenburg, Sweden 2014
ALE TRYCKTEAM AB

Det ordnar sig alltid

Juvenile Chronic Arthritis

From Childhood to Adolescence and Adulthood

Lennart Bertilsson

Center for Bone and Arthritis Research, Department of Rheumatology and Inflammation Research, Institute of Medicine
Sahlgrenska Academy at University of Gothenburg
Göteborg, Sweden

ABSTRACT

Juvenile chronic arthritis (JCA) is characterized by arthritis and onset before 16 years of age and of unknown etiology with an annual incidence between 7 and 23/100,000 in the Nordic countries. Several studies report different results concerning long-term outcomes. There are few population based longitudinal long-term follow-up studies of JCA.

We have conducted a longitudinal population based study of one cohort of incidence and one of prevalence cases of JCA. Out of 132 patients in the prevalence cohort, 128 were followed for 5 years with annual reports. At the 5-year follow-up the disease was active in 12%, stable in 28%, inactive in 25% and in remission in 34%. Thirty-four percent had changed subgroup, 8% had developed uveitis and the median Childhood Health Assessment Questionnaire (CHAQ) score was 0.13 (range 0.0–1.9). The number of involved joints at inclusion predicted active disease. Disease onset age, number of involved joints and joints with arthritis at inclusion were positively correlated with continuous disease and the CHAQ score at the 5-year-follow-up.

After an average of 17 years from disease onset 86 individuals of the incidence cohort participated in a follow-up. Forty percent were in remission, 44% had changed subgroups, the median HAQ score was 0.0 (0.0–1.5) and Keitel functional test score 100 (54–100). Health related quality of life evaluated by the Short Form-36 was found significantly lower in JCA compared to a reference group. Thirty-nine percent of the individuals in remission at the 5-year follow-up were no longer in remission. Long-term outcome was predicted by characteristics at the 5-year follow-up rather than at the onset.

Calcanear bone mineral density (BMD) was measured with dual-energy absorptiometry and laser in 85 individuals of the incidence cohort at the 17-year follow-up. The BMD Z-scores were significantly lower in both sexes compared to the reference population, also in the individuals in remission. A BMD Z-score < -1SD was associated with the use of hormonal contraceptives in the women and the disease activity at the 17-year follow-up in the men.

To investigate long-term socioeconomic outcomes the prevalence cohort was examined at an average of 22 years after disease onset when the patients had reached 28–35 years of age. Ninety-five participants, 71% of the original cohort, were followed-up. The participants answered a questionnaire concerning education, income, disability benefits, marital/civil status and children. Among the women 14.9% had full or partial disability pension compared to 3.0% in the general population ($p<0.001$). The men had borderline lower education compared to the general population ($p=0.051$). No significant differences in income, marital/civil status and reproduction either for men or women were demonstrated; no predictors during the early disease course and socioeconomic outcomes were identified.

To conclude, in these two longitudinal long-term outcome studies, JCA was shown to be heterogeneous both concerning course of subgroup and disease activity and only 40% were in remission at the 17-year follow-up. The quality of life and the calcanear BMD were negatively affected. No large impact on socioeconomic outcomes was found on group level.

Keywords: Juvenile idiopatic arthritis, outcome study, longitudinal study

ISBN: 978-91-628-9013-1

SAMMANFATTNING PÅ SVENSKA

BAKGRUND

Varje år drabbas i Sverige uppemot 200 barn och indirekt deras familjer av juvenil artrit. Juvenil artrit är en grupp av reumatologiska autoimmuna och autoinflammatoriska sjukdomar med inflammation i olika leder eller i ryggen som medför risk för inskränkningar i funktion och aktivitet samt svårigheter att delta fullt ut i ett normalt liv. Juvenil artrit hos barn kan te sig på många olika sätt med inflammation i många olika leder, med skiftande mönster av utbredning i lederna och med varierande prognos. Ibland dominerar så kallade systemmanifestationer med bland annat feber. Det har också funnits olika sätt att dela in sjukdomen där juvenil kronisk artrit (JCA) tidigare användes i Europa men där juvenil idiopatisk artrit (JIA) nu har använts globalt under det senaste decenniet.

Det finns få långtidsuppföljningar av JCA/JIA och de som har utförts bygger framför allt på patienter från specialistkliniker och utgör på så sätt en grupp med sannolikt svårare sjukdom. I uppföljningar där deltagarna sökts/inkluderats från på alla vårdnivåer saknas ingående kännedom om den långsiktiga sjukdomsutvecklingen såsom risken för kvarstående aktiv sjukdom, bestående funktionsinskränkningar och socioekonomiska aspekter.

HUVUDSYFTEN

Syftet med projektet är att få mer kunskap om långtidsförloppet vid JCA genom uppföljning 5 år och mer än 15 år efter sjukdomsdebuten:

- Avseende typiska drag för sjukdomen såsom förändring av undergrupp, sjukdomsaktivitet och funktionsförmåga samt att söka faktorer som kan förutsäga sjukdomsaktivitet och funktionsförmåga, delarbete I.
- Avseende typiska drag för sjukdomen såsom förändring av undergrupp, sjukdomsaktivitet, funktionsförmåga och livskvalitetsaspekter samt att söka faktorer som kan förutsäga sjukdomsaktivitet, funktionsförmåga och livskvalitetsaspekter, delarbete II.
- Avseende benhälsa och faktorer som kan förutsäga risk för sämre benhälsa, delarbete III.

- Avseende konsekvenser av utbildningsnivå, inkomst, förtidspension samt familjeförhållande i jämförelse med vanlig befolkning, delarbete IV.

METOD

Projektet består av uppföljningar som löper över tid. Två patientgrupper undersöktes mer än 15 år efter deltagarnas insjuknande. Patienterna i projektet värvades ursprungligen i Västsverige till så kallade epidemiologiska studier 1984 till 1986 där man undersökte hur vanligt förekommande sjukdomen var. En grupp bestod av patienter som insjuknat under perioden (incidenskohort) och en grupp bestod av patienter som hade sjukdomen den 31:a december 1988 (prevalenskohort). De europeiska kriterierna för att beskriva sjukdomen JCA användes för att identifiera barnen och för att dela upp dem i undergrupper. Undergrupperna bestod av systemisk form, polyartikulär form (påverkan av minst fem leder), pauciartikulär form (påverkan av mindre än fem leder), monoartikulär form (påverkan av en led), ankyloserande spondylit (inflammation i ryggen/bäckenlederna), psoriasis artrit (ledinflammationer tillsammans med hudpsoriasis) samt formen som är associerad med inflammatorisk tarmsjukdom.

Vid uppföljningarna utfördes bland annat ledundersökning och blodprover togs. Vid 5-årsundersökningen av incidenskohorten utfördes också ögonundersökning samt röntgen av leder som var inflammerade om det inte gjorts det närmaste året. Deltagarna undersöktes också med ett formulär för att skatta den fysiska funktionen, så kallat Childhood Health Assessment Questionnaire (CHAQ) och deras medicinering kartlades.

Vid uppföljningen mer än 15 år efter insjuknandet utfördes också ledundersökning, blodprovstagning samt kartläggning av medicinering. Ett funktionsskattningsformulär, Health Assessment Questionnaire (HAQ) samt en livskvalitetsenkät, Short Form 36 (SF-36) fylldes i av deltagarna. Ett funktionstest av enkla rörelsemönster, Keitel functional test (KFT) genomfördes. Deltagarna i incidenskohorten undersöktes även med bentäthetsmätning av hälbenen med en metod som kombinerar röntgen och laser. Deltagarna i prevalenskohorten fick fylla i uppgifter om utbildning, inkomst, förtidspension/sjukersättning samt familjeförhållanden.

RESULTAT

Delarbete I, baseras på incidenskohorten. Vid 5 år efter insjuknande hade 40 % fortfarande en aktiv sjukdom och 34 % var i remission medan 25 % inte hade tecken till sjukdomsaktivitet men hade behövt medicinering de sista två åren. Åttiofyra patienter röntgades varav 24 % hade röntgenförändringar av vilka hälften mer avancerade förändringar. Vid 5-årskontrollen var medianen för CHAQ 0,13 med spridning från 0,0 till 1,9. Stort antal involverade leder (endera värmeökning, ömhet, svullnad eller rörelseinskränkning) vid inklusion medförde ökad risk för aktiv sjukdom vid 5-årskontrollen. Hög ålder vid insjuknande, stort antal involverade leder och antal leder med ledinflammation vid inklusion resulterade i ökad risk för mer kontinuerlig sjukdom och påverkad funktionsförmåga enligt CHAQ. Slutligen var röntgenförändringar oftare förekommande i den polyartikulära undergruppen.

Delarbete II, baseras på incidenskohorten. Vid i genomsnitt 17 år efter insjuknande fann vi att 41 % hade aktiv sjukdom och att 40 % var i remission medan 19 % inte hade tecken till sjukdomsaktivitet men hade behövt medicinering de 2 föregående åren. Av de med aktiv sjukdom hade ungefär hälften antireumatisk medicinering. Vi fann att 44 % hade ändrat undergrupp och 39 % av de deltagare som var i remission efter 5 år var inte i remission efter 17 år. Medianen för HAQ var 0,0 med spridning från 0,0 till 1,5 och för KFT 100 (spridning 54 – 100). SF-36, d.v.s. den hälsorelaterade livskvaliteten var signifikant lägre jämfört med ålders- och könsmatchad normalbefolkning avseende samtliga delskalor. Sjukdomsrelaterade faktorer vid 17-årskontrollen var mera kopplat till tillståndet vid 5-årskontrollen än med faktorer vid insjuknandet.

Delarbete III, baseras på incidenskohorten. Benhälsan var påverkad med signifikant sänkt bentäthet för både män och kvinnor jämfört med en referenspopulation. Vi fann också att bentätheten för deltagarna som var i remission var sänkt. Låg bentäthet för män var korrelerad till mer aktiv sjukdom vid undersökningen och för kvinnor var låg bentäthet korrelerad till användning av p-piller.

Delarbete IV. I prevalenskohorten där individerna var mellan 28 och 35 år vid uppföljningen fann vi att 14,9 % av kvinnorna i kohorten hade hel eller deltids förtidspension/sjukersättning jämfört med 3,0 % i vanlig befolkning vilket var en signifikant skillnad. För männen var det ingen skillnad. Utbildningsnivån bland männen i kohorten var gränssignifikant lägre jämfört normalbefolkningen ($p=0.051$) men det fanns ingen skillnad för kvinnorna. Den genomsnittliga inkomsten av tjänst eller ersättning från

försäkringskassan, andelen som var sambo eller gifta och andelen som hade barn skiljde sig inte signifikant jämfört med normalbefolkningen varken för män eller för kvinnor. Vi fann inga faktorer från tidigt skede i sjukdomen som medförde ökad risk för avvikande socioekonomiska aspekter jämfört med normalpopulationen.

SLUTSATSER

De här två kohorterna visade att JCA kan ha mycket varierande långsiktigt förlopp både avseende utveckling av undergrupper och av sjukdomsaktivitet. Vid undersökningen efter 17 år var bara 40 % i remission och den hälsorelaterade livskvaliteten var signifikant lägre än förväntat. Mer än hälften hade någon påverkan av den fysiska funktionen. Sjukdomsrelaterade faktorer efter 17 år var mer kopplade till utfallet vid 5-årskontrollen än vid början av sjukdomen. Bentätheten i hälbenen var signifikant lägre än förväntat. Lägre bentäthet var associerat med aktiv sjukdom vid undersökningen för män och användning av p-piller för kvinnor.

Socioekonomiskt medförde sjukdomen inte någon kraftig långsiktig påverkan på gruppnivå. Vi fann inga faktorer från tidigt skede i sjukdomen som medförde ökad risk för inverkan ur socioekonomiskt avseende.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Bertilsson L, Andersson-Gäre B, Fasth A, Forsblad-d'Elia H. A 5-year prospective population-based study of juvenile chronic arthritis: onset, disease process, and outcome. Scand J Rheumatol. 2012 Oct;41(5):379-82.

II. Bertilsson L, Andersson-Gäre B, Fasth A, Petersson IF, Forsblad-D'elia H. Disease course, outcome, and predictors of outcome in a population-based juvenile chronic arthritis cohort followed for 17 years. J Rheumatol. 2013 May;40(5):715-24.

III. Lennart Bertilsson, Boel Andersson Gäre, Anders Fasth, Ingemar F Petersson, Helena Forsblad-d'Elia. Bone Mineral Density and Predictors Thereof in a Population Based Cohort of Individuals with Juvenile Chronic Arthritis 17 Years after Disease Onset. Submitted

IV. Lennart Bertilsson, Boel Andersson Gäre, Anders Fasth, Ingemar F Petersson, Helena Forsblad-d'Elia. Socioeconomic consequences of Juvenile Chronic Arthritis in a Population Based Cohort of Individuals 22 Years after Disease Onset. Manuscript

CONTENT

ABBREVIATIONS XIV
1 INTRODUCTION 1
1.1 Classification 1
1.2 Epidemiology 2
1.3 Etiology 3
2 OUTCOMES 5
2.1 Disease activity 5
2.2 Physical function 6
2.3 Health related quality of life 7
2.4 Radiographic examination 8
3 LONG-TERM OUTCOME INVESTIGATIONS 9
4 AIMS 11
5 METHOD 12
5.1 Design 12
5.2 Inclusion and classification criteria 12
5.3 Clinical examinations and questionnaires 14
5.4 Laboratory analyses 16
5.5 Radiographs 17
5.6 Assessment of bone mineral density 17
5.7 Ethics 17
5.8 Statistical methods 17
6 MAIN FINDINGS 19
6.1 Paper I and II: 19
6.2 Paper III: 24
6.3 Paper IV: 25
7 DISCUSSION 27
ACKNOWLEDGEMENT 36
REFERENCES 38

ABBREVIATIONS

ACR	American College of Rheumatology
ANA	antinuclear antibody
ARA	American Rheumatology Association
BMD	bone mineral density
BMI	body mass index
BP	bodily pain
CHAQ	childhood health assessment questionnaire
DAS	disease activity score
DMARD	disease modifying anti-rheumatic drugs
DXA	Dual-energy X-ray absorptiometry
DXL	Dual-energy X-ray absorptiometry and laser
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
GH	general health
HAQ	health assessment questionnaire
HLA	human leukocyte antigen
IBD	arthritis associated with inflammatory bowel disease
ILAR	International League of Associations for Rheumatology
JADAS	juvenile arthritis disease activity score
JAS	juvenile ankylosing spondylitis

JCA	juvenile chronic arthritis
JIA	juvenile idiopathic arthritis
JPA	juvenile psoriatic arthritis
JRA	juvenile rheumatoid arthritis
KFT	Keitel functional test
MCS	mental component score
MDA	minimal disease activity
MH	mental health
MRI	magnetic resonance imaging
NSAID	non-steroidal anti-inflammatory drugs
PCS	physical component score
PF	physical functioning
RA	rheumatoid arthritis
RE	role emotional
RF	rheumatoid factor
RP	role physical
SD	standard deviation
SF	social functioning
SF-36	Short-form 36 health survey
VAS	visual analogue scale

1 INTRODUCTION

1.1 Classification

Although some earlier descriptions of childhood arthritis may exist, George F Still's observation of juvenile arthritis from 1897 is considered to be the one of the most important in the 19th century, describing a series of children with chronic arthritis, seven girls and five boys[1]. He stated that the disease differed from adult rheumatoid arthritis (RA) and had a character of heterogeneity. Since then many different classifications have been used. Childhood arthritis are broad terms that describe a clinically heterogeneous group of arthritis, which begin before 16 years of age[2]. In the recent decades mainly three criteria are used: juvenile rheumatoid arthritis (JRA)[3], juvenile chronic arthritis (JCA)[4] and juvenile idiopathic arthritis (JIA)[5,6].

The American Rheumatology Association (ARA) criteria for JRA were revised by the American College of Rheumatology (ACR) in 1977. These JRA criteria require at least six weeks of disease duration and have three onset types: the systemic form, the polyarticular form with more than 5 joints with arthritis and the pauciarticular form with arthritis in one to four joints. The JRA criteria were especially used in America while the JCA criteria that were proposed by the European League Against Rheumatism (EULAR) were used in Europe.

The JCA criteria require tree months of disease duration and there are six subgroups: (a) onset with systemic features; (b) onset with polyarthritis in the absence of marked systemic features, five or more joints affected; (c) onset with arthritis affecting four joints or fewer – pauciarticular. Within these groups children with probable juvenile ankylosing spondylitis (JAS), juvenile psoriatic arthritis (JPA), and arthritis associated with inflammatory bowel disease (IBD) were also possible to identify[4].

In the end of the 20th century the International League of Associations for Rheumatology (ILAR) proposed a set of criteria for JIA that requires six weeks of disease duration like the JRA criteria but contains more subtypes like the JCA criteria. These subtypes are the systemic arthritis, polyarthritis, oligoarthritis, psoriatic arthritis, enthesitis related arthritis and

undifferentiated arthritis. The polyarthritis subtype requires that at least five joints are affected with arthritis and is further divided into rheumatoid factor (RF) negative and RF positive RF should be positive on two occasions at least three months apart and within the first six months. The oligoarticular subtype is further divided into oligoarticular persistent if the number of joints with arthritis remains less than five throughout the disease course and oligoarticular extended if the cumulative number of joints with arthritis is five or more after six months of disease[5,6].

These JIA criteria are now used globally but the criteria of arthritis in childhood are still a matter for discussions. Some believe that the criteria should include antinuclear antibody (ANA) positivity in order to better identify homogeneous patient populations for future genetic and immunopathogenetic investigations, outcome studies, and clinical trials[7]. Others believe that criteria resembling that for adult RA should be applied to distinguish a group with childhood-onset RA[8].

1.2 Epidemiology

Juvenile arthritis is a rare disease and the classification issues discussed above further complicates comparison of different epidemiological studies. In the Nordic countries different studies show an annual incidence rate of between 7 and 23 children/100,000 inhabitants[9-11]. In South-Western Sweden the incidence of population based JCA in the 1980s was found to be 10.9 children/100,000[12]. In Costa Rica the incidence for JCA was found to be 6.8 children/100,000[13], in Catalonia, Spain the incidence of JIA was found to be 6.9 children/100,000[14] and recently a study of health plan participants in Northern California showed an incidence of JIA to be 11.5 children/100,000[15].

The prevalence of juvenile arthritis also varies between studies. A population based study in South-Western Sweden 1988 showed a prevalence of JCA to be 64.1/100,000[12]. In another population based study in Rochester Minnesota 1980 the prevalence was found to be 113/100,000 for ARA criteria and 84/100,000 for EULAR criteria. In Northern California 2009 the prevalence in health plan participants was found to be 44.7/100,000 with ILAR criteria[15].

In Costa Rica 1995 the prevalence was 31.4/100,000[13] and in Spain 2006 39.7/100,000[14] according to population based studies.

These epidemiological studies of juvenile arthritis revile the complexity of interpreting the results due to many influencing factors; the classification criteria is such a factor, but differences in methodology, for instance population based contra referral based, are also of great importance[16]. In a systematic review of the literature, pooled data was used to estimate of the incidence and prevalence of JIA in the European population in 2010. The incidence for girls was estimated to 10.0/100,000 and the prevalence to 19.4/100,000 and for boys 5.7/100,000 and 11.0/100,000, respectively. The direct standardized incidence rate was 8.2/100,000 and the prevalence 70.2/100,000[17].

1.3 Etiology

Juvenile arthritis are a clinically heterogeneous group of unknown cause[2]. Generally rheumatologic diseases are often autoimmune and have a complex etiology where genetics and environmental factors are considered to be important. Furthermore, some of the subgroups of juvenile arthritis are regarded as autoinflammatory rather than autoimmune[18].

Genetics are also of importance for juvenile arthritis displayed for instance by familial aggregation of JIA found in the US[19]. Data support that multiple genes influence the susceptibility to juvenile arthritis[20]. The human leukocyte antigen region (HLA) seems to be a major susceptibility locus for JIA but also many non-HLA loci have been found[21]. A sibling ratio (lambdas) for a full sibling with JRA is estimated to be 15[22].

Infections might also be of importance in the development of juvenile arthritis. A register-based study showed associations between infections during the first year of life and JIA[23]. In addition, infections play a role in the initiation and augmentation of the symptoms of JIA[24]. Higher rates of infections with for instance Epstein-Barr virus, Parvovirus B19 and streptococcus have been reported in children with juvenile arthritis[24-27].

However, the underlying mechanisms between infections and autoimmune disease are multiple and complex and not fully understood[28].

2 OUTCOMES

2.1 Disease activity

In the assessment of juvenile arthritis not only is the classification diversified but also the outcome instruments. As an instrument for evaluation of remission many earlier studies of juvenile arthritis have used the ARA criteria for remission that were proposed for RA[29]. These criteria were often used with various modifications. While the ARA criteria either described a spontaneous remission or a state of drug-induced remission, EULAR in 1983 developed a set of criteria where remission required no use of medication for at least 2 years[30]. The EULAR criteria were divided into four categories: active = increasing number of joints irrespective of drug therapy; stable = stable number of joints but requiring drug therapy; inactive = no evidence of active synovitis and/or active extraarticular features and without drugs for less than two years; or remission = no evidence of active synovitis and/or active extraarticular features and without drugs for two years or more. All disease modifying anti-rheumatic drugs (DMARD) including biologics as well as analgesics, non-steroidal anti-inflammatory drugs (NSAID) and glucocorticosteroids were considered as drugs.

New criteria for remission has emerged and are divided into two types: clinical remission on medication with no signs of active disease for a minimum of six continuous months and clinical remission off medication with no signs of active disease for a minimum of twelve continuous months[31]. Also criteria for clinical inactive disease according to ACR have recently been published[32]. A definition of minimal disease activity (MDA) was developed and consists for oligoarthritis of physician global assessment ≤ 2.5 cm on 10 cm VAS and a swollen joint count of 0 and for polyarthritis of physician global assessment ≤ 3.4 and a swollen joint count ≤ 1[33].

In the 1990s a tool for assessing disease activity for RA in clinical practice with a disease activity score (DAS) was developed[34]. It was a composite instrument of four variables: Ritchie index (a graded tender joint count), swollen joints, erythrocyte sedimentation rate (ESR) and patients' general health assessed on VAS. Later a similar instrument Disease Activity Score 28

(DAS28) was developed, including the 28 most frequently affected joints in RA instead of the 66/68 joint count applied with the Ritchie index[35].

DAS28 is however developed and validated for RA[36] and subsequently a similar disease activity tool has been developed for JIA, juvenile arthritis disease activity score (JADAS)[37]. The JADAS is composed of active joint count, physician global assessment of disease activity on VAS (0–10), patient/parent assessment of well being on VAS (0–10) and a normalized value of a laboratory measure of inflammation, ESR (ESR–20)/10 with possible values 0–10. These four variables are added together and the minimum value is zero. There are three versions of active joint count: JADAS-10 with any joint with active arthritis up to a maximum of 10 and a total maximum JADAS score of 40, JADAS-27 with 27 joints and a total maximum score of 57, and JADAS-71 with 71 joints and a total maximum score of 101. The JADAS measures are validated in some studies but not in an adult population of JIA[37-41].

Recently, Consolaro et al validated cutoff scores for all versions of JADAS; the classification inactive disease in all JIA was determined to 1, minimal disease activity for oligoarticular JIA was 2 and minimal disease activity for polyarticular JIA was 3.8[42]. The most commonly used response criteria for juvenile arthritis are the ACR pediatric 30 response criteria which requires at least 30% improvement in three of any six core set criteria with no more than one worsening by more than 30%[43].

2.2 Physical function

The earlier widely used Steinbrocker's functional classification[44] was considered to have low sensitivity for chronic arthritis since the majority of patients were categorized in the first two out of four classes. In addition, it was not tested for reliability or validity in chronic arthritis[45,46]. This classification of functional ability has been replaced by other instruments such as the health assessment questionnaire (HAQ)[47,48]. This is a self-administered questionnaire with questions of functional ability in everyday life for instance dressing and grooming. The response alternatives are graded from zero to three and the HAQ score is an average. The answers should

reflect functional status during the last week. The lowest total score is zero if all questions are answered with the "without difficulty" alternative and the highest score three if the questions are answered with "unable to do" alternative.

An adapted version of HAQ for children and adolescents, childood health assessment questionnaire (CHAQ), has been developed and validated[45,49]. The questions were modified to reflect activities typical of children and the wordings were simplified. Discomfort was determined by the presence of pain measured on VAS, and by the duration of morning stiffness[45,49]. In recent years modified versions of CHAQ have been constructed[50]. CHAQ is not validated in JIA adult population and neither is HAQ.

Finally, Keitel functional test (KFT) is an instrument developed as a global measure of function with validated RA-specific measures. It consists of 24 simple movement patterns. These movements are assessed and graded according to a template. The scores for each movement are added together and a maximum score of 100 represents the normal functional movement patterns[51-53].

2.3 Health related quality of life

Short-form 36 health survey (SF-36) is a self administered questionnaire containing 36 items for general health survey and it was developed from an original instrument containing 108 items[54]. It was used in English spoken countries and a project was established to translate and adapt the instrument in other countries and thus a version was translated into Swedish and validated in 1995[55]. The 36 item questionnaire contains four domains of physical health; physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH) and 4 domains of mental health; vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH). Scores range from 0-100, higher score reflecting better health. The eight subscales can be summarized to one physical component score (PCS) and one mental component score (MCS) standardized to a mean (SD) value of 50. Sullivan et al has created a national normative database (n=8930) for the Swedish version of SF-36 which enables comparisons with cohorts of interests[56].

2.4 Radiographic examination

Juvenile arthritis is sometimes characterized by prolonged synovial inflammation that can lead to destruction of the joints[2]. Previously only conventional radiographs were available for the detection and assessment of erosive disease, however, in the last decades the use of ultrasonography and magnetic resonance imaging (MRI) has enabled a better and earlier assessment of synovial, cartilage and bone abnormalities[57,58]. Even if the erosive process is an important factor of managing juvenile arthritis there is no golden standard for radiographic classification. In a publication from 1977, Cassidy and Martel classified radiographical changes as: normal, stage I - early changes (periarticular soft tissue swelling/ periarticular osteoporosis/ periosteal new bone formation), or stage II - advanced changes (cartilage destruction/ bone destruction /bony ankylosis /large joint subluxations, /epiphyseal fractures/ vertebral compression fractures)[59].

A study revealed that even after modification the Larsen's radiographic classification system had low inter- and intra-reader concordance rates for juvenile arthritis[60]. In recent years more radiographic scoring systems have emerged such as an adapted version of the Sharp/van der Heijde score for JIA[61]. In contrast to RA, radiographic evaluations are often not used for structural outcome assessment in clinical trials of JIA[62].

3 LONG-TERM OUTCOME INVESTIGATIONS

There are a number of long-term studies of juvenile arthritis but many of them are retrospective, cross-sectional or selective with varying classification criteria and assessment tools and outcomes[63-69], table 1. Due to the development of new classification criteria of juvenile arthritis many studies have changed classification system between the inclusion and follow-up which may be questionable. Even if the same set of classification is used during a longitudinal study it can be difficult to use and interpret[8]. Some of these long-term studies are population based and others are hospital based. Also age characteristics and range of the individual follow-up period vary between the studies, see table 1. These conditions make it difficult to compare the different studies. Although many of the studies have accumulated much information, predictors of long-term outcomes that are identified early after disease presentation are still scanty[70].

Long-term follow-up studies are displayed in table 1. Peterson et al found in a population based follow-up that 29/44 (66%) participants with JRA reported evidence of active arthritis after a median of 21 years[63]. Zak et al on the other hand reported 24/65 (37%) of patients with JCA to have active disease at a follow-up after an average of 26.4 years[65]. Minden et al reported in 2002 40% of a cohort with 248 JIA patients to be in remission after 16.5 years while Flatö et al in 2003 reported 50% of 268 patients with JRA to be in remission after 14.9 years[66,68]. Packham et al found in a hospital based cohort of 246 individuals with JIA 56.7% to have no disease activity after a median of 28.3 years but with a range of 8 to 73 years[67]. Also in a hospital based cohort Foster et al found 39% of patients with JIA to be in remission after a median of 21 years and a range of 3 to 61 years[69]. We found 34/86 (40%) of the participants to be in remission at an average of 17 years after onset of JCA (paper II).

Table 1 Long-term outcome studies of juvenile arthritis.

Reference	Geographic location	Type of cohort	Classification	Participants, n	Follow-up, yrs	Age at follow-up, yrs	Disease activity	HAQ, score
Peterson et al 1997[63]	Minnesota, USA	Population based	ACR	44	21 (3–61)	33.5 (19–49)	65.9% active arthritis, questionnaire	Worse than controls
Ruperto et al 1997[71]	USA/Italy	Hospital based	ACR	227	14.9 ±7.8 (mean ±1SD)	21 ± 9.6 (mean ±1SD)		HAQ/CHAQ 0.0 (0.0–3.0)
Zak et al 2000[65]	Denmark	Referral based	EULAR	65	26.4 ± 5.6 (mean ±1SD)	32.2 ± 5.7 (mean ±1SD)	37% active disease, EULAR	0.4 ± 0.7 (mean ±1SD)
Minden et al 2002[66]	Germany	Population based/ Referral based	ILAR	74 pop based/ 141 ref based	16.5 (10–30)	22 (14–35)	40% remission, ACR 2 months	0.0 (0–2.5)
Packham el al 2002[67]	Canada	Hospital based	ILAR	246	28.3 (8–73)	35.4 (19–78)	56.7% None, TK index	0–1.5, 57.1%
Flatø et al 2003[68]	Norway	Population based/ referral based	ACR	268	14.9 (11.7–25.1)	22.1 (13.2–31.1)	50% remission ACR 2 years	> 0.0, 36%
Foster et al 2003[69]	Great Britain	Hospital based	ILAR	82	21 (3–61)	30 (17–68)	39% active joint disease, PGAS > 0	1.1 (0.0–3.0)
Bertilsson et al 2013(paper II)	Sweden	Population based	EULAR	86	16.9 ± 1.0 (mean ±1SD)	24.3 ± 4.6 (mean ±1SD)	40% remission EULAR	0.0 (0.0–1.8)

Median and range, otherwise specified, HAQ = health assessment questionnaire, ACR = American College of Rheumatology, CHAQ = childhood health assessment questionnaire, EULAR = European League Against Rheumatism, ILAR = International League of Associations for Rheumatology, TK index = Thompson-Kirwan index, PGAS = physicians global measurement scale of disease activity

4 AIMS

The main objectives of this thesis were to study the long-term disease course and outcomes in two population-based cohorts of patients with juvenile chronic arthritis and to search for predictors of long-term outcomes.

Specific aims

Paper I: To characterize disease manifestations in a cohort of incidence cases of children with juvenile chronic arthritis at disease onset and during the first 5 years of disease and to search for predictors for outcomes after disease duration of 5 years.

Paper II: To study disease course, outcomes and predictors of long-term outcomes in a cohort of incidence cases with juvenile chronic arthritis followed for 17 years.

Paper III: To measure bone mineral density in the calcaneus in a cohort of incidence cases with juvenile chronic arthritis and to identify predictors of low bone mineral density 17 years after disease onset.

Paper IV: To investigate the socioeconomic status in a cohort with prevalence cases of individuals with juvenile chronic arthritis after an average of 22 years after disease onset compared to the general population and to search for predictors of socioeconomic outcomes.

5 METHOD

5.1 Design

Multicenter prospective, longitudinal and population based long-term outcome studies on JCA.

5.2 Inclusion and classification criteria

The patients in Paper I, II and III, designated cohort A were recruited from a prospective population-based epidemiological study of JCA in southwestern Sweden[12]. The cohort A consists of the incidence cases identified from January 1, 1984 to December 31, 1986, n=132 as illustrated in figure 1[72].

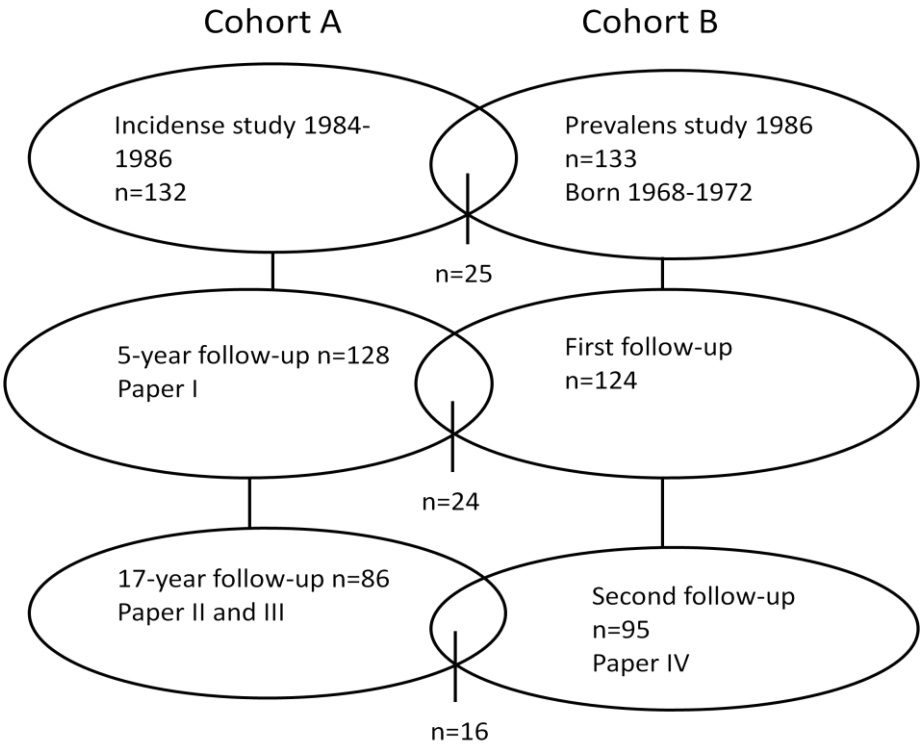


Figure 1. *The flow of patients from the inclusion in cohort A and B and a graphic illustration of the follow-ups with the corresponding papers.*

The patients in paper IV, designated cohort B were recruited from a prospective population-based epidemiological study of JCA in southwestern Sweden[12]. The cohort B consists of the prevalence cases identified in December 31, 1988 and who were borne 1968–1972, figure 1[73].

Paper I covers cohort A from disease onset and during the first 5 years of disease including a follow-up examination (BAG) after these 5 years. In paper II and III the cohort A is examined (LB) in a long-term follow-up at an average of 17 years after disease onset. Cohort B is examined at two follow-ups, the first at an average of 7 years after disease onset (BAG) and the second at an average of 22 years after disease onset (LB).

All patients with onset of JCA during the study period from pediatric clinics and all local pediatricians in the area were reported. Patients with JCA born after 1967 were also searched for at adult rheumatology clinics and orthopedic clinics. In the long-term follow-ups, paper II-IV the individuals were identified by the Swedish national civil register.

The EULAR criteria[4] were used to define cases of JCA and to divide patients into subgroups : (a) onset with systemic features; (b) onset with polyarthritis in the absence of marked systemic features, five or more joints affected; (c) onset with arthritis affecting two to four joints - pauciarticular, (d) or in the case of only one joint – monoarticular subgroup. This subgroup was separated from c) although it is not formally a subgroup within JCA. Within these groups children with probable juvenile ankylosing spondylitis (JAS), juvenile psoriatic arthritis (JPA), and arthritis associated with inflammatory bowel disease (IBD) were also identified. Cases were identified as JAS if peripheral arthritis was combined with radiological evidence of sacroiliitis or with clinical evidence of sacroiliitis or axial involvement in combination with enthesitis. JPA was defined as arthritis in combination with psoriasis diagnosed by a dermatologist. To identify a case of arthropathy associated with IBD, an intestinal mucosal biopsy indicating ulcerative colitis or Crohn's disease was required.
These EULAR criteria were used since it was used for patient retrieval and classification in the original epidemiological study and it was not possible to convert the patients into the new set of criteria for JIA from ILAR[5,16] retrospectively as the inclusion criteria differs. The onset time of disease was defined as the time when onset of symptoms occurred.

5.3 Clinical examinations and questionnaires

Questionnaires were used in cohort A (paper I) to collect data at onset and at the consecutive annual reports during the first 5 years of disease. These questionnaires recorded data on subgroup, joint assessment, disease activity, eye examinations, existing laboratory and radiological findings. The questionnaires were filled out by pediatricians at the participating pediatric departments. The follow-up at 5 years, cohort A (paper I) and at 7 years, cohort B[73,74] included clinical examination with joint assessment and doctor's assessment of disease activity. It also included ophthalmologic examination, laboratory investigations, radiographic examination, and patients' assessment of functional ability.

The long-term follow-ups at 17 years, cohort A (paper II and III) and 22 years, cohort B (paper IV) included clinical examination with joint assessment, doctor's assessment of disease activity, laboratory investigations, and patients' assessment of functional ability and health related quality of life. It also included functional assessment with Keitel functional test[51].

Heat, pain (either tenderness or pain on motion), soft tissue swelling and restricted range of motion were recorded when examining the joints. If at least two of the factors were present, the joint status was considered as *arthritis* and if any of the factors was present, the joint status was considered as *involved*.

The disease activity was evaluated by the physician's overall assessment according to EULAR[30,73]: active = increasing number of joints irrespective of drug therapy; stable = stable number of joints but requiring drug therapy; inactive = no evidence of active synovitis and/or active extraarticular features and without drugs for less than two years; or remission = no evidence of active synovitis and/or active extraarticular features and without drugs for two years or more. All DMARD including biologics as well as analgesics, NSAIDs and glucocorticosteroids were considered as drugs. The disease activity levels were designated as remission=1, inactive=2, stable=3, and active=4. Non-remission was defined as inactive, stable or active.

At the long-term follow-ups JADAS-10[37] was assessed. JADAS-10 has a minimum score of 0 and a maximum of 40 and involves physician global assessment on VAS in cm, patient global assessment on VAS, the number of joints with arthritis (maximum of 10) and (ESR – 20)/10 (minimum of 0 and maximum of 10).

A "disease activity duration index" was calculated for the first 5 years of disease in cohort A (paper I, II and III) and was defined as the percentage of time of active and stable disease during the observation period.

Height and weight were measured at the 17-year follow-up and body mass index (BMI) was calculated. A Swedish survey from 2008/2009[75] with 975 women and 973 men 20 – 29 years of age was used to estimate Z-scores for height, weight and BMI by calculating $Z = (X-\mu)/\sigma$ (μ = mean of the reference and σ = standard deviation (SD) of the reference).

Questionnaires

Medication and rheumasurgery was registered annually during the first 5 years for cohort A and at the follow-ups for both cohorts. The medication was divided into analgesics, NSAIDs, glucocorticosteroids, DMARDs and biologics. Rheumasurgery was divided into major events (= joint replacement arthroplasty) and minor events (= other rheuma surgery). Also the occurrence of iridiocyclitis was recorded.

Childhood health assessment questionnaire (CHAQ)[45] was used to evaluate functional status at the 5-year follow-up in cohort A (paper I) and at the 7-year follow-up in cohort B[73,74]. If the child was less than 9 years of age, one parent was asked to answer the questionnaire. At the long-term follow-ups functional status was evaluated by HAQ[48] (paper II, III, and IV). The individuals self-reported health related quality of life was assessed by usage of the Swedish version of short-form 36 health survey (SF-36)[76] (paper II, III, and IV). In order to be able to compare the patients to a normative database an age and sex-matched reference group (n=520) was randomly drawn from the Swedish SF-36 national normative database (n=8930)[56].

Socioeconomic outcomes

Socioeconomic outcomes were registered in the long-term follow-up in cohort B. The individuals answered a questionnaire about education, income during the last year, disability benefits, marital/civil status and about children (paper IV). The education was divided into 4 categories: primary school, 2-year upper secondary school, 3-year upper secondary school and tertiary studies. The income for 2002 was registered in Swedish crowns (SEK), and included salary from work and payments from the Swedish Social Security Agency[77] declared to the internal revenue service. The disability benefit was divided into 4 categories depending on percentage of full disability pension. The marital/civil status was divided into living with partner or living single and the individuals were asked if they had any children and if yeas how many.

Data from open registers in Statistics Sweden[78], the Swedish Social Security Agency[77], and from the Public Health Survey 2003 in the Region Västra Götaland of the general population in the Region Västra Götaland[79] were used as the reference populations .

5.4 Laboratory analyses

ESR was measured using standard procedures and was analyzed at inclusion and follow-ups. At inclusion, antinuclear antibodies (ANA) were analyzed by indirect immunofluorescense using rat kidney sections and rheumatoid factor (RF) was analyzed by latex slide agglutination test, where titers of >1/25 and >1/20 respectively, were considered positive, according to the clinical laboratories involved at that time.

Since some earlier studies[80,81] have shown class-specific RF to be of importance in some childhood arthritis IgM RF and IgA RF were analyzed at the 5-year follow-up in cohort A and 7-years follow-up in cohort B using an enzyme immunoassay (Pharmacia RF IgM EIA and RF IgA EIA, Pharmacia diagnostics, Uppsala, Sweden). Serum concentrations > 7.34 and > 3.58 arbitrary units/ml respectively, were considered positive[82].

5.5 Radiographs

Radiographs of the affected joints were performed at the 5-year follow-up in cohort A and at the 7-year follow-up in cohort B or could also have been carried out during the preceding year. The radiographs were evaluated and classified as: Normal; Stage I - early changes (periarticular soft tissue swelling, periarticular osteoporosis, periosteal new bone formation); or Stage II - advanced changes (cartilage destruction, bone destruction, bony ankylosis, large joint subluxations, epiphyseal fractures, vertebral compression fractures)[59].

5.6 Assessment of bone mineral density

At the 17-year follow-up BMD was measured in cohort A in the calcaneus with Dual-energy X-ray absorptiometry and laser (DXL) Calscan (Demetech, Stockholm, Sweden) (paper III). Both sides were measured and a mean BMD was calculated. BMD values were expressed in g/cm² and as a Z-score which is the comparison to the age and sex-matched normal reference database consisting of 1452 individuals from southern Sweden provided by the manufacturer[83]. A Z-score of < -2.0 is defined as below the expected range for age[84].

5.7 Ethics

Paper I-IV. The study was conducted according to the principles of the Helsinki declaration and approved by the regional ethics committee at the University of Gothenburg. All participants in the long term follow-ups gave their informed written consent.

5.8 Statistical methods

Data were analyzed using PASW Statistics 18 (SPSS inc., Chicago, IL) in paper I – III and IBM SPSS Statistics 21 in paper IV. Values are expressed as mean ± 1 standard deviation (SD) or median and range. Comparisons between groups were analyzed by the Mann-Whitney U-test (2-tailed) and

Student's t-test when appropriate. Chi-square test was used for categorical data and Fisher's exact test was computed when cells had expected values of less than five. Correlations were calculated using Spearman's rank correlation coefficient (r_S). One-Way ANOVA with Post Hoc Games-Howel for unequal variances was applied for comparison between multiple groups. After initial univariate analysis the statistically significant variables were used in multiple logistic regression analysis with forward conditional method or in multiple linear regression analysis with forward method. Dichotomous variables were created by coding event as 1, and no event as 0. The limit value for significance was set at $p < 0.05$ for all tests performed.

6 MAIN FINDINGS

Out of 132 included patients in cohort A 128 (97%) attended the 5-year follow-up visit, and 86 (65%) individuals participated in the long-term follow-up at 17 years after disease onset. The sex distribution in the cohort at the17-year follow-up was numerically slightly higher for the girls (61/86, 71%) compared to baseline (84/132, 64%) but not significantly elevated ($p = 0.32$). The individuals lost between the 5-year and the 17-year follow-ups did not differ significantly from the individuals examined at 17-year follow-up with respect to age at onset ($p = 0.69$), presence of RF ($p = 0.56$) and of ANA ($p = 0.88$) at baseline, number of joints with arthritis ($p = 0.16$) or joints with involvement ($p = 0.81$) during the first year of disease, disease activity duration score during the first 5 years of disease ($p = 0.78$) or disease activity ($p = 0.54$), number of joints with arthritis ($p = 0.28$) or joints with involvement ($p = 0.34$) and CHAQ at the 5-year follow-up ($p = 0.30$) (paper II and III).

Out of 133 patients in cohort B that were included in the initial epidemiological study, 124 (93%) individuals were examined in the first follow-up at 7 years after disease onset and 95 (71%) in the second follow-up at 22 years after disease onset. There was no significant difference in sex distribution ($p = 0.981$), onset subgroup distribution ($p = 0.967$) or onset age ($p = 0.654$) between the 133 patients included and the 95 individuals examined at the second follow-up. There was no significant difference between the 124 individuals that participated in the first follow-up and the 95 individuals in the second follow-up concerning disease duration ($p = 0.701$), disease activity ($p = 0.796$), weight ($p = 0.357$) or height ($p = 0.648$) at the first follow-up.

6.1 Paper I and II:

"A 5-year prospective population based study of juvenile chronic arthritis; onset, disease process and outcome" and " Disease Course, Outcome and Predictors of Outcome in a Population Based Cohort of Individuals with Juvenile Chronic Arthritis Followed for 17 Years"

Onset

In cohort A girls predominated over boys 82/46 (64%). The median age at onset was 7.8 years for both the girls and the boys with range 0.6 – 15.8 years for the girls and 0.6 – 15.0 years for the boys, figure 2. There was no significant difference in age at onset between the polyarticular, pauciarticular and monoarticular subgroups.

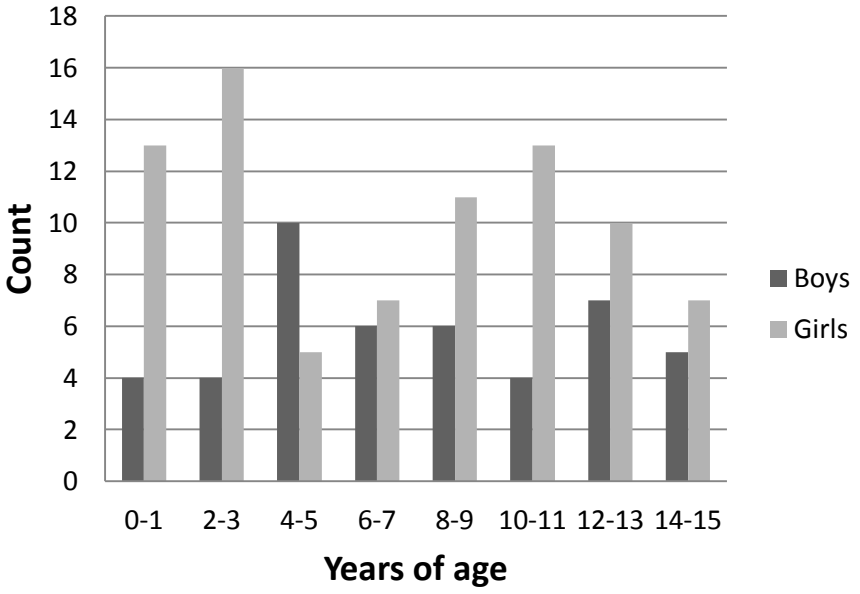


Figure 2. *Age and sex distribution at disease onset in the patients of cohort A with juvenile chronic arthritis in southwestern Sweden.*

In the *polyarticular* onset group, n = 34 most patients had involvement of both large and small joints 22/34 (65%) while 2/34 patients (7%) had only large joints involved and 3/34 patients (9%) only small joints but in 7/34 patients (21%) there was no detailed information. In the *pauciarticular* onset group the pattern of joint involvement was asymmetrical in 30/51 (59%). For both the pauciarticular and *monoarticular* subgroups the knee joint was the most commonly involved as illustrated in Figure 3.

Progression of subgroup distribution

The subgroup distribution for cohort A from onset and during the first 5 years is illustrated in figure 1 in paper I and during the first 17-years in figure 2 in

paper II. The main findings were: 1) In the cohort A 43/128 (34%) changed subgroup during the first 5-year period and between the 5-year follow-up and the 17-year follow-up 11/86 (13%) changed disease course subgroup. 2) The polyarticular group increased to be the largest subgroup from 19/86 (22%) at onset to 29/86 (34%) at the 5-year follow-up and to 33/86 (38%) at the 17-year follow-up. 3) The monoarticular group diminished from 22/86 (26%) to

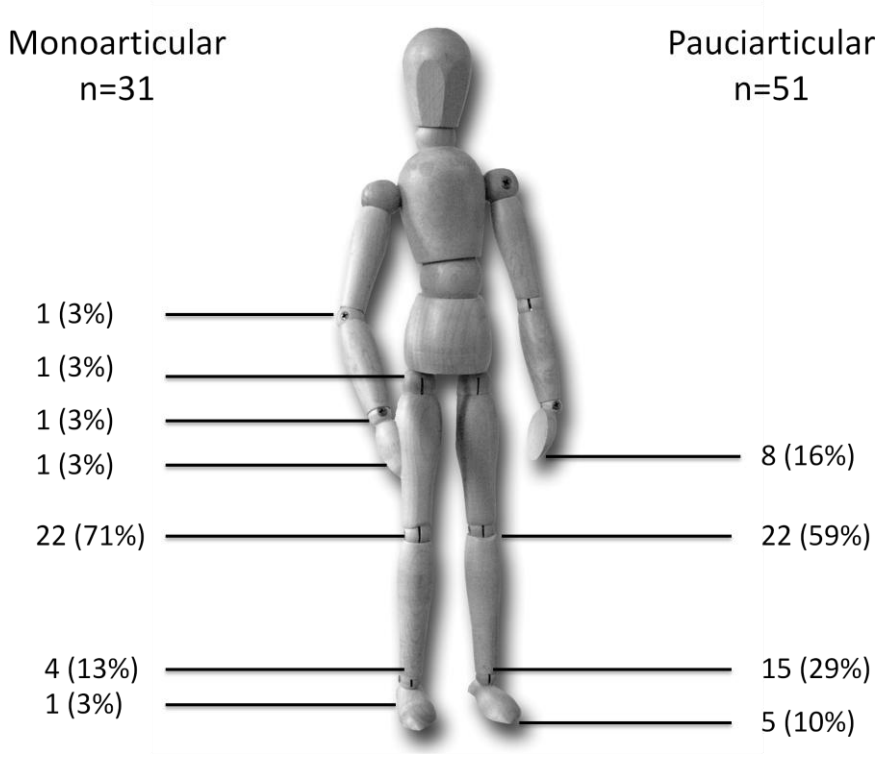


Figure 3*. Joint patterns showing involved joints at onset for the patients in the monoarticular and pauciarticular onset subgroups in the cohort A with juvenile chronic arthritis in southwestern Sweden.*

6/86 (7%) at the 5-year follow-up and to 5/86 (6%) at the 17-year follow-up. 4) The JPA group increased from 2/86 (2%) to 4/86 (5%) at the 5-year follow-up and to 8/86 (9%) at the 17-year follow-up. 5) The subgroup changes occurred during the whole period.

Progression of disease activity

In cohort A most of the patients in the subgroups with monoarticular onset and pauciarticular onset had inactive disease or disease in remission within 2 and 3 years from onset. In the subgroup with polyarticular onset less than half had inactive disease or disease in remission during the first 5 years of the disease course, figure 2 in paper I. Of the 33/86 individuals (38%) who were in remission at the 5-year follow-up only 20/33 (61%) remained in remission at 17-year follow up while 4/33 (12%) were in the stable category and 9/33 (27%) in the inactive category.

Progression of medication

Forty-two out of 128 patients (33%) in cohort A received DMARDs sometime during the first 5 years of the disease course, usually in combination with NSAIDs and sometimes together with glucocorticosteroids. The most frequently used DMARD was hydroxychloroquine 36/42 (87%) followed by oral gold 9/42 (21%), sulphasalazine 7/42 (16%), methotrexate 6/42 (14%), penicillamine 2/42 (5%) and podophylline 1/42 (2%). Fifteen out of forty-two patients (36%) tried two or more DMARDs. The majority of patients given DMARDs had polyarticular disease, 32/42 (76%); only 6/42 (14%) had pauciarticular JCA and 4/42 (10%) had JAS. Of those who had received DMARDs, 7/42 (17%) had disease in remission and 8/42 (19%) inactive disease at the 5-year follow-up, while the majority, 27/42 (62%), were still on medication. Totally 19/128 (15%) of the patients were treated with oral glucocorticosteroids any time during the first 5 years of the disease course, mainly in combination with NSAIDs and/or DMARDs and intraarticular glucocorticosteroids were given to half of the patients.

At the 17-year follow-up 20/86 individuals (23%) were currently treated with DMARDs including corticosteroids and biologics: methotrexate 12/20 (60%), sulfasalazin 5/20 (25%), hydroxychloroquine 1/20 (5%), prednisone 2/20 (10%) and TNF-inhibitors 2/20 (10%). Two out of eighty-six individuals (2%) had undergone major arthroplasty, one of whom with shoulder replacement, elbow replacement and bilateral hip replacement and the other one with wrist arthrodesis. Both individuals were in the polyarticular onset subgroup.

During the first 5 years of the disease course 10/128 (8%) developed uveitis and at the 17-year follow-up 11/86 (13%) reported uveitis any time during the disease course.

At the 5-year follow-up 44/128 participants in cohort A (34%) were in remission and 32/128 (25%) were inactive. At the 17 year follow-up 34/86 (49%) were in remission and 16/86 (19%) were inactive. The age at disease onset and the number of involved joints and joints with arthritis during the first year of disease were positively associated with a more continuous disease during the first 5 years. The number of involved joints at the inclusion was positively associated with active disease at the 5 year follow-

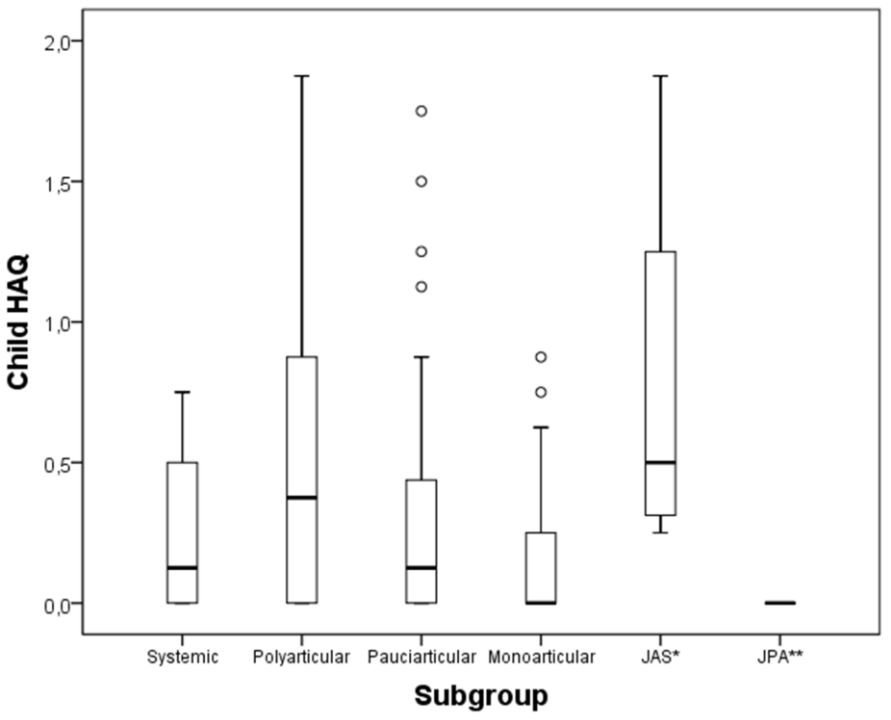


Figure 4. *The CHAQ score at the 5-year follow-up according to disease onset type for the individuals in cohort A with juvenile chronic arthritis in southwestern Sweden. Each box shows the median, quartiles, and extreme values within a category.*

up. In a multiple logistic regression remission at the 17-year follow-up was predicted by remission at the 5-year follow-up (OR 4.8, 95% CI 1.8 – 12.5).

Among those 84/128 (66%) who were radiographically examined at the 5-year follow-up, 20/84 (24%) had radiological changes and 10/84 (12%) had more severe changes. Radiological changes were more often found in the polyarticular onset subgroup. The patients with the more severe stage II changes had significantly higher onset age compared to those without changes.

The CHAQ score at the 5-year follow-up was median 0.13 (range 0.0 –1.9). The age at disease onset and the number of involved joints and joints with arthritis during the first year of disease were positively associated with the CHAQ score at the 5-year follow-up. The polyarticular group had significantly higher disability score compared to the monoarticular group ($p = 0.002$) but there was no significant difference for the pauciarticular group in relation to neither the polyarticular group nor the monoarticular group. The CHAQ scores for the subgroups are illustrated in Figure 4.

At the 17-year follow-up the median HAQ score was 0.0 (range 0.0 –1.5). In a multiple logistic regression, RF positivity present at the 5-year follow-up predicted a HAQ score > 0 (OR 3.6, 95% CI 1.0 – 13.3) at the 17 year follow-up. At the 17-year follow-up the median KFT was 100 (range 54 100). A KFT < 100 was predicted by non-remission at the 5-year follow-up (OR 11.3, 95% CI 2.7 – 47.9) and RF positivity present at the 5-year follow-up (OR 5.6, 95% CI 1.0 – 30.6).

In cohort A, at the 17-year follow-up SF-36 was significantly lower compared to a reference group. In a multiple logistic regression the physical component summation score in SF-36 above average of the reference group was best predicted by remission at the 5-year follow-up (OR 5.8, 95% CI 2.2 – 15.4).

6.2 Paper III:

"Bone Mineral Density and Predictors Thereof in a Population Based Cohort of Individuals with Juvenile Chronic Arthritis 17 Years after Disease Onset"

In cohort A, at the 17-year follow-up the BMD Z-score was -0.55 ± 0.95 (mean ± 1SD). For the woman in the cohort the average BMD Z-score was -0.41 ± 0.86 and for the men -0.89 ± 1.08. BMD Z-score, in both sexes were significantly lower compared to the reference population in both women (p =

0.001) and men ($p < 0.001$). The BMD Z-score for the individuals in remission was also significantly lower than the reference population ($p = 0.007$). The mean height and the mean weight of the men was significantly lower compared to the reference group ($p = 0.006$ and $p = 0.011$) but the mean BMI did not differ significantly ($p = 0.21$), figure 2 in paper III. The mean height, weight and BMI of the women did not differ from the reference group ($p = 0.99$, $p = 0.16$, and $p = 0.13$).

In a multiple linear regression low BMD in women was determined by low weight and the use of hormonal contraceptives ($R^2 = 0.32$) and in men continuously active disease during the 3 first years of disease ($R^2 = 0.49$). BMD was divided into a Z-score ≤ -1 SD and > -1 SD. In a multiple logistic regression the use of hormonal contraceptives predicted a BMD Z-score ≤ -1SD in women (OR 4.9, 95% CI 1.4–17.2). A JADAS-10 score higher than 1 at the 17-year follow-up predicted a BMD Z-score ≤ -1SD in men (OR 16.7, 95% CI 2.3–122.2).

6.3 Paper IV:

"Socioeconomic Consequences of Juvenile Chronic Arthritis; A Population-Based Study 22 Years after Disease Onset"

In cohort B, 6/95 of the participants (6%) had primary school as the highest educational level, 43/95 (45%) 2-year upper secondary school, 20/95 (21%) 3-year upper secondary school and 26/95 (27%) tertiary studies. The men had lower education level of borderline significance compared to the general population ($p = 0.051$) while there was no difference for the women ($p = 0.491$). In a multiple logistic regression analysis patients' pain VAS at the second follow-up was related to lower education in the women (OR 0.97, 95% CI 0.94–0.99).

The mean income during the year 2002 for the participants in cohort B was 228 300 SEK for the men and 179 200 SEK for the women. The men in cohort B had significantly higher income compared to the women ($p = 0.005$), but the incomes did not differ significantly in either sex compared to the general population ($p = 0.36$ and $p = 0.76$) (figure 1 and table 2 in paper

IV). There were no significant associations between disease-related variables and income in the women in the cohort. In the men, there were significant univariate correlations between income and the following variables at the long-term follow-up: disease activity (r_s = -0.45, p = 0.009), JADAS-10 (r_s = -0.43, p = 0.014), patient's global VAS (r_s = -0.40, p = 0.021) and patients' pain VAS (r_s = -0.38, p = 0.030).

Five of ninety-five individuals (5%) had complete/100% disability pension, 3/95 (3%) had 50% and 4/95 (4%) had 25% disability pension. The women in the cohort had significantly higher degree of disability pension compared to women in the general population (p < 0.001). With disability pension divided into the two categories "any degree of pension" and "no pension", receiving DMARDs (including glucocorticosteroids and TNF-inhibitors) at the long-term follow-up had an OR 8.0 (95% CI 1.7–37.8) for the women in a multiple logistic regression analysis.

Sixty-five out of ninety-five participants in cohort B (68%) lived with a partner. There was no significant difference in the proportion of those living with a partner compared to those living single in the cohort between men and women or between the cohort and the general population. In the women low SF-36 PCS was associated with living single (p = 0.014). In a multiple logistic regression analysis in the men, active disease at the second follow-up had an OR 3.6 (95% CI 1.4–9.0) for living single.

In the cohort B 41/94 (44%) had no children while 53/94 (66%) had at least one child. The women in the cohort had more children than the men but compared to the general population there was no significant difference neither for the women, nor for the men. In a multiple logistic regression analysis for women, affected physical function measured by KFT was associated with "no children" (OR 1.06, 95% CI 1.01–1.12) as opposed to "any number of children".

7 DISCUSSION

This thesis is based on two unique population based longitudinal long-term prospective studies of incidence (cohort A) and prevalence (cohort B) cases of juvenile arthritis showing the diversity of disease course and disease outcome for JCA. The first years of disease very few patients received powerful DMARDs and the 5-year follow-up period for cohort A is close to natural history of the disease since the study was conducted before methotrexate became the regular treatment of choice. Some individuals in both cohorts were lost between inclusion and the long-term follow-ups. However, they did not significantly differ in the tested variables from the individuals that participated at the inclusion or in the earlier follow-ups. The cohorts are also comparable to other population-based cohorts regarding sex, subgroup distribution, average age at disease onset, and changes of subgroup distribution[9,11,66,85,86]. This infers that the cohorts were representative for population based and unselected cohorts of JCA patients.

The individuals in cohort A showed a large variability of disease courses during the whole follow-up period. At the 5-year follow-up 66% of the individuals were not in remission and at the 17-year follow-up 60% were not in remission. Moreover, 39% of the individuals who were in remission at the 5-year follow-up were not in remission at the 17-year follow up. More than half of the individuals had affected physical function after 5 years. After 17 years still half of the individuals had affected physical function. They also had impaired health related quality of life compared to a reference group.

In cohort A the age at disease onset was median 7.8 years and the sex distribution 64% girls which is in accordance with both a later study in the Nordic countries and a study in Catalonia[11,87]. In Costa Rica, Arguedas et al found the median onset age 10.3 years but the ANA positive early onset disease phenotype which often has been described was not found in that population based study[88]. The subgroup distribution in cohort A with 27% polyarticular onset was also in accordance with others[11,89]. The joint involvement at onset with predominance for the knee joint and for the joints in the lower extremities for the monoarticular and pauciarticular subgroups was also found in other studies[88,90].

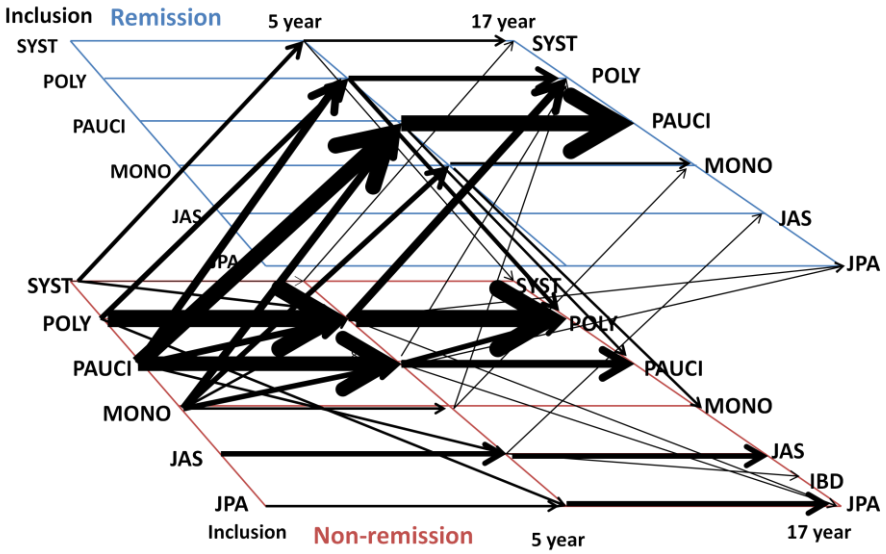
At the 5-year follow-up 16% of the participants in cohort A had active disease and 26% had stable disease while 16% had inactive disease and 34% were in remission. These results are comparable to Selvaag et al who found 26.9% to be in remission at 3-year follow-up in a cohort of 185 patients but they were partly referral patients and they used 6 months without medication for defining remission[91]. In a cohort of 47 patients in Costa Rica with follow-up after median disease duration of 4.1 years Arguedas et al found 49% to still have active or stable disease according to EULAR criteria, but the incidence rate of ANA positive oligoarticular onset subgroup was substantially lower in Costa Rica[88].

The disease activity after 5 years was positively associated with age at onset and number of joints with arthritis and involvement. More continuously active disease during the first 5 years of disease was also positively associated with age at onset. No radiological changes were found in 76% of the participants that were examined and radiological changes were more frequent in the polyarticular group. RF positivity was a risk factor for more serious radiological changes (stage II) which is in accordance to other studies[73,92]. Even if this result is difficult to interpret since the radiographic examination was not comprehensive or performed uniformly RF positivity and polyarticular onset disease seems to be risk factors for erosive disease which should be taken in consideration when the treatment is decided. All of these risk factors could also indicate a type of disease that has been described as childhood-onset RA[8] but further studies are needed in order to get increased knowledge of that category.

Most of the 8% of patients in cohort A who developed uveitis during the first 5 year of disease course had the typical characteristics with ANA positivity and low age at disease onset in accordance with another study[93]. At the 17-year follow-up 13% in cohort A reported having developed uveitis sometime during the disease course which is in accordance to Bolt et al (13.3%)[93] and Heiligenhaus et al (12%)[94] but lower compared to Grassi et al (20.1%)[95]. The study eligibility could be a factor where the latter had a hospital based study design.

At the 17-year follow-up 40% of the individuals in cohort A were in remission. The progression of the disease is very complex as illustrated in figure 5. Other studies of long-term follow-ups have reported remission rates between one third to two thirds[63,65-69,96]. However, as shown in table 1 the classification criteria, the ages of the participants and the range of ages also vary. Our results are in accordance to the studies with population based cohorts where the follow-up times and the range of ages are similar to our cohort A[66,68]. Like Minden et al 16.5 years after disease onset[66] we did not find any correlation between baseline variables and disease activity at the 17-year follow-up. However, our study has identified that remission at the 17-year follow-up was associated with low disease activity duration index during the first 3, 4 and 5 years of disease and low CHAQ score and remission at the 5-year follow-up. Although remission at the 5-year follow-up was the most important variable for remission at 17-year follow up our study also showed that 39% of the individuals who were in remission at the 5-year follow-up were not in remission at the 17-year follow up. Flatø el al found in a study of 268 JRA patients followed-up after 15 years that half were in remission but about one fourth of them had had one or more periods of previous remission and among the half in non-remission 74 out of 135 patients had had one or more previous periods of remission[68]. These findings, that have been possible to report due to the longitudinal study design, imply that remission is unfortunately not a guaranteed life-long remission and relapse of disease can occur even after longer periods of remission. Hence, both the patients and health professionals should be prepared for the event that relapses can occur and enable easy access to the health system for professional assessment.

Forty-four percent of the participants in cohort A changed subgroup and the changes occurred during the whole follow-up period. During the first 5 years 17/82 (21%) of the patients from both the monoarticular and pauciarticular onset groups changed to polyarticular disease, which is corresponding to the oligoarticular extended subgroup in the ILAR criteria. From the monoarticular and pauciarticular onset groups another 6/55 (11%) changed to the polyarticular disease course between the 5-years and 17 year follow-ups and resulted in totally 16/55 (29%) during the 17 years. At the 17-year follow-up the polyarticular disease course subgroup was the largest. Minden et al[97] recognized that 5/102 patients with oligoarticular onset disease changed to polyarticular subgroup during an observation period of 7.4 years


Inclusion
Remission
5 year
17 year
SYST
POLY
PAUCI
MONO
JAS
JPA
SYST
POLY
PAUCI
MONO
JAS
JPA
SYST
POLY
PAUCI
MONO
JAS
JPA
SYST
POLY
PAUCI
MONO
JAS
IBD
JPA
Inclusion
Non-remission
5 year
17 year

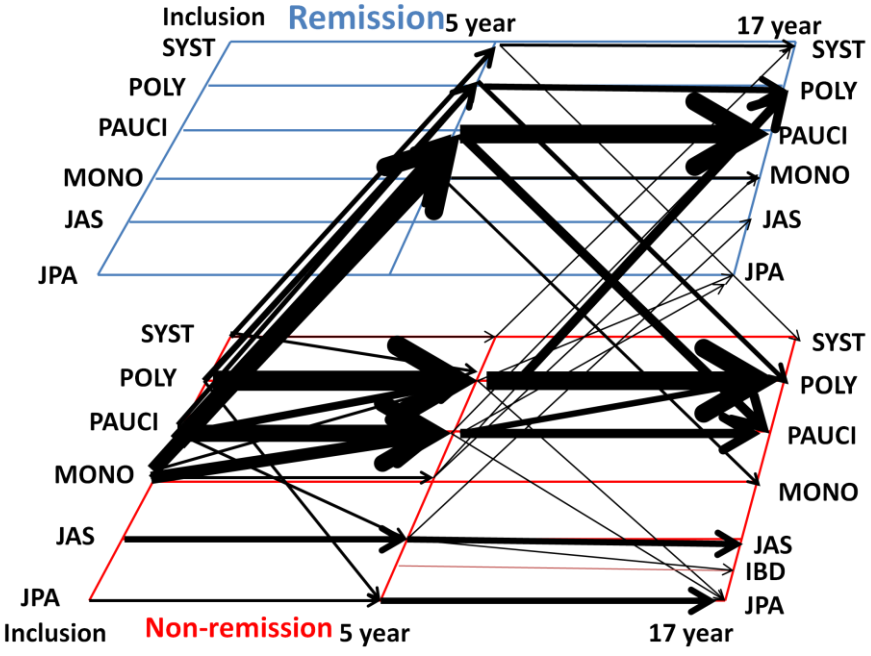

Inclusion
Remission
5 year
17 year
SYST
POLY
PAUCI
MONO
JAS
JPA
SYST
POLY
PAUCI
MONO
JAS
JPA
SYST
POLY
PAUCI
MONO
JAS
JPA
SYST
POLY
PAUCI
MONO
JAS
IBD
JPA
Inclusion
Non-remission
5 year
17 year

Figure 5*. Progression of disease activity in the horizontal planes and the progression of subgroups in the depth dimension at the disease onset, at the 5-year follow-up and at the 17-year follow-up. The number of individuals are represented by the thickness of the arrows. The chart is illustrated from two different angels. SYST = systemic, POLY = polyarticular, PAUCI = pauciarticular, MONO = monoarticular, JAS = juvenile ankylosing spondylitis, IBD = inflammatory bowel disease, JPA = juvenile psoriatic arthritis.*

and approximately one-third after a median of 16.5 years of disease[66]. On the other hand, Guillaume et al[98] found in a 6-year longitudinal study of patients with oligoarticular onset disease that the probability of a change to polyarticular disease was 50% but that was referral patients. Our findings show that the change to, according to JIA criteria, extended oligoarticular disease subtype as opposed to the persistent can occur also many years after disease onset.

The median value of the CHAQ score in cohort A at 5-year follow-up was 0.13 and 42% had a CHAQ score = 0 which is in accordance with other studies [74,91]. At the 17-year follow-up the median HAQ score was 0.0 with range 0.0 – 1.5 and 54 % of the participants had HAQ = 0. These results are also in accordance with similar studies with the exception of the German study showing a range of 0.0 – 2.5[66,68]. In a 9.7-year follow-up of 72 referral patients Flatø et al found that 60% of the participants had a CHAQ/HAQ of 0[92]. They also found that persistent disease and polyarticular disease course during the first 5 years of disease was associated with CHAQ/HAQ > 0 at the follow-up. In our study persistent disease during the first 5 years also was associated with HAQ > 0 but there was no significant difference between subgroup disease course at the 5-year follow-up in relation to HAQ > 0. We found RF-positivity to be a predictor for HAQ > 0 but the confidence interval was broad owing to few RF positive patients. Studies have shown that elevated HAQ in RA is associated with chronic changes[99] and that is congruent with the variables we found associated with HAQ > 0. With a more modern early treatment of more effective DMARDs/biologics the long-term outcome should be better for JIA patients today. However, this study provides an important reference for such future studies.

SF-36 score at the 17-year follow-up in the cohort A was significantly lower compared to age and sex matched normal population for all of the SF-36 domains. Other long-term follow-up studies of juvenile arthritis also have found similar results[68,69]. We found that worse score of the physical domains were significantly associated with non-remission and functional disability according to HAQ and Keitel functional test at the 17-year follow up. For the mental domains there was a tendency for unfavorable scores for the individuals in non-remission and with functional disability but there was significant association only to HAQ which could be due to the limited number of individuals. A study of a cohort of 55 patients with JIA and median of 8.7 years after symptom onset also found PCS and MCS to be significantly associated with the HAQ-score[100]. Since HAQ in RA is associated with chronic changes it is important with treatment to prevent these changes. Not only medication is effective but also physical exercise have shown benefit for improving physical function[101].

At the 17-year follow-up the mean BMD Z-scores for calcaneal DXL were significantly lower compared to the reference population for both men and women in cohort A. Also the individuals in remission at the 17-year follow-up had BMD Z-scores significantly lower compared to the reference population. Dual-energy X-ray absorptiometry (DXA) is considered to be the golden standard method for measuring BMD. An alternative is Dual-energy X-ray absorptiometry and laser (DXL) that measures BMD in the calcaneus. DXL, which is a portable device and easy to use, was shown to significantly correlate with BMD in the hip and spine measured by DXA in children 2.2 – 20.6 years of age[102]. BMD measured by DXL technique has also been shown to predict fracture risk in Swedish women [103].Only five participants in cohort A had BMD Z-score < -2 SD measured with calcaneal DXL which is considered to be below the expected range for age in individuals < 50 years[84]. Since BMD Z-score -1 SD divided the cohort more evenly that limit was chosen which also made comparisons with other studies possible. BMD Z-score < -1SD with calcaneal DXL was associated with use of hormonal contraceptives for women and high JADAS-10 for men. For women also low weight at the 17-year follow-up was associated with low BMD as a continuous variable and for the men continuous active disease during the first 3 years was an important predictor for low BMD. Height and weight in the men were lower compared to the reference group. Packham et al found that

both men and women in a hospital based study of adult JIA were shorter than the general population but that the weight were similar to the mean weight in the general population[67]. Like others we found disability and disease activity, in our whole cohort not divided by sex, to be important determinants for BMD[104-107] but we also found continuous active disease in the early stage of the disease to be of importance in men. Thornton et al found oral corticosteroids to be negatively associated with BMD[105]. Only two individuals in our cohort received glucocorticosteroids at the 17-year follow-up. Both of them had Z-score < -2 SD or close to -2 SD but due to few individuals statistical analyses on the impact of glucocorticosteroids was not preformed. Based on our results displaying reduced BMD, even in individuals in remission, we encourage physicians to be aware of the bone health in this group of patients especially since it is important for the risk of osteoporosis later in life[108]. The awareness should enable prevention with control of disease activity, more physical exercise and right dietary intake[109-111]. The association of low BMD and hormonal contraceptives is surprising since estrogen is associated with increased BMD in other studies[112]. However, another study has shown that hormonal contraceptives could have a negative impact on BMD in young women and it could be an effect of progestogen[113].

Cohort B was followed-up after a median of 21.5 years from disease onset. Among the women 5.3% had full disability pension and 9.6% partial compared to 2.2% and 0.8%, respectively in the general population but there was no difference in the men compared to the general population. There was no significant difference between the men and women in the cohort. Other studies have not found higher degree of disability pension[63,66] but a Norwegian study has analyzed combined disability and unemployment pension and found the combination to be significantly higher than in the control group[68].

The men in the JCA cohort had borderline lower education compared to the general population but there was no difference for the women. Other studies have shown varying results but many have not reviled any difference compared to the reference population[66,68,114,115].Concerning income, marital/civil status and reproduction, no difference could be identified, either for men or women, in comparison with the general population. We did not find any predictors among our reported earlier disease-related variables and

socioeconomic outcome in the long-term follow-up. In the men lower education was associated with the number of involved joints at the long-term follow-up and concerning the women lower education was related to higher pain assessed by VAS at the long-term follow-up. Receiving DMARDs was related to being on disability pension in women. For men active disease was associated with living single and for women low SF-36 PCS was associated with living single. For the women many disease-related variables at the long-term follow-up were associated with less number of children. Strengths of this long-term follow-up on socioeconomic consequences are that Cohort B consists of individuals of similar-age with JCA. The majority of the participants was established in the sense that they had started working after their education and had stable relationships. The cohort is also well documented in an earlier follow-up[73,74]. In other long-term studies of population-based cohorts the participants either had lower average age [66,68,115,116], or their age range at follow-up was very wide[63]. We did not find any predictors for socioeconomic outcome from early disease course but on a group level the outcome compared to the general population is encouraging and better than we expected. However, on the individual level some participants have poor outcomes. Our results indicate that a good control of disease activity and physical exercise could be of benefit.

In conclusion, in this thesis we have found that juvenile arthritis is a heterogeneous disease with a variety of long-term disease courses from childhood onset into adolescence and adulthood. After 17-years 60% were not in remission, almost half of the individuals had some physical disability according to HAQ and/or Keitel functional test and we did not find any prominent early predictors for long-term outcomes. However, this longitudinal study design has enabled us to reveal the diversity of disease courses for subgroup development and disease activity. Many individuals changed subgroup also after 5 years of disease and many individuals with early remission and remission at 5-year follow-up were not in remission at the 17-year follow-up. Other studies have shown a cross sectional picture but this study show that the outcome is even more complicated with no definite endpoints. Since the most recent treatment strategies are more efficient we can hopefully expect better long-term outcome in the future, but we can still expect a variety of disease courses that are difficult to predict. Hence, both

patient and health professionals have to be prepared for these different and unpredictable disease courses.

This longitudinal long-term study of a population based cohort may also be able to serve as an important comparison for investigations with modern treatment in the future. Further long-term follow-ups will also be important for studying the development of comorbidity such as vascular disease[117], malignancy, osteoporosis and fractures in patients with juvenile arthritis in comparison to the normal population. Still search for early predictors such as biomarkers in serum should be of importance to identify and we can expect the classification criteria still to be modified in the future.

ACKNOWLEDGEMENT

I am very grateful to the patients and their parents participating in this study. I am also very grateful to everyone who has helped and contributed in different ways to this thesis.

I especially want to thank:

Helena Forsblad-d'Elia, my supervisor, for her patients with me, for her support and for being available for discussions at all time; also for all of her stubbornness and good advice in guiding me in my research and methodology

Anders Fasth, my co-supervisor, for wisdom in the field and very fast response with valuable views

Boel Andersson Gäre, my co-supervisor, for her original ground work that this thesis is built on and for her inspiration during the years

Ingemar F Petersson, my former co-supervisor and former colleague, for his advice and ideas in the earlier part of this project

Frida Christiansson at Spenshult Hospital for Rheumatic Diseases, for her help with all the examinations

Maria Andersson at the Research and Development Centre at Spenshult Hospital for Rheumatic Diseases, for her help with laboratory procedures

Birgitha Archenholtz at Sahlgrenska University Hospital for her advice on functional tests

Göran Kvist, Rheumatology clinic of Södra Älvsborg Hospital, Borås, Karin Svensson, Rheumatology clinic of Skaraborg Hospital, Skövde, and
Dan Norberg, Rheumatology clinic of NU Hospital Group, Uddevalla, for assisting in organising the examinations of the participants.

My colleagues and staff at the department for their help and support

My former colleagues at the Rheumatology Unit at Sahlgrenska University Hospital and my, so far, present colleagues and staff at Spenshult Hospital for Rheumatic Diseases/Axess Medica for providing support

My parents Thea and Bertil for their encouragement and support through life and my brothers and sisters for their support

My dear wife Maria and our dear daughters Hanna and Matilda for the happiness in my life and great support

Funding:
This study was supported by grants from The Health and Medical Care Executive Board of Region Västra Götaland, The Rune and Ulla Amlöv Foundation for Rheumatology Research, The Swedish Rheumatism Association, The Rheumatism Association District of Gothenburg, The Medical Society of Göteborg, RegionVästra Götaland (agreement for research and education of medical students between the Swedish government and the university hospitals).

REFERENCES

1. Still GF. On a Form of Chronic Joint Disease in Children. Med Chir Trans 1897;80:47-60 9.

2. Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet 2007;369:767-78.

3. Brewer EJ, Jr., Bass J, Baum J, et al. Current proposed revision of JRA Criteria. JRA Criteria Subcommittee of the Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Section of The Arthritis Foundation. Arthritis Rheum 1977;20:195-9.

4. Wood PH. Nomenclature and classification of arthritis in children. . Basel: EULAR publishers; 1978.

5. Petty RE, Southwood TR, Baum J, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. J Rheumatol 1998;25:1991-4.

6. Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390-2.

7. Ravelli A, Varnier GC, Oliveira S, et al. Antinuclear antibody-positive patients should be grouped as a separate category in the classification of juvenile idiopathic arthritis. Arthritis Rheum 2011;63:267-75.

8. Ferrell EG, Ponder LA, Minor LS, et al. Limitations in the Classification of Childhood-onset Rheumatoid Arthritis. J Rheumatol 2014;41:547-53.

9. Moe N, Rygg M. Epidemiology of juvenile chronic arthritis in northern Norway: a ten-year retrospective study. Clin Exp Rheumatol 1998;16:99-101.

10. Ostergaard PA, Lillquist K, Rosthoj S, Urfe P. [Occurrence and types of juvenile rheumatoid arthritis in the County of Jutland 1970-1977 and 1978-1986]. Ugeskr Laeger 1988;150:342-6.

11. Berntson L, Andersson Gare B, Fasth A, et al. Incidence of juvenile idiopathic arthritis in the Nordic countries. A population based study with special reference to the validity of the ILAR and EULAR criteria. J Rheumatol 2003;30:2275-82.

12. Gare BA, Fasth A. Epidemiology of juvenile chronic arthritis in southwestern Sweden: a 5-year prospective population study. Pediatrics 1992;90:950-8.

13. Arguedas O, Fasth A, Andersson-Gare B, Porras O. Juvenile chronic arthritis in urban San Jose, Costa Rica: a 2 year prospective study. J Rheumatol 1998;25:1844-50.

14. Modesto C, Anton J, Rodriguez B, et al. Incidence and prevalence of juvenile idiopathic arthritis in Catalonia (Spain). Scand J Rheumatol 2010;39:472-9.

15. Harrold LR, Salman C, Shoor S, et al. Incidence and prevalence of juvenile idiopathic arthritis among children in a managed care population, 1996-2009. J Rheumatol 2013;40:1218-25.

16. Andersson Gare B. Juvenile arthritis - who gets it, where and when? A review of current data on incidence and prevalence. Clin Exp Rheumatol 1999;17:367-74.

17. Thierry S, Fautrel B, Lemelle I, Guillemin F. Prevalence and incidence of juvenile idiopathic arthritis: A systematic review. Joint Bone Spine 2013.

18. Ramanan AV, Grom AA. Does systemic-onset juvenile idiopathic arthritis belong under juvenile idiopathic arthritis? Rheumatology (Oxford) 2005;44:1350-3.

19. Prahalad S, O'Brien E, Fraser AM, et al. Familial aggregation of juvenile idiopathic arthritis. Arthritis Rheum 2004;50:4022-7.

20. Thompson SD, Moroldo MB, Guyer L, et al. A genome-wide scan for juvenile rheumatoid arthritis in affected sibpair families provides evidence of linkage. Arthritis Rheum 2004;50:2920-30.

21. Chistiakov DA, Savost'anov KV, Baranov AA. Genetic background of juvenile idiopathic arthritis. Autoimmunity 2014.

22. Glass DN, Giannini EH. Juvenile rheumatoid arthritis as a complex genetic trait. Arthritis Rheum 1999;42:2261-8.

23. Carlens C, Jacobsson L, Brandt L, Cnattingius S, Stephansson O, Askling J. Perinatal characteristics, early life infections and later risk of rheumatoid arthritis and juvenile idiopathic arthritis. Ann Rheum Dis 2009;68:1159-64.

24. Huang JL. New advances in juvenile idiopathic arthritis. Chang Gung Med J 2012;35:1-14.

25. Massa M, Mazzoli F, Pignatti P, et al. Proinflammatory responses to self HLA epitopes are triggered by molecular mimicry to

Epstein-Barr virus proteins in oligoarticular juvenile idiopathic arthritis. Arthritis Rheum 2002;46:2721-9.

26. Barash J, Goldzweig O. Possible role of streptococcal infection in flares of juvenile idiopathic arthritis. Arthritis Rheum 2007;57:877-80.

27. Oguz F, Akdeniz C, Unuvar E, Kucukbasmaci O, Sidal M. Parvovirus B19 in the acute arthropathies and juvenile rheumatoid arthritis. J Paediatr Child Health 2002;38:358-62.

28. Bach JF. Infections and autoimmune diseases. J Autoimmun 2005;25 Suppl:74-80.

29. Pinals RS, Masi AT, Larsen RA. Preliminary criteria for clinical remission in rheumatoid arthritis. Arthritis Rheum 1981;24:1308-15.

30. Minutes from the meeting of the EULAR standing committee on pedriatric rheumatology. In: EULAR standing committee. Moscow: EULAR; 1983.

31. Wallace CA, Ruperto N, Giannini E. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. J Rheumatol 2004;31:2290-4.

32. Wallace CA, Giannini EH, Huang B, Itert L, Ruperto N. American College of Rheumatology provisional criteria for defining clinical inactive disease in select categories of juvenile idiopathic arthritis. Arthritis Care Res (Hoboken) 2011;63:929-36.

33. Magni-Manzoni S, Ruperto N, Pistorio A, et al. Development and validation of a preliminary definition of minimal disease activity in patients with juvenile idiopathic arthritis. Arthritis Rheum 2008;59:1120-7.

34. van der Heijde DM, van 't Hof MA, van Riel PL, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis 1990;49:916-20.

35. Smolen JS, Breedveld FC, Eberl G, et al. Validity and reliability of the twenty-eight-joint count for the assessment of rheumatoid arthritis activity. Arthritis Rheum 1995;38:38-43.

36. van Riel PL, van Gestel AM, van de Putte LB. Development and validation of response criteria in rheumatoid arthritis: steps towards an international consensus on prognostic markers. Br J Rheumatol 1996;35 Suppl 2:4-7.

37. Consolaro A, Ruperto N, Bazso A, et al. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. Arthritis Rheum 2009;61:658-66.

38. McErlane F, Beresford MW, Baildam EM, et al. Validity of a three-variable Juvenile Arthritis Disease Activity Score in children with new-onset juvenile idiopathic arthritis. Ann Rheum Dis 2013;72:1983-8.

39. McErlane F, Beresford MW, Baildam EM, Thomson W, Hyrich KL. Recent developments in disease activity indices and outcome measures for juvenile idiopathic arthritis. Rheumatology (Oxford) 2013;52:1941-51.

40. Nordal EB, Zak M, Aalto K, et al. Validity and predictive ability of the juvenile arthritis disease activity score based on CRP versus ESR in a Nordic population-based setting. Ann Rheum Dis 2012;71:1122-7.

41. Ringold S, Bittner R, Neogi T, Wallace CA, Singer NG. Performance of rheumatoid arthritis disease activity measures and juvenile arthritis disease activity scores in polyarticular-course juvenile idiopathic arthritis: Analysis of their ability to classify the American College of Rheumatology pediatric measures of response and the preliminary criteria for flare and inactive disease. Arthritis Care Res (Hoboken) 2010;62:1095-102.

42. Consolaro A, Bracciolini G, Ruperto N, et al. Remission, minimal disease activity, and acceptable symptom state in juvenile idiopathic arthritis: defining criteria based on the juvenile arthritis disease activity score. Arthritis Rheum 2012;64:2366-74.

43. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum 1997;40:1202-9.

44. Steinbrocker O, Traeger CH, Batterman RC. Therapeutic criteria in rheumatoid arthritis. J Am Med Assoc 1949;140:659-62.

45. Andersson Gare B, Fasth A, Wiklund I. Measurement of functional status in juvenile chronic arthritis: evaluation of a Swedish version of the Childhood Health Assessment Questionnaire. Clin Exp Rheumatol 1993;11:569-76.

46. Liang MH, Jette AM. Measuring functional ability in chronic arthritis: a critical review. Arthritis Rheum 1981;24:80-6.

47. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in rheumatoid arthritis. Arthritis and Rheumatism 1980;23:137-45.

48. Ekdahl C, Eberhardt K, Andersson SI, Svensson B. Assessing disability in patients with rheumatoid arthritis. Scandinavian Journal of Rheumatology 1988;17:263-71.

49. Billings AG, Moos RH, Miller JJ, 3rd, Gottlieb JE. Psychosocial adaptation in juvenile rheumatic disease: a controlled evaluation. Health Psychol 1987;6:343-59.

50. Groen W, Unal E, Norgaard M, et al. Comparing different revisions of the Childhood Health Assessment Questionnaire to reduce the ceiling effect and improve score distribution: Data from a multi-center European cohort study of children with JIA. Pediatr Rheumatol Online J 2010;8:16.

51. Eberl DR, Fasching V, Rahlfs V, Schleyer I, Wolf R. Repeatability and objectivity of various measurements in rheumatoid arthritis. A comparative study. Arthritis Rheum 1976;19:1278-86.

52. Keitel W, Hoffmann H, Weber G, Krieger U. [Evaluation of the percentage of functional decrease of the joints using a motor function test in rheumatology]. Dtsch Gesundheitsw 1971;26:1901-3.

53. Kalla AA, Kotze TJ, Meyers OL, Parkyn ND. Clinical assessment of disease activity in rheumatoid arthritis: evaluation of a functional test. Ann Rheum Dis 1988;47:773-9.

54. Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. BMJ 1992;305:160-4.

55. Sullivan M, Karlsson J, Ware JE, Jr. The Swedish SF-36 Health Survey--I. Evaluation of data quality, scaling assumptions, reliability and construct validity across general populations in Sweden. Soc Sci Med 1995;41:1349-58.

56. Sullivan M KJ TC, Ware JE. . SF-36 Health Survey: Swedish Manual and Interpretation Guide, 2nd Edition. In: Hospital SU, ed. 2nd ed. Gothenburg; 2002.

57. Magni-Manzoni S, Malattia C, Lanni S, Ravelli A. Advances and challenges in imaging in juvenile idiopathic arthritis. Nat Rev Rheumatol 2012;8:329-36.

58. Laurell L, Court-Payen M, Boesen M, Fasth A. Imaging in juvenile idiopathic arthritis with a focus on ultrasonography. Clin Exp Rheumatol 2013;31:135-48.

59. Cassidy JT, Martel W. Juvenile rheumatoid arthritis: clinicoradiologic correlations. Arthritis Rheum 1977;20:207-11.

60. Doria AS, de Castro CC, Kiss MH, et al. Inter- and intrareader variability in the interpretation of two radiographic classification systems for juvenile rheumatoid arthritis. Pediatr Radiol 2003;33:673-81.

61. Ravelli A, Ioseliani M, Norambuena X, et al. Adapted versions of the Sharp/van der Heijde score are reliable and valid for assessment of radiographic progression in juvenile idiopathic arthritis. Arthritis Rheum 2007;56:3087-95.

62. Ravelli A. The time has come to include assessment of radiographic progression in juvenile idiopathic arthritis clinical trials. J Rheumatol 2008;35:553-7.

63. Peterson LS, Mason T, Nelson AM, O'Fallon WM, Gabriel SE. Psychosocial outcomes and health status of adults who have had juvenile rheumatoid arthritis: a controlled, population-based study. Arthritis Rheum 1997;40:2235-40.

64. Ruperto N, Ravelli A, Levinson JE, et al. Long-term health outcomes and quality of life in American and Italian inception cohorts of patients with juvenile rheumatoid arthritis. II. Early predictors of outcome. J Rheumatol 1997;24:952-8.

65. Zak M, Pedersen FK. Juvenile chronic arthritis into adulthood: a long-term follow-up study. Rheumatology (Oxford) 2000;39:198-204.

66. Minden K, Niewerth M, Listing J, et al. Long-term outcome in patients with juvenile idiopathic arthritis. Arthritis Rheum 2002;46:2392-401.

67. Packham JC, Hall MA. Long-term follow-up of 246 adults with juvenile idiopathic arthritis: functional outcome. Rheumatology (Oxford) 2002;41:1428-35.

68. Flato B, Lien G, Smerdel A, et al. Prognostic factors in juvenile rheumatoid arthritis: a case-control study revealing early predictors and outcome after 14.9 years. J Rheumatol 2003;30:386-93.

69. Foster HE, Marshall N, Myers A, Dunkley P, Griffiths ID. Outcome in adults with juvenile idiopathic arthritis: a quality of life study. Arthritis Rheum 2003;48:767-75.

70. Ravelli A. Toward an understanding of the long-term outcome of juvenile idiopathic arthritis. Clin Exp Rheumatol 2004;22:271-5.

71. Ruperto N, Levinson JE, Ravelli A, et al. Long-term health outcomes and quality of life in American and Italian inception cohorts of

patients with juvenile rheumatoid arthritis. I. Outcome status. J Rheumatol 1997;24:945-51.

72. Bertilsson L, Andersson-Gäre B, Fasth A, Forsblad d'Elia H. A 5-year prospective population based study of juvenile chronic arthritis; onset, disease process and outcome. Scandinavian Journal of Rheumatology.

73. Gare BA, Fasth A. The natural history of juvenile chronic arthritis: a population based cohort study. I. Onset and disease process. J Rheumatol 1995;22:295-307.

74. Gare BA, Fasth A. The natural history of juvenile chronic arthritis: a population based cohort study. II. Outcome. J Rheumatol 1995;22:308-19.

75. Undersökningarna av levnadsförhållanden. In: Statistiska centralbyrån.

76. Sullivan M, Karlsson J, Ware JR. The Swedish SF-36 Health Survey. Evaluation of data quality, scaling assumptions, reliability and construct validity across general populations in Sweden. Social Science&Medicine 1995?;in press.

77. Försäkringskassan.(Accessed at: www.forsakringskassan.se)

78. Statistikdatabasen. (Accessed at: www.scb.se)

79. Liv och hälsa 2003. (Accessed at: www.vgregion.se)

80. Saulsbury FT. Prevalence of IgM, IgA and IgG rheumatoid factors in juvenile rheumatoid arthritis. Clin Exp Rheumatol 1990;8:513-7.

81. Walker SM, McCurdy DK, Shaham B, et al. High prevalence of IgA rheumatoid factor in severe polyarticular-onset juvenile rheumatoid arthritis, but not in systemic-onset or pauciarticular-onset disease. Arthritis Rheum 1990;33:199-204.

82. Andersson Gare B, Fasth A. Serum concentration of hyaluronan, IgM and IgA rheumatoid factors in a population based study of juvenile chronic arthritis. Scand J Rheumatol 1994;23:183-90.

83. Kullenberg R. Reference database for dual X-ray and laser Calscan bone densitometer. J Clin Densitom 2003;6:367-72.

84. 2013 ISCD Official Positions – Adult. The International Society for Clinical Densitometry, 2013. (Accessed at http://www.iscd.org/documents/2013/07/2013-iscd-official-positions-adult.pdf.)

85. Bertilsson L, Andersson-Gare B, Fasth A, Petersson IF, Forsblad-D'elia H. Disease course, outcome, and predictors of outcome in a population-based juvenile chronic arthritis cohort followed for 17 years. J Rheumatol 2013;40:715-24.

86. Bertilsson L, Andersson-Gare B, Fasth A, Forsblad-d'Elia H. A 5-year prospective population-based study of juvenile chronic arthritis: onset, disease process, and outcome. Scand J Rheumatol 2012;41:379-82.

87. Modesto C, Anton J, Rodriguez B, et al. Incidence and prevalence of juvenile idiopathic arthritis in Catalonia (Spain). Scand J Rheumatol 2010.

88. Arguedas O, Fasth A, Andersson-Gare B. A prospective population based study on outcome of juvenile chronic arthritis in Costa Rica. J Rheumatol 2002;29:174-83.

89. Pruunsild C, Uibo K, Liivamagi H, Tarraste S, Talvik T, Pelkonen P. Prevalence and short-term outcome of juvenile idiopathic arthritis: a population-based study in Estonia. Clin Exp Rheumatol 2007;25:649-53.

90. Huemer C, Malleson PN, Cabral DA, et al. Patterns of joint involvement at onset differentiate oligoarticular juvenile psoriatic arthritis from pauciarticular juvenile rheumatoid arthritis. J Rheumatol 2002;29:1531-5.

91. Selvaag AM, Lien G, Sorskaar D, Vinje O, Forre O, Flato B. Early disease course and predictors of disability in juvenile rheumatoid arthritis and juvenile spondyloarthropathy: a 3 year prospective study. J Rheumatol 2005;32:1122-30.

92. Flato B, Aasland A, Vinje O, Forre O. Outcome and predictive factors in juvenile rheumatoid arthritis and juvenile spondyloarthropathy. J Rheumatol 1998;25:366-75.

93. Bolt IB, Cannizzaro E, Seger R, Saurenmann RK. Risk factors and longterm outcome of juvenile idiopathic arthritis-associated uveitis in Switzerland. J Rheumatol 2008;35:703-6.

94. Heiligenhaus A, Mingels A, Heinz C, Ganser G. Methotrexate for uveitis associated with juvenile idiopathic arthritis: value and requirement for additional anti-inflammatory medication. Eur J Ophthalmol 2007;17:743-8.

95. Grassi A, Corona F, Casellato A, Carnelli V, Bardare M. Prevalence and outcome of juvenile idiopathic arthritis-associated uveitis and relation to articular disease. J Rheumatol 2007;34:1139-45.

96. Fantini F, Gerloni V, Gattinara M, Cimaz R, Arnoldi C, Lupi E. Remission in juvenile chronic arthritis: a cohort study of 683 consecutive cases with a mean 10 year followup. J Rheumatol 2003;30:579-84.

97. Minden K, Kiessling U, Listing J, et al. Prognosis of patients with juvenile chronic arthritis and juvenile spondyloarthropathy. J Rheumatol 2000;27:2256-63.

98. Guillaume S, Prieur AM, Coste J, Job-Deslandre C. Long-term outcome and prognosis in oligoarticular-onset juvenile idiopathic arthritis. Arthritis Rheum 2000;43:1858-65.

99. Drossaers-Bakker KW, Kroon HM, Zwinderman AH, Breedveld FC, Hazes JM. Radiographic damage of large joints in long-term rheumatoid arthritis and its relation to function. Rheumatology (Oxford) 2000;39:998-1003.

100. Ostile IL, Johansson I, Aasland A, Flato B, Moller A. Self-rated physical and psychosocial health in a cohort of young adults with juvenile idiopathic arthritis. Scand J Rheumatol 2010;39:318-25.

101. Baillet A, Vaillant M, Guinot M, Juvin R, Gaudin P. Efficacy of resistance exercises in rheumatoid arthritis: meta-analysis of randomized controlled trials. Rheumatology (Oxford) 2012;51:519-27.

102. Soderpalm AC, Kullenberg R, Swolin-Eide D. The relationship between dual energy X-ray absorptiometry (DXA) and DXA with laser (DXL) measurements in children. J Clin Densitom 2008;11:555-60.

103. Brismar TB, Janszky I, Toft LI. Calcaneal BMD Obtained by Dual X-Ray and Laser Predicts Future Hip Fractures-A Prospective Study on 4 398 Swedish Women. J Osteoporos 2010;2010:875647.

104. Zak M, Hassager C, Lovell DJ, Nielsen S, Henderson CJ, Pedersen FK. Assessment of bone mineral density in adults with a history of juvenile chronic arthritis: a cross-sectional long-term followup study. Arthritis Rheum 1999;42:790-8.

105. Thornton J, Pye SR, O'Neill TW, et al. Bone health in adult men and women with a history of juvenile idiopathic arthritis. J Rheumatol 2011;38:1689-93.

106. Lien G, Flato B, Haugen M, et al. Frequency of osteopenia in adolescents with early-onset juvenile idiopathic arthritis: a long-term outcome study of one hundred five patients. Arthritis Rheum 2003;48:2214-23.

107. French AR, Mason T, Nelson AM, et al. Osteopenia in adults with a history of juvenile rheumatoid arthritis. A population based study. J Rheumatol 2002;29:1065-70.

108. Seeman E. Pathogenesis of bone fragility in women and men. Lancet 2002;359:1841-50.

109. Sandstedt E, Fasth A, Fors H, Beckung E. Bone health in children and adolescents with juvenile idiopathic arthritis and the influence of short-term physical exercise. Pediatr Phys Ther 2012;24:155-61; discussion 62.

110. Wardlaw GM. Putting body weight and osteoporosis into perspective. Am J Clin Nutr 1996;63:433S-6S.

111. Heaney RP, Abrams S, Dawson-Hughes B, et al. Peak bone mass. Osteoporos Int 2000;11:985-1009.

112. D'Elia HF, Larsen A, Mattsson LA, et al. Influence of hormone replacement therapy on disease progression and bone mineral density in rheumatoid arthritis. J Rheumatol 2003;30:1456-63.

113. Warholm L, Petersen KR, Ravn P. Combined oral contraceptives' influence on weight, body composition, height, and bone mineral density in girls younger than 18 years: a systematic review. Eur J Contracept Reprod Health Care 2012;17:245-53.

114. Archenholtz B, Nordborg E, Bremell T. Lower level of education in young adults with arthritis starting in the early adulthood. Scand J Rheumatol 2001;30:353-5.

115. Arkela-Kautiainen M, Haapasaari J, Kautiainen H, Vilkkumaa I, Malkia E, Leirisalo-Repo M. Favourable social functioning and health related quality of life of patients with JIA in early adulthood. Ann Rheum Dis 2005;64:875-80.

116. Miller JJ, 3rd, Spitz PW, Simpson U, Williams GF. The social function of young adults who had arthritis in childhood. J Pediatr 1982;100:378-82.

117. Aulie HA, Selvaag AM, Gunther A, et al. Arterial haemodynamics and coronary artery calcification in adult patients with juvenile idiopathic arthritis. Ann Rheum Dis 2014.