Disease progression and cardiovascular risk into adulthood in juvenile idiopathic arthritis

Thesis for the degree of philosophiae doctor (Ph.D.)
Hanne Aaserud Aulie

Rheumatology Unit
Oslo University Hospital Rikshospitalet

Institute of Clinical Medicine
Faculty of Medicine
University of Oslo
2015
# Table of Contents

Acknowledgements .............................................................................. 4
List of papers ..................................................................................... 6
Abbreviations ..................................................................................... 7

1. Introduction ................................................................................... 9

2. Background .................................................................................. 10

   JIA ................................................................................................. 10
      Definition and classification ......................................................... 10
      Epidemiology ............................................................................... 12
      Aetiology and pathogenesis ......................................................... 12
      JIA disease course and outcome ............................................... 13
      Medical treatment of JIA ........................................................... 16
      Prognostic factors ...................................................................... 16
      Patient-reported health status .................................................... 17
      Evaluation of active disease ....................................................... 17

   CVD ............................................................................................... 18
      Definition and epidemiology ....................................................... 18
      Pathogenesis of atherosclerosis ............................................... 18
      Inflammation and atherosclerosis/IHD ...................................... 19
      Markers of subclinical CVD ...................................................... 20

3. Aims of study ................................................................................ 22

4. Patients and Methods .................................................................... 23

   Study design .................................................................................. 23

   Patients and controls ..................................................................... 23
      Patients ...................................................................................... 23
      Non-participating patients ....................................................... 24
      Controls ..................................................................................... 25

   Traditional cardiovascular risk factors ........................................ 26

   Laboratory data ............................................................................ 27

   Arterial stiffness ......................................................................... 27

   Coronary artery calcification ..................................................... 29

   Echocardiography ....................................................................... 30

   Electrocardiography .................................................................... 33

   Clinical JIA data ......................................................................... 33

   Remission .................................................................................... 34

   Measures of health status .......................................................... 34

   JADAS ........................................................................................... 35

   Statistics ....................................................................................... 36

   Ethics ............................................................................................ 37

5. Summary of results ....................................................................... 38

6. Discussion ..................................................................................... 42

   Methods, strengths and limitations ........................................... 42
      Study design .............................................................................. 42
      Patients ...................................................................................... 43
      Controls ..................................................................................... 44
Acknowledgements

The present work was carried out at the Department of Rheumatology, Oslo University Hospital, Rikshospitalet, during the period 2010 to 2014. I am very grateful for the support I have received from Extrastiftelsen – Helse og rehabilitering which made this work possible, and for grants from the Scandinavian Rheumatology Research Foundation and Eimar Munthes legat. I am also very thankful for support from the Department of Rheumatology.

Many people have been involved in this project, and I am very thankful to all of them. First of all, I want to thank the patients with juvenile idiopathic arthritis and the randomly selected controls for their time and patience while being involved in this study.

I want to give my deepest gratitude to my main supervisor, Berit Flatø, who started to follow these patients in the early 1980s and started the present project. Her impressive knowledge in the field of paediatric rheumatology and scientific work together with a contagious enthusiasm has made this work possible. Having an enormous scientific and clinical capacity and efficiency, warmth, and honesty, she is a role model for me both as a doctor and as a person.

I also want to thank my co-supervisor in cardiology, Svend Aakhus. I am very grateful that he enthusiastically opened the doors at the “echo laboratory” at Rikshospitalet teaching me how to perform echocardiographic imaging. Learning from his impressive knowledge in the field of cardiology and echocardiography has been a privilege. I am also very thankful to Mette-Elise Estensen, who encouraged and helped me to learn cardiology and echocardiography and introduced me to Svend Aakhus. A special thanks to Pia Elisabeth Bryde and Richard Massey for teaching me how to do proper echocardiographic imaging and assisting me when imaging was difficult.

Warmest thanks to my colleague and co-author Anne Marit Selvaag. Her thorough, experienced work and support have been very important to me. I also want to thank Vibke Lilleby for her comprehensive clinical examinations of the patients. Furthermore, I want to thank Øyvind Molberg, who has been a second co-supervisor in this project. I am also very grateful to my current leader at the Rheumatology Unit, Inge-Margrethe Gilboe, for her kind help. She takes very good care of all of us at the department of Rheumatology.

I want to thank Anders Hartmann and Hallvard Holdaas for their brilliant contributions and the Laboratory of Renal Physiology for their help. I am very thankful to Anne Günther, who
organised and scored the cardiac CT of the patients with great efficiency. Thanks also go to Klaus Murbraech for his contributions to paper II.

I would like to thank Torhild Garen for her help with preparation of questionnaires, scanning of questionnaires, and practical guidance. Furthermore, I want to thank Helga Vonheim Bruaseth for her valuable help in taking care of and showing the patients around the hospital.

Thanks also go to Lars Mørkrid for making it possible to obtain laboratory assessments of the controls included in the project and to Cathrine Brunborg for statistical support. A warm thanks to my dear friend Cathrine Schermann for technical support.

I am grateful to all of my colleagues at the Rheumatology Unit and at the “Forvalterbolig” for support and help, long talks and professional discussions. Especially, I want to thank Anna Hoffmann-Vold, Dag Olav Dahle, Lene Anette Rustad, Cecilie Dobloug, Kristin Schjander-Berntsen, Siri Opsahl-Hetlevik, Silje Reiseter, Marianne Angelshaug and Karin Kilian for sharing times of frustration and joy.

Finally, I want to express my deepest gratitude to my family and friends. A thanks to my father for his everlasting belief in my skills, and special thanks to my fantastic and patient sister Stine for whom no subject is too boring to discuss. And thanks also to my sweet and funny nieces Hermine and Josefine who taught me everything I know about child communication.

Finally, warmest thanks go to my dear boyfriend Petter, who has put up with me during these sometimes frustrating years and who has encouraged me to continue with this work and told me to relax.
List of papers

I. Hanne A Aulie MD, Anne M Selvaag MD PhD, Anne Gunther MD, Vibke Lilleby MD Phd, Øyvind Molberg MD PhD, Anders Hartmann MD PhD, Hallvard Holdaas MD PhD, Berit Flatø MD PhD. Arterial haemodynamics and coronary artery calcification in adult patients with juvenile idiopathic arthritis. Ann Rheum Disease Published online first [2.april 2014] doi:10.1136/ard-2013-204804.

II. Hanne A Aulie, Mette-Elise Estensen, Anne Marit Selvaag, Vibke Lilleby, Klaus Murbraech, Berit Flatø, Svend Aakhus. Cardiac function in adult patients with juvenile idiopathic arthritis. In press

Abbreviations

ACR = American College of Rheumatology
AIx = Augmentation Index
ANA = Antinuclear antibodies
AUC = Area under the curve
BMI = Body mass index
BP = Blood pressure
CRP = C-reactive protein
CT = Computed tomography
CVD = Cardiovascular disease
DBP = Diastolic blood pressure
DMARD = Diseases-modifying anti-rheumatic drug
DT = Deceleration time
E = Early diastolic flow velocities
E´ = Mitral annular velocity in diastole
E/A ratio = Peak early-to-late ratio mitral flow velocity
ECG = Electrocardiography
EF = Ejection fraction
ESR = Erythrocyte sedimentation rate
EULAR = European League Against Rheumatism
FPS = Frames per second
HAQ = Health Assessment Questionnaire
HBA1c = Glycated haemoglobin
HDL = High-density lipoprotein
HF = Heart failure
HLA = Human leukocyte antigen
HOMA-IR = Homeostasis model assessment for insulin resistance
HRQoL = Health-related quality of life
hs-CRP = High-sensitivity C-reactive protein
IHD = Ischaemic heart disease
IL = Interleukine
ILAR = International League of associations for Rheumatology
IQR = Interquartile range
IVRT = Isovolumic relaxation time
JADAS = Juvenile Arthritis Disease Activity Score
JCA = Juvenile chronic arthritis
JIA = Juvenile idiopathic arthritis
JRA = Juvenile rheumatoid arthritis
LA = Left atrium
LDL = Low-density lipoprotein
LROM = Limited range of motion
LV = Left ventricle
NSAID = Non-steroidal Anti-Inflammatory Drug
OUH = Oslo University hospital
PWV = Pulse wave velocity
QTc = Corrected QT
RA = Rheumatoid Arthritis
RF = Rheumatoid factor
S´ = Mitral annular velocity in systole
SBP = Systolic blood pressure
SD = Standard deviation
SF-36 = Short Form-36 health survey
SPSS = Statistical Package for the Social Sciences
TNF = Tumor necrosis factor
VAS = Visual analogue scale
1. INTRODUCTION
Juvenile idiopathic Arthritis (JIA) is the most common inflammatory rheumatic disease in childhood. The disease is heterogeneous, divided into seven categories, with a disease activity that varies from affecting only a few joints for a limited period of time to long-lasting active disease until adulthood.\(^1\) The medical treatment for JIA has gone through great improvements during the last decades and today includes numerous options with proved efficacy.\(^2\) When we started our study, few long-term follow-up studies had evaluated the level of disease activity and long-term outcome in JIA patients.

A strong link between atherosclerosis and inflammation has been established,\(^3\) and sustained inflammation is believed to accelerate atherosclerosis in patients with adult arthritis such as rheumatoid arthritis (RA).\(^4\) Given the overlap in pathogenesis between RA and JIA, interest has increased concerning cardiovascular risk in JIA. At the time our study was started, the cardiovascular risk in adults with long-standing JIA had not previously been evaluated.

Because of the Norwegian population register, it is possible to trace patients still living in Norway who no longer are in the system of the Oslo University Hospital (OUH), providing excellent conditions for carrying out a long-term follow-up study. Inspired by our research group’s previous follow-up studies of JIA patients and concurrent work by Dr. Provan at Diakonhjemmet Hospital on cardiovascular risk in RA patients, we decided to carry out a long-term follow-up study in adult JIA patients with a focus on disease progression and cardiovascular risk.
2. BACKGROUND

JIA

Definition and classification

JIA is a heterogeneous disease defined by synovial inflammation of the joints that persists for at least 6 weeks in patients younger than 16 years, with other causes of arthritis excluded. It is categorised according to number and location of joints affected, involvement of other organ systems, patient characteristics, and presence of the autoantibody rheumatoid factor (RF). The International League of Associations for Rheumatology (ILAR) has developed the most recent classification criteria for JIA, the ILAR criteria. These criteria comprise seven categories: systemic arthritis, RF-negative polyarthritis, RF-positive polyarthritis, oligoarthritis, enthesitis related arthritis, psoriatic arthritis, and undifferentiated arthritis (Table 1). Earlier, two classification criteria were used: the criteria for juvenile rheumatoid arthritis (JRA) that excluded childhood arthritis associated with axial disease or psoriasis, and the criteria for juvenile chronic arthritis (JCA) that included these categories in addition to arthritis related to inflammatory bowel disease, thus comprising a more heterogeneous patient group.

Uveitis is an important feature of JIA most often seen in patients with early onset of arthritis and antinuclear antibody (ANA) positivity.
### Table 1. The ILAR criteria for the classification of JIA

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
<th>Exclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic arthritis</td>
<td>Arthritis and quotidian fever for at least 2 weeks + at least one of the following:</td>
<td>a – d</td>
</tr>
<tr>
<td></td>
<td>- Non-fixed erythematous rash</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Generalised lymph node enlargement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Hepatomegaly and/or splenomegaly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Serositis</td>
<td></td>
</tr>
<tr>
<td>RF-negative polyarthritis</td>
<td>Arthritis affecting 5 or more joints during the first 6 months. RF-negative.</td>
<td>a - e</td>
</tr>
<tr>
<td>RF-positive polyarthritis</td>
<td>Arthritis affecting 5 or more joints during the first 6 months. RF-positive.</td>
<td>a, b, c, e</td>
</tr>
<tr>
<td>Oligoarthritis</td>
<td>Arthritis affecting 1-4 joints during the first 6 months of the disease course.</td>
<td>a - e</td>
</tr>
<tr>
<td></td>
<td>Two subcategories:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Persistent oligoarthritis: arthritis affecting 1-4 joints throughout the disease course</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Extended oligoarthritis: arthritis affecting 1-4 joints during the first 6 months, but affecting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a total of more than 4 joints after 6 months</td>
<td></td>
</tr>
<tr>
<td>Enthesitis related arthritis</td>
<td>Arthritis and/or enthesitis + at least 2 of the following:</td>
<td>a, d, e</td>
</tr>
<tr>
<td></td>
<td>- Sacroiliac joint tenderness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- HLA-B27 positivity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Male onset age &gt;6 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Anterior uveitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- HLA-B27 related disease in first-degree relative</td>
<td></td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>Arthritis and psoriasis, or arthritis + at least 2 of the following:</td>
<td>b - e</td>
</tr>
<tr>
<td></td>
<td>- Dactylitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Nail pitting or oncholysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Psoriasis in a first-degree relative</td>
<td></td>
</tr>
<tr>
<td>Undifferentiated arthritis</td>
<td>Arthritis that does not fulfil criteria in any category or in 2 or more of the above categories.</td>
<td></td>
</tr>
</tbody>
</table>

JIA = juvenile idiopathic arthritis, ILAR = International League of Associations for Rheumatology, RF = rheumatoid factor

**Exclusions:**

a. Presence of psoriasis or psoriasis in a first-degree relative
b. HLA-B27 positive male >6 years old
c. Presence of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter’s syndrome, or acute anterior uveitis in patient or first-degree relative
d. RF-positivity
e. Presence of systemic arthritis
Epidemiology

JIA is the most common rheumatic disease in childhood. The disease has a female predominance (60-70%), except for an equal to male predominance seen in enthesitis related arthritis.\textsuperscript{13,14} Average age at onset is found to be 7 years,\textsuperscript{9,10} and a tendency to bimodal age distribution with a slightly elevated incidence in the age groups 1-3 and 8-9 years is reported in Nordic studies.\textsuperscript{9,15}

The annual incidence of JIA is approximately 15 per 100,000 children up to age 16 years, ranging from 11-23 in the Nordic countries to 6.6-10 in Germany and the United Kingdom.\textsuperscript{9,10,15-18} The worldwide prevalence is 16-150/100000, including studies from the Nordic countries that have reported a prevalence rate of 86-148/100 000.\textsuperscript{10,14,18}

Aetiology and pathogenesis

The aetiology of JIA is mainly unknown but most likely it is multifactorial. It may be triggered by an interaction between a particular complex polygenic predisposition, autoimmunity and various unknown environmental factors.\textsuperscript{11} The human leukocyte antigen (HLA) gene is the best documented genetic predisposition found to determine development of JIA, and the haplotype HLA-DR8 has been identified to associate with most RF-negative JIA subtypes.\textsuperscript{19-21} Additionally, non HLA-related immune genes including cytokine genes and other immune genes, also play a role in the susceptibility for JIA.\textsuperscript{22,23} Infections, vaccinations, and trauma have been investigated as possible triggers of the disease, but a clear association has so far not been found.\textsuperscript{11,24,25}

The process of synovial inflammation in JIA is characterised by infiltration of T-cells, B-cells, macrophages, plasma cells, and dendritic cells, leading to hypertrophy of the synovia.\textsuperscript{26} Elevated levels of pro-inflammatory cytokines such as tumor necrosis factor (TNF) \( \alpha \), interleukin (IL) -1 and IL-6 are identified in the synovial tissue and fluid of children with
JIA and believed to play a central role in the inflammatory process.\textsuperscript{27-29} JIA shares pathogenic features with adult RA concerning the process of synovial inflammation,\textsuperscript{30} but the genetic markers identified in JIA differ greatly from those presented in RA.

RF antibody is seen in a small subset of JIA patients with a polyarthritis that resembles adult RF-positive RA.\textsuperscript{31} ANA is mainly present in girls with early onset of oligoarthritis or polyarthritis with late onset,\textsuperscript{32} and its presence is associated with an increased risk of uveitis.\textsuperscript{7,8}

**JIA disease course and outcome**

The disease course and outcome in JIA are heterogeneous. Some patients experience affection of a few joints only and disease remission after a few years without any sequelae. Others have persistently active disease also in adulthood or experience different degrees of active disease varying with periods of remission. Numerous outcome studies following juvenile arthritis patients for 10-20 years have been presented since the year 2000 (Table 2), but the remission rates reported vary from 33 to 63\%.\textsuperscript{13;33-41} Studies have been difficult to compare because of differences in classification and criteria for remission used. The Wallace criteria for remission and the ILAR classification criteria for JIA developed in 2004 will hopefully lead to less variability among studies in the future.\textsuperscript{1;42} Patients with RF-positivity and/or in the polyarticular and extended pauciarticular disease categories have been found to be less likely to experience remission while the greatest remission rates have been identified in the persistent oligoarticular and systemic disease categories.\textsuperscript{34;35;38;39;41}
### Table 2. Follow-up studies for 10 years or more after 2000

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Disease duration (mean/median, yrs)</th>
<th>Pts (no.)</th>
<th>Remission criteria</th>
<th>Remission (%)</th>
<th>Classification criteria</th>
<th>Presence of each JIA category (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zak et al. 2000</td>
<td>26 (SD 6)</td>
<td>65</td>
<td>No symptoms or objective signs of active JCA and normal ESR &gt;2 years without any anti-rheumatic treatment</td>
<td>63</td>
<td>JCA/EULAR</td>
<td>Systemic art.: 8 Polyart.: 26 Pauciart. pers.: 32 Pauciart. ext.: 34</td>
</tr>
<tr>
<td>Packham et al. 2002</td>
<td>28 (range 8-73)</td>
<td>246</td>
<td>The absence of clinical inflammation determined with the Thompson-Kirwan scale,(^1) and normal inflammatory markers (CRP and ESR)</td>
<td>Clinically: 57 Laboratory: 46</td>
<td>JIA/ILAR</td>
<td>Systemic art.: 21 Polyart. RF-: 17 Polyart. RF+: 15 Oligoart. pers.: 6 Oligoart. ext.: 22 Enthesitis art.: 13 Psoriatic art.: 5</td>
</tr>
<tr>
<td>Oen et al. 2002</td>
<td>11 (range 5-23)</td>
<td>392</td>
<td>Absence of active arthritis while off all anti-rheumatic medications for at least 2 years</td>
<td>39</td>
<td>JRA/ACR</td>
<td>Systemic art.: 12 Polyart. RF-: 20 Polyart. RF+: 10 Pauciart. pers.: 46 Pauciart. ext.: 11</td>
</tr>
<tr>
<td>Minden et al. 2002</td>
<td>17 (range 10-30)</td>
<td>215</td>
<td>At least 5 of: no joint pain, tenderness or swelling, no morning stiffness or fatigue and normal ESR, and not received anti-rheumatic drugs for 2 or more months (ACR criteria for remission in RA).(^4) Plus no inflammatory spinal pain or active uveitis</td>
<td>40</td>
<td>JIA/ILAR</td>
<td>Systemic art.: 14 Polyart. RF-: 1 Polyart. RF+: 13 Oligoart.: 40 Enthesitis art.: 15 Psoriatic art.: 1 Other art.: 16</td>
</tr>
<tr>
<td>Fantini et al. 2003</td>
<td>10 (SD 7)</td>
<td>683</td>
<td>No signs of disease activity in the absence of anti-rheumatic therapy for at least 6 months</td>
<td>33</td>
<td>JCA/EULAR</td>
<td>Systemic art.: 13 Polyart. RF-: 12 Polyart. RF+: 3 Oligoart. pers.: 47 Oligoart. ext.: 15 Psoriatic art.: 3 Ankylosing spondylitis: 1 Art. associated with IBD: 0.4 Undifferented spondyloarthropathies: 5</td>
</tr>
<tr>
<td>Study</td>
<td>Arthritides</td>
<td>Physician’s global assessment scale of disease activity</td>
<td>JIA/ILAR</td>
<td>Systemic art.:</td>
<td>Polyart. RF:-</td>
<td>Polyart. RF+:</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------</td>
<td>--------------------------------------------------------</td>
<td>----------</td>
<td>---------------</td>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Foster et al. 2003</td>
<td>21 (range 3-61)</td>
<td>82</td>
<td>61</td>
<td>JIA/ILAR</td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td>Flatø et al. 2003</td>
<td>15 (range 12-25)</td>
<td>268</td>
<td>50</td>
<td>JRA /ACR</td>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td>Flatø et al. 2006</td>
<td>15 (range 12-22)</td>
<td>55</td>
<td>44</td>
<td>JIA/ILAR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arkela-Kautiainen et al. 2005</td>
<td>16 (range 6-24)</td>
<td>123</td>
<td>35</td>
<td>JIA/ILAR</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>Flatø et al. 2009</td>
<td>15 (SD 2)</td>
<td></td>
<td>55 (Psoriasis art.)</td>
<td>ILAR</td>
<td>Psoriasis art.:</td>
<td>13</td>
</tr>
</tbody>
</table>

*Inactive disease is defined as having no active arthritis, fever, serositis, rash, splenomegaly, or generalised lymphadenopathy attributable to JIA, no active uveitis, normal CRP or ESR, and a physician’s global assessment of disease activity rated as the best possible score for the instrument used. Clinical remission on medication is defined as minimum 6 continuous months of inactive disease on medication. Clinical remission off medication is defined as minimum 12 months of inactive disease off all anti-arthritic and anti-uveitis medication.42

SD = standard deviation, JCA = juvenile chronic arthritis, ESR = erythrocyte sedimentation rate, EULAR = European League Against Rheumatism, CRP = C-reactive protein, JIA = juvenile idiopathic arthritis, ILAR = International League of Associations for Rheumatology, RF = rheumatoid factor, JRA = juvenile rheumatoid arthritis, IQR = interquartile range, ACR = American College of Rheumatology, RA = rheumatoid arthritis, IBD = inflammatory bowel disease.
Medical treatment of JIA

The medical treatment of JIA has evolved considerably in recent decades, from involving only a few treatment options with uncertain effect toward an early aggressive treatment approach that includes numerous options.

Glucocorticoid joint injections of affected joints in active oligo- or polyarthritis are recommended as first-line therapy or in combination with the below-mentioned treatments. A clinical improvement for at least 6 months after an injection have been found in 69% of the joints injected.45

Monotherapy with non-steroidal anti-inflammatory drug (NSAID) for 1-2 months is used as treatment for patients with newly diagnosed oligoarticular JIA.2 If NSAID response is insufficient, or there is an initially high disease activity or polyarthritis, then disease-modifying anti-rheumatic drugs (DMARD) are recommended. The most widely used DMARD, methotrexate, is a folic acid analogue that interferes with DNA production. Methotrexate has been used to reduce disease activity in JIA patients since the early 1980s.46,47 The emergence of biologic therapy in 1999 resulted in a great enhancement of JIA treatment efficacy.48-50 TNF inhibitors are recommended as second- or third-line therapy after 3 months of insufficient outcome with treatment with methotrexate in oligo- or polyarticular JIA, but might also, in cases with active sacroiliitis, be chosen as second line therapy if insufficient response of NSAID.2

The treatment of systemic JIA differs from the other subtypes. Monotherapy with NSAID is rarely sufficient in these patients, but systemic glucocorticoids and anti-IL-1 or anti-IL-6 agens are often needed.2

Prognostic factors

The evaluation and measurement of active disease is an essential feature in JIA because
persistently active disease may cause joint damage and a reduction in physical function. When we started our study, only two publications reported investigations into the factors that might predict long-term active disease. In a study from 2000, Zak et al. reported that a longer disease duration was a predictor of unfavorable disease outcome in patients with persistent JCA 26 years after disease onset. In 2003, Flatø et al. found that a long duration of elevated erythrocyte sedimentation rate (ESR), young age at onset, DRB1*08, RF-positivity, and a large number of affected joints within the first 6 months were risk factors for persistently active disease after 15 years.

**Patient-reported health status**

As defined by the World Health Organization, health is a “state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”. Because JIA is a chronic disease from childhood, physical, mental, and social well-being are important aspects of the disease course. The Health Assessment Questionnaire (HAQ) was developed in the 1980s with the goal of measuring long-term health outcomes and function in patients with arthritis and has been used in numerous long-term follow-up studies of juvenile arthritis patients. Most studies report that approximately 40% of patients have some limitation of their physical function after more than 10 years of disease duration as measured by HAQ>0, but severe limitations were found in a small group (around 10%) of the patients.

Health related quality of life (HRQoL) has been a focus for several studies of juvenile arthritis patients with long-term disease duration reporting a poorer HRQoL in young adults with juvenile arthritis compared to matched controls from the general population.

**Evaluation of active disease**

In adult rheumatology, scores like Disease Activity Score 28 are developed by pooling
disease activity measures into one composite score\textsuperscript{56}. Interest has increased in recent years in developing a standardised measure for the evaluation of JIA disease activity resulting in the Juvenile Arthritis Disease Activity Score (JADAS), a composite disease activity score for JIA that was developed in 2009.\textsuperscript{57} JADAS is found to enable monitoring of the JIA disease course over time and comparisons of disease activity across groups.\textsuperscript{57}

A longitudinal follow-up study of JIA patients for 30 years has not previously been performed. Additionally, long-term follow-up studies using the recently developed criteria for remission and the JADAS for evaluation of disease activity are lacking.

**Cardiovascular disease (CVD)**

**Definition and epidemiology**

Ischaemic heart disease (IHD) including angina pectoris, myocardial infarction, and ischaemic heart failure (HF), is most commonly caused by atherosclerosis. CVD, especially myocardial infarction and stroke, is the cause of death for approximately 17 million people annually, and thus is the most important cause of death by non-communicable diseases worldwide.\textsuperscript{58} The well-defined risk factors for IHD; smoking, diabetes, hypertension, abdominal obesity, dyslipidemia, psychosocial factors, low consumption of fruit and vegetables, high levels of alcohol consumption, and physical inactivity together account for 90\% of the risk for myocardial infarction worldwide.\textsuperscript{59} Different tools have been developed for calculating individual cardiovascular risk in patients based on these established risk factors. Such tools are the US Framingham general CVD risk score,\textsuperscript{60} the European SCORE (Systematic COronary Risk Evaluation) for CVD,\textsuperscript{61} and the Norwegian NORRISK cardiovascular risk score.\textsuperscript{62}

**Pathogenesis of atherosclerosis**
An initial event of the atherosclerotic process is endothelial dysfunction, which induces expression of adhesion molecules that enables T-lymphocytes and monocytes to migrate into the intima, the inner layer of the arterial wall, and accumulate. In the presence of oxidised low-density lipoprotein (LDL), monocytes mature into activated macrophages that internalise lipoproteins and turn into foam cells.\textsuperscript{63} The accumulation of foam cells together with T-cells, mast cells, and dendritic cells initiates the formation of the atherosclerotic lesion, and the secretion of pro-inflammatory cytokines promotes local inflammation and plaque growth.\textsuperscript{64} Further accumulation of smooth muscle cells, connective tissue, T-lymphocytes, and lipids contributes to the expansion and development of the atherosclerotic lesions.\textsuperscript{63} These lesions may gradually be covered by a fibrous cap, intrude into the arterial wall, and change the blood flow.\textsuperscript{65} Ulceration of an atherosclerotic plaque may lead to thrombosis, which may trigger myocardial infarction and ischaemic stroke.

Autopsies of the aorta and coronary arteries of children and young adults dying from various causes have revealed that the atherosclerotic process in some cases, begins already in childhood and youth.\textsuperscript{66,67} In fact, evidence suggests that fatty streak formation may begin in utero.\textsuperscript{68}

**Inflammation and atherosclerosis/IHD**

A strong link between atherosclerosis and inflammation has been established.\textsuperscript{3} Inflammatory processes may cause endothelial dysfunction through oxidative stress and inhibited NO-mediated vasodilatation,\textsuperscript{69} and elevated levels of C-reactive protein (CRP) has been shown to suppress the production of NO and its bioactivity.\textsuperscript{70} Mediated through endothelial dysfunction, inflammation may promote changes in the extracellular matrix as a result of smooth muscle cell proliferation and increased collagen stiffening, leading to stiffening of the large arteries.\textsuperscript{71} Increased levels of immune cells, adhesion molecules, and cytokines are identified in
hypertension, but an exact pathology is not yet established. HF and left ventricular (LV) diastolic dysfunction are also found to be associated with cardiac inflammation.

Markers of subclinical CVD

Early detection is crucial for the prevention of IHD. Novel non-invasive methods allow assessment of arterial properties, subclinical atherosclerosis, and cardiac function. Arterial pulse wave velocity (PWV) is a marker of large arterial stiffness, and the augmentation index (AIx) reflects arterial stiffness by a combination of pulse wave reflection, LV ejection, and heart rate. Coronary artery calcification is a marker of coronary atherosclerosis and may be determined by computed tomography (CT). These markers are proved to be associated with subsequent CVD and all-cause mortality in various populations. Cardiac ultrasound, i.e. echocardiography provides detailed information on cardiac morphology, systolic and diastolic function, and general haemodynamics such as cardiac output and filling parameters, and is an important tool for diagnosis of HF in clinical cardiology.

Inflammatory arthritis and cardiovascular risk

Adult onset inflammatory arthritides are associated with an increased risk of cardiovascular mortality and morbidity, independent of the presence of traditional cardiovascular risk factors. Extensive research on subclinical CVD has demonstrated increased arterial stiffness, coronary atherosclerosis, and carotid atherosclerotic plaques in RA patients. Evidence also points to a higher prevalence of diastolic dysfunction and an increased risk of HF in RA patients. Sharing pathogenic similarities such as T-cell activation, production of pro-inflammatory cytokines, and increased expression of adhesion molecules, systemic inflammation is believed to play an important role in the accelerated atherosclerotic process
seen in RA. In light of an overlap in pathogenesis between JIA and RA, interest has increased concerning cardiovascular risk in JIA.

The prevalence of traditional cardiovascular risk factors such as hypertension, dyslipidaemia, and a sedentary lifestyle has scarcely been investigated in children with JIA. Two studies have showed increased levels of blood pressure (BP) in children with juvenile arthritis while analysis of serum cholesterol levels in children with juvenile arthritis has yielded contradictory results. Furthermore, lower levels of physical activity and physical fitness as measured by $V_{\text{O}}^{2}\text{peak}$ are found in JIA patients when compared to healthy children. The use of anti-rheumatic drugs may also be a possible risk factor for developing early atherosclerosis in JIA. Methotrexate increases the level of homocysteine by the inhibition of folic acid, which again is associated with accelerated atherosclerosis. The use of corticosteroids has been linked to an increased risk of myocardial infarction and hypertension in RA patients. Additionally, a link has been established between NSAID use and increased BP in healthy individuals, and both high-dose regimens of ibuprofen and diclofenac have been associated with a moderately increased risk of vascular events. On the other side, anti-rheumatic drugs may act cardio-protective by reducing inflammation.

Only a few studies have reported the prevalence of subclinical CVD in JIA patients. In one study, PWV, as measured by magnetic resonance imaging, was higher in 31 JIA patients with a mean age of 14 years compared to matched controls. Additionally, cardiac function was evaluated in two small studies, with results suggesting impaired diastolic function in children with juvenile arthritis when compared to controls.

To the best of our knowledge, traditional cardiovascular risk factors, arterial properties, and cardiac function have not yet been studied in adult JIA patients.
3. AIMS OF STUDY

Main aim
To describe long-term disease activity and cardiovascular risk in a cohort of well-characterised adult JIA patients.

Specific aims

- To describe arterial stiffness and BP in JIA patients with active disease for at least 15 years compared to that of age- and gender-matched controls and to assess the level of coronary artery calcification in adults with JIA (paper I).

- To evaluate and compare LV systolic and diastolic function in JIA patients with active disease for at least 15 years to that in age- and gender-matched controls (paper II).

- To assess the level of traditional cardiovascular risk factors in JIA patients with long-term active disease compared to that in controls (papers I,II).

- To determine a possible influence of traditional cardiovascular risk factors and JIA disease characteristics on the level of arterial haemodynamics, coronary artery calcification and cardiac function (papers I,II).

- To longitudinally assess the disease activity and health status in JIA patients during 30 years of disease duration and investigate possible predictors of long-term active disease (paper III).
4. PATIENTS AND METHODS

Study design

Our study is a longitudinal, partly retrospective study of a cohort of JIA patients. Papers I and II have a case-control design, while paper III is an observational study. For papers I and II, only patients with active disease for at least 15 years were included. The patient:control ratios were 1:1 in paper I and 2:1 in paper II. In paper III, both patients with active disease and patients with disease in remission were included.

The 87/85 patients included in papers I and II were examined after a median of 29.2 years, and altogether the 176 included patients (paper III) were examined after 29.6 years. The follow-up is therefore referred to as the 30-year follow-up throughout this thesis.

Patients and controls

Patients

The patients invited to the study were selected from a cohort of 260 JIA patients who were referred for the first time to OUH from 1980 through September 1985 and later examined clinically after a median 15 years of disease duration (15-year follow-up), and by mailed questionnaires after a median 23 years (23-year follow-up). These patients have been described in detail in previous publications.\textsuperscript{13,35,36} Of the 260 patients, 6 had died, thus, 254 patients were invited to participate in the present study.

After a median 30 years of disease duration, the 127 patients in the original cohort who still had active disease at the 15-year and 23-year follow-up were invited to participate in a clinical examination while the 127 patients who did not have active disease at the 15- and 23-year follow-up received a mailed questionnaire. To capture possible patients with a relapse of disease activity after 30 years, questions elicited data on received anti-rheumatic or anti-uveitis medication, history of joint injections, and the presence of uveitis during the last year.
To capture possible patients with a relapse of disease activity at the 23-year follow-up, the patients were asked if they used anti-rheumatic medication and if they recently had visited a rheumatologist. Of the patients expected to be in remission, 96 returned the questionnaire (30-year follow-up). Ten of these patients had disease relapse and were invited to participate in the clinical examination, by which 7 accepted. Together, 90 JIA patients with persistently active disease consented and enrolled in an extended clinical examination at OUH between May 2011 and March 2012 (30-year follow-up). All of the patients received one written reminder if they did not answer the first invitation. In all, 176 patients participated in the study.

Three patients were excluded from studies I and II because of pregnancy, which may influence arterial haemodynamics and cardiac function. Two patients were additionally excluded from study II because of technical complications with the ultrasound scanner (n=1) or severe heart disease without relation to JIA (n=1).

The patients were initially classified according to the ACR criteria for the classification of JRA and reclassified according to the ILAR criteria based on clinical examination at the 15-year follow-up and retrospective chart reviews.

Non-participating patients
Sixty-seven patients did not respond to the invitation, and 11 chose not to participate. The 176 participants were comparable to the 84 non-participants (including the 6 deceased patients) with regard to gender, disease category, and disease duration, as well as physician’s global assessment of disease activity, number of active joints, remission rate, the level of HAQ, and Short Form-36 health survey (SF-36) after 15 years, but the non-participants were slightly but statistically significant younger at onset than the participant group. When analysing the 47
eligible but not participating patients with active disease at the 15-year follow-up and the 87 included patients for paper I, the same trend was found.

**Controls**

In the first study (paper I), controls were matched one to one by age, gender, and living in a rural or not rural area. Patients living in the county of Oslo were matched with controls living in Oslo while patients living in the rest of Norway were matched with controls living in the county of Akershus. A company called Ergo Group AS, licensed to do searches in the National Population Register of Norway, made a random selection of 10 controls per patient. Controls were invited to participate in the study by one mailed letter, and no reminders were sent. If a response to the invitation was not received within 3 weeks, an invitation was sent to the next control on the list. Because the patient group consisted of only Caucasians, non-European controls were not invited. All responders were contacted and interviewed briefly by telephone before inclusion. Exclusion criteria for participating in the study were the presence of inflammatory arthritis, diabetes mellitus, or previous cardiovascular events. One potential control was excluded because of diabetes mellitus, and 3 potential controls were excluded because of the presence of inflammatory arthritis including JIA, ankylosing spondylitis, or gout. A letter of invitation to participate in a one-day examination was sent to 185 controls. Half of the controls were randomly chosen to participate in examinations for paper II (echocardiography) after accepting the invitation.
* Signs of active disease and/or on anti-rheumatic medication and/or off medication less than 2 years at 15- and/or 23-year follow-up.
** No sign of active disease and no use of anti-rheumatic or anti-uveitis medication for at least 2 years at 15- and/or 23-year follow-up.
† Excluded because of pregnancy.
‡ Excluded because of technical complications with the ultrasound scanner (n=1) or severe heart disease without relation to JIA (n=1).
§ Excluded because of the presence of diabetes mellitus or inflammatory arthritis.

**Traditional cardiovascular risk factors**

Traditional cardiovascular risk factors were measured in the 87 patients with long-term active disease and controls. Body mass index (BMI) and waist circumference were assessed.

Information about smoking habits and physical activity was collected by a self-reported questionnaire. The validated Norwegian short International Physical Activity Questionnaire was used to assess the total physical activity of work and leisure time, separated into moderate and vigorous intensity.\(^{108,109}\) Patients and controls were interviewed about family history of
premature CVD, defined as CVD in a first-degree relative before the age of 55 in men and 65 in women.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured after 5 minutes of rest in a supine position, and three measurements with a variance of <5 mmHg were averaged. The BP was assessed by use of oscillometric technique with Dinamap ProCare 300-Monitor (Criticon, GE Medical System, USA). The presence of arterial hypertension was defined as SBP/DBP >140/90 mmHg or use of antihypertensive medication.

**Laboratory data**

Blood screening was carried out in the morning after an overnight fast. LDL, high-density lipoprotein (HDL), and total cholesterol, triglycerides, high-sensitivity CRP (hs-CRP), glucose, glycated haemoglobin (HBA1c), insulin, and prohormone of brain natriuretic peptide were measured. The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated from the product of fasting glucose (mmol/L) and insulin (pmol/L) divided by the constant 22.5.\textsuperscript{110,111} One JIA patient had diabetes type 2 and was therefore excluded from analyses concerning HbA1c, glucose, and insulin. ESR and platelets were additionally assessed in the patients. ESR and platelet areas under the curve (AUCs) were calculated from parameters measured at disease onset and at the 15-year and 30-year follow-up. CRP AUC was calculated from the parameters assessed at the 15-year and 30-year follow-up.

**Arterial stiffness**

A Sphygmocor apparatus (Atcor Medical, Sidney, Australia) was used to assess PWV and AIx in patients and controls for paper I. The author of the thesis performed all measurements. The participants did not eat, drink (except water), or smoke for at least 3 hours before the examination.
To measure PWV, sequential recordings of pulse wave forms from the right common carotid artery and the left femoral artery were obtained and gated to an electrocardiogram for the assessment of transit time (Figure 1). The PWV was estimated as the surface distance between the two recording sites divided by the time delay between the feet of the two waveforms. The surface distance was assessed as the distance from the suprasternal notch to the umbilicus plus 10 cm. Measurements fulfilled the automatic quality control (specified by the Sphygmocor apparatus) in 78 patients and 84 controls, and the mean of two measurements with a variance of <0.5 m/s was used in the statistical analysis.

Figure 1: Measurements of PWV by use of the Sphygmocor apparatus. Left: recordings of pulse wave forms from the right common carotid artery, right: recordings of pulse wave forms from the left femoral artery.

AIx was defined as the change in pressure between the second and first systolic peaks of the central pressure waveform, expressed as a percentage of the pulse pressure and standardised to a heart rate of 75 beats/minute. The aortic pressure waveform and AIx were generated from recordings of the radial artery waveform by use of an integrated transfer
The average of three AIx measurements, all having a quality index score >85%, was used for analysis. Measurements of sufficient quality were obtained in 79 patients and 87 controls.

PWV and AIx are markers expressing somewhat different aspects of arterial stiffness recommended to be coupled for the measurement of arterial function. PWV is the speed by which the pressure wave moves down the aorta and is thus a direct measure of large arterial stiffness. AIx is more of an indirect measure of arterial stiffness that quantifies the combination of the forward pressure from LV contraction, the amplitude from the reflected peripheral wave, and the heart rate. PWV has a well-documented ability to predict CVD and is regarded as the “gold standard” for the assessment of arterial stiffness. AIx is proved to have predictive value for CVD in selected diseases.

**Coronary artery calcification**

Coronary artery calcification was quantified by use of a 320-detector row CT scanner (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) for paper I and calculated as an Agatston score (figure 2). A dedicated workstation (Vitrea fX, Vital Images, Minnetonka, Minnesota, USA) with a computerised program (Coronary Artery Calcium Scoring) with a threshold of 130 HU was used to estimate the amount of coronary calcification as an Agatston score. A total of 84 patients underwent coronary calcification scoring. Because of a small potential risk associated with radiation, controls were not included.

The presence of coronary artery calcification is demonstrated as a predictor of cardiovascular events, and survival rates are found to be closely associated with the total amount of coronary calcification. Furthermore, the coronary artery calcification score may provide additional and independent predictive information about cardiovascular events and
all-cause mortality beyond the traditional risk factor models such as the Framingham risk model.\textsuperscript{114,115}

Figure 2: Coronary artery calcification as measured by coronary CT.

**Echocardiography**

Standard transthoracic echocardiographic examination was performed using a Vivid 7 or E9 ultrasound scanner (GE Vingmed Ultrasound, Horten, Norway) with the participants in standard parasternal (short- and long-axis) and apical (four-chamber, two-chamber, and long-axis) projections (paper II).\textsuperscript{116} All recordings were measured after at least 5 minutes of rest, and 3 consecutive heart cycles were stored for offline analyses using dedicated software (BT 12, EchoPAC, GE Vingmed Ultrasound). Frame rate was >100 frames per second (FPS) at the time of tissue Doppler recordings, and >40 FPS during 2D imaging.
LV end-diastolic volume and ejection fraction (EF) were measured by Simpson’s modified biplane rule using endocardial contours in the four- and two-chamber views.\textsuperscript{117} LV dimensions were assessed per convention from parasternal M-mode registrations. Left atrial (LA) area was measured in the four-chamber view.

Pulsed-wave Doppler signal with the sample volume at the tip of the mitral leaflets (apical position) was used to record LV early (E) and late (A) diastolic flow velocities, deceleration time (DT), and isovolumic relaxation time (IVRT).\textsuperscript{118} LV mitral annular velocities in systole (LV s´) and early diastole (LV e´), were measured in the septal and lateral mitral annulus by colour tissue Doppler imaging (Figure 3). The E/e´ ratio was calculated.\textsuperscript{119}

Global longitudinal strain was measured to obtain regional and global myocardial function by use of speckle tracking echocardiography (2D strain method, EchoPac, GE Vingmed, BT 11/12) in an 18-segment model.\textsuperscript{120}

All echocardiographic recordings and analyses were carried out by one investigator (HAA). Offline data reanalyses were blinded for patient/control identity and clinical information. All parameters were averaged from three heart cycles, except for the global longitudinal strain, which was obtained from analyses of single beat recordings of 3 apical image projections.
Echocardiography is an effective method for the evaluation of systolic and diastolic cardiac function and has evolved as a widely used tool in the clinical practice of cardiology and research.

*Systolic dysfunction* is characterised by a decrease in ventricular myocardial contractility followed by a reduction in EF. Several echocardiographic methods provide information about ventricular systolic function such as EF, and fractional shortening, s´ and longitudinal peak-systolic global strain are newly developed echocardiographic modalities that provide additional information on regional and global systolic myocardial function and contractility.\(^{120-122}\)
**Diastolic dysfunction** is mainly dependent on myocardial relaxation, compliance, and LV load and may initially present as cardiac dysfunction with preserved EF. Impaired relaxation of the LV is characterised by prolonged transmitral IVRT and DT and decreased peak early-to-late ratio mitral flow velocity (E/A ratio). To compensate for the impaired relaxation, LV filling pressure will increase to maintain the SV, resulting in a pseudonormal filling pattern with early and late mitral inflow velocities of similar magnitudes. A further rise in LA pressure will result in a restrictive filling pattern, which is characterised by an increased E/A ratio, shortening of the IVRT and DT, and increased E/e′. E/e′ ratio is shown to be a non-invasive parameter of LV filling pressure. An E/e′ >15 can be categorised as an elevated LV filling pressure, while E/e′ <8 indicates a normal LV filling pressure. For values between 8 and 15, additional echocardiographic diastolic parameters are needed to evaluate if the filling pressure is abnormal.

**Electrocardiography (ECG)**

A standard 12-channel ECG recording was performed in patients and controls for paper II. The ECG recordings were reviewed for abnormalities such as corrected QT (QTc) prolongation, T wave abnormalities, bundle branch blockage, and chamber enlargement by a researcher blinded to clinical information and patient/control identity. Abnormal ECG recordings were classified as pathologic ECG or borderline pathologic ECG. The rhythm, PR-interval, QRS duration, and QTc interval were measured.

**Clinical JIA data**

A clinical examination was performed in the patients with long-term active disease by one of three senior physicians (BF, AMS, VL) experienced in paediatric rheumatology. The clinical examination included general organ status, registration of the use of medication since last
follow-up, registration of number of joints (71 joint count) with swelling, tenderness, and limited range of motion (LROM), number of active joints (swelling or both tenderness and LROM), and a physician’s global assessment of disease activity (on a 10-cm visual analogue scale (VAS), where 0 means no disease activity and 10 means severe disease activity, and on a 5-point Likert scale where 1 means inactive and 5 very severe disease activity.)

Disease onset was defined as the date that arthritis was documented by a physician. Medical records were retrospectively reviewed at the 15-year follow-up for variables concerning onset of the disease.\textsuperscript{13,35,36} The controls underwent a general clinical examination by a doctor (HAA).

**Remission**

Inactive disease was defined according to the criteria for clinical remission in JIA; as having no active arthritis, fever, serositis, rash, splenomegaly, or generalised lymphadenopathy attributable to JIA, no active uveitis, normal CRP or ESR, and a physician’s global assessment of disease activity rated as the best possible score for the instrument used, for all the patients at the 15-year follow-up, and for patients clinically examined at the 30-year follow-up.\textsuperscript{42} For patients not examined at the 30-year follow-up, i.e. in remission off medication for at least 12 months at the 15-year follow-up, inactive disease at the 30-year follow-up was defined as no history of flare after 23 and 30 years. Clinical remission on medication was defined as a minimum of 6 continuous months of inactive disease on medication. Clinical remission off medication was defined as a minimum of 12 months of inactive disease off all anti-arthritic and anti-uveitis medication.

**Measures of health status**

For the assessment of health status, questionnaires on physical function including the HAQ
and SF-36 were used. The HAQ includes 8 areas of daily activities; dressing, arising, eating, walking, hygiene, reach, grip, and activities, and a subjective estimate of pain and mental functioning, and only the patients completed it. Each area was scored from 0 to 3, and a HAQ disability index of 0 was the best possible score, indicating no functional limitation.

SF-36 is a generic measure of HRQoL, by which the Norwegian version 1.0 was used in this study. The SF-36 consists of 36 items divided into eight scales aggregated into a Physical Component Summary score and a Mental Component Summary Score. Both scores are reported to have a mean of 50 based on the 1998 US general population. The HAQ and SF-36 were used in paper III to compare health status and HRQoL in JIA patients between the 15- and 30-year follow-up.

JADAS

Disease activity was also measured by JADAS, a composite score calculated on the basis of four JIA disease activity measurements including number of joints with active disease, the physician’s global assessment of disease activity measured on a 10-cm VAS where 0 means no activity and 10 means maximum activity, patient’s global assessment of well-being measured on a 10-cm VAS where 0 means doing very well and 10 means doing very poorly, and standardised ESR. Recently, a JADAS3 was created and evaluated to calculate a score without ESR. We used the JADAS3 version (paper III) for the purpose of also including the patients who were in remission. Missing data for the physician’s global assessment of patients without signs of disease activity or off anti-rheumatic medication were replaced by 0, in accordance with the median score for the patients we had examined who were in remission. A JADAS below 4.5 has been found to correlate as a cut-off value for an acceptable symptom state for children with JIA. Consequently, we chose JADAS3 >4.5 as a level of a high symptom state.
Statistics

Comparisons between JIA patients and matched controls (papers I and II) or between the two patient groups (papers II and III) were made using the two-tailed paired sample t test (paper I) and independent sample t test (papers II and III) for continuous normally distributed variables, the Wilcoxon rank-sum test (paper I) and Mann-Whitney U test (paper II) for continuous non-normally distributed values, and McNemar´s test (paper I) and the \( \chi^2 \) test (papers II and III) for categorical variables. The Wilcoxon rank-sum test was also used for comparisons of continuous non-normally distributed data from the 15- and 30-year follow-up, and Friedman’s two-way analysis of variance was utilized for comparisons at more than two time points (paper III).

The Kruskal-Wallis test was used to analyse differences between more than two groups regarding non-normally distributed continuous variables (the JADAS3 across the JIA categories). Spearman’s correlation was used to measure the association among cumulative inflammatory burden, years on prednisolone, and LV diastolic function (paper II), and between the JADAS3 and categories of disease activity (paper III).

To explore associations between traditional cardiovascular risk factors and disease variables and arterial haemodynamics, age- and gender-adjusted linear regression analyses were applied. Multivariate analyses with backward deletion of possible determinants based on the previously performed age- and gender-adjusted linear regression analyses/Spearman’s correlation were used to identify determinants of arterial stiffness and LV diastolic function (papers I and II). Age- and gender-adjusted logistic regression analyses were used to explore associations with traditional cardiovascular risk factors as well as disease variables and coronary artery calcification (paper I). Logistic regression analyses were also used to assess predictors of active disease at 30 years from baseline/15-year follow-up (paper III).
All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) Versions 18 and 20 (SPSS, Chicago, IL, USA). For all analyses, p values <0.05 (2 tailed tests) were considered statistically significant.

**Ethics**

The study was approved by the Regional Ethics Committee for Medical Research (regional komité for medisinsk og helsefaglig forskningsetikk Sør-Øst (No.2011/982)), and all participants gave written informed consent according to the Declaration of Helsinki (2008).
5. SUMMARY OF RESULTS

PAPER I

The aims of paper I were to identify the level of arterial haemodynamics and traditional cardiovascular risk factors in adult JIA patients with long-term disease activity as compared to controls, and to assess coronary artery calcification in JIA patients. Furthermore, we wanted to investigate the possible influence of traditional cardiovascular risk factors and JIA disease characteristics on the level of arterial haemodynamics and coronary artery calcification.

This study included 87 patients with well-characterised JIA and a median disease duration of 29.2 (range 28.2-30.6) years and 87 randomly selected age- and gender-matched controls. The markers for arterial stiffness, PWV and AIx, blood pressure, and traditional cardiovascular risk factors were measured in patients and controls. Coronary artery calcification was measured in patients.

The findings were as follows:

- Mean PWV was higher in JIA patients than controls (7.2 m/s versus 6.9 m/s, p=0.035). AIx also tended to be higher in patients than controls, but no statistically significant difference was found (p=0.154). The SBP and DBP were higher in patients than controls (p=0.050 and p=0.029). A total of 7% of 84 JIA patients had a coronary artery calcification score above 10, and 19% had a score from 1 to 10.

- A higher frequency of the JIA patients than the controls were daily smokers (25% versus 13%, p=0.043). Arterial hypertension was present in 11% of patients and 2% of controls (p=0.039). The levels of HOMA-IR and hs-CRP were higher in patients than controls (p=0.034 and p=0.001). The JIA patients reported performing more physical activity of moderate intensity than the controls (p=0.001).

- DBP was the only determinant of PWV in multivariate analyses. Concerning AIx, markers identified as determinants were age, female gender, DBP, daily smoking, less
vigorous physical activity, platelets AUC, number of joints with LROM, and years on prednisolone. A coronary calcification score >0 in the JIA patients was associated with SBP, years on prednisolone, blood glucose, waist circumference, and BMI. Our results demonstrate altered arterial haemodynamics in JIA patients with long-term active disease as compared to controls. Arterial stiffness as measured by PWV was mainly determined by increased DBP, a parameter that again was associated with JIA disease activity and treatment variables.

Paper II

The aims of paper II were to compare the cardiac function in adult JIA patients with long-term active disease to that of age- and gender-matched controls and to assess whether a larger inflammatory burden, more severe disease, or the use of anti-rheumatic medication had an adverse effect on cardiac function.

This study included 85 patients with well-characterised JIA and a median disease duration of 29.2 (range 28.2-30.6) years and 46 randomly selected age- and gender-matched controls. Cardiac function was measured by echocardiography and ECG in patients and controls.

The findings were as follows:

- The parameters of systolic function were comparable between JIA patients and the controls. Interventricular septum thickness was thicker in patients than controls (p=0.036). Echocardiographic parameters of diastolic function were within normal range for patients, but when compared to controls, transmirtal DT was lower (p=0.029), and lateral E/e´ and LA area were higher (p=0.036, p=0.015, respectively).
- E/e´ measured at the 30-year follow-up was higher in the JIA patients with hs-CRP ≥2, a polyarticular disease course, and/or ≥3 joints with LROM compared to those with
less severe disease (p=0.004, p=0.050, and p=0.016, respectively). Cumulative
markers of disease activity such as longer duration of active disease, ESR AUC, CRP
AUC, and years on daily prednisolone correlated positively with higher lateral E/e´
(p=0.023, p=0.042, p=0.033, and p=0.021, respectively). Age (p=0.010) and duration
of active disease (p=0.046) were identified as determinants of higher lateral E/e´ at the
30-year follow-up.

- The QTc interval was comparable between patients and controls (p=0.409), but the
  heart rate as measured by ECG was higher in patients (p=0.001).

These results show that JIA patients with long-term active disease had altered LV morphology
and diastolic function compared to controls. Higher LV filling pressure was correlated with
large inflammatory burden, severe disease, and prolonged daily prednisolone use.

**Paper III**

The aims of paper III were to longitudinally assess disease activity and health status in JIA
patients during 30 years of disease duration and investigate possible predictors of long-term
active disease.

This study included 176 patients (median age 38.8 years) previously examined after 15
and 23 years. Patients were assessed by questionnaires after a median of 29.6 years (range
20.6-39.9) of disease duration. Ninety patients were also clinically examined. JADAS was
used to measure disease activity, and health status was assessed by HAQ and SF-36.

The findings were as follows:

- A total of 41% of the patients had active disease or were in remission on medication,
  and 59% were in clinical remission off medication at the 30-year follow-up. A total of
  87% of patients in remission off medication at the 15-year follow-up were still in
  remission at the 30-year follow-up, and 64% of the patients with active disease at the
15-year follow-up had active disease at the 30-year follow-up. Altogether, 70% of the patients had an unchanged category of disease activity from the 15- to 30-year follow-up. The remission rates were highest in patients with persistent oligoarticular and systemic JIA (80% and 83%, respectively) and lowest in those with polyarticular RF-positive and enthesitis related juvenile arthritis (17% and 37%, respectively, p=0.001).

- At 30-year follow-up 56% of the patients who were not in remission off medication used DMARDs and/or prednisolone, 12% used NSAIDs, and 32% used no medication.
- The JADAS3 median value was 1.9 (range 0.2-23.1) for the total study group. Patients with systemic JIA or persistent oligoarthritis had lower values for JADAS3 than those with polyarticular RF-positive JIA. The JADAS3 had a strong correlation with disease activity categories (active disease, remission on/off medication) with a Spearman’s correlation coefficient of 0.73 (p<0.001). A total of 41% of the patients had JADAS3 ≤1.0, 13% had JADAS3 between 1.1 and 2.0, 18% had JADAS3 between 2.1 and 4.5, and 28% had JADAS3 >4.5. All patients with a JADAS3 ≤1.0 were in remission.

- There were significant improvements in the physician’s global assessment of disease activity, number of active joints, ESR, and CRP (all p<0.05) from the 15- to 30-year follow-up, but no difference in number of joints with LROM, patient’s global assessment, HAQ, and SF-36 in patients with long-term active disease.
- Predictors of active disease or being on anti-rheumatic medication after 30 years were: HLA-DRB1*01 positivity, physician’s global assessment of disease activity at the 15-year follow-up, and a short duration of total time in remission at the 15-year follow-up. A higher physician’s global assessment of disease activity at the 15-year follow-up was a predictor of a high symptom state (JADAS3 >4.5) at the 30-year follow-up.
6. DISCUSSION

The first part of the discussion will address the strengths and limitations of the methodology used in the papers included in this thesis. The second part will be a discussion of the main results.

Methods, strengths and limitations

Study design

The major strength of this study is the long-term follow-up of a well-characterised cohort of JIA patients with a median disease duration of 30 years. The same doctor who included the patients at disease onset, Dr Berit Flåtø, has been the head of the project during the whole observational period.

Our study has several limitations concerning study design. All participants were assessed by questionnaires at 30-year follow-up, but an invitation to a 1-2 day clinical examination was sent to the JIA patients with long-term active disease only for two reasons, as follows:

- Previous studies in adult RA patients have shown that patients with disease in remission had a comparable cardiovascular risk to controls, and we wanted to assess patients with long-term inflammation from childhood.

- It is challenging economically and practically to clinically examine a high number of patients who have gone into early remission.

As explained in the methods chapter of this thesis, the questionnaires screened for relapse of disease activity. However, we cannot exclude that some of the patients who were expected to be in remission had disease activity that had been discovered by a clinical examination, but went undetected with the questionnaire.
Ideally, the patients should have been examined more often during the disease course than at the median 15-, 25-, and 30-year follow-up, but because the patients were included from the whole country, more frequent follow-ups would have been too challenging economically and practically.

**Patients**

The participation rate for the patients in this study was 69%, and because 31% of patients were lost to follow-up, the remission rate reported in paper III may not be completely correct. The non-participants were younger but otherwise comparable to participants in regard to gender, disease category, disease duration, and disease activity at the 15-year follow-up.

The patients were all referred to the hospital, which usually indicates inclusion of patients with more severe disease than population based cohorts like in the study by Bertilsson et al. The access to specialist care for patients with chronic diseases is good in Scandinavia, and all JIA patients are usually referred to a specialist at least for diagnosis. However, our hospital is a secondary or tertiary referral center for patients outside the Oslo area, indicating that patients with mild disease may not have been referred. On the other hand, the patient characteristics such as gender distribution and age at disease onset in our cohort were comparable to those in epidemiological studies in Scandinavia. Furthermore, the representation of JIA disease categories resembles the distribution in a German cohort followed for 16.5 years by Minden et al., but consists of more patients with oligoarticular and fewer with polyarticular JIA compared to a cohort from UK followed for 21 years by Foster et al. (Table 2). JIA patients followed routinely by adult rheumatologists will include patients with more long-term active disease than a cohort including all first referrals from a given period, indicating less bias toward patients with severe disease in our total cohort (paper III).
Controls
The controls were matched one-to-one to the patients by age, gender, and urban versus non-urban regions (paper I), and 51% of the invited controls agreed to join the study. A weakness of this study is the relatively large number of non-participating controls, which may have caused a selection bias. By investigating CVD, the study might have attracted individuals concerned about their health because of an increased cardiovascular risk. On the other side, the study also might have attracted very healthy and physically active individuals interested in their cardiovascular status. Patients living in Oslo were matched to controls living in Oslo while patients living in the rest of Norway were matched with controls living in the county of Akershus, a more rural county situated next to the county of Oslo. Ideally, controls should have been recruited from the county where the patients were situated, but because Norway is such a big country, doing so was not possible for practical and economic reasons.

Assessment of cardiovascular status
Different methods can be used for the detecting of subclinical CVD. By choosing markers for arterial stiffness, coronary atherosclerosis, and cardiac function, we tried to capture the different stages of subclinical CVD.

Blood pressure and arterial stiffness show a diurnal variation, and these markers should therefore be measured at the same time of day in all participants when comparing two groups. Additionally, abstention from smoking, food, and alcohol for 3 hours prior to the examination is recommended for the assessment of arterial stiffness. These guidelines were followed in our study. For the estimation of the surface distance travelled by the PWV, we chose to assess the distance from the suprasternal notch to the umbilicus plus 10 cm as recommended by the manufacturer. The procedures measuring the PWV travel distance varies among studies and comparisons of PWV values between studies may therefore be
difficult. Nonetheless, the same method was used for patients and controls in our study.

The determination of aortic AIx from peripheral recorded pulse pressure waveforms has been controversial. The proximal arteries exhibit greater elastic properties than the distal arteries in young and healthy individuals while the elasticity of the proximal arteries diminishes in older people and in the presence of CVD. However, the method used in our study is found to correspond with aortic pressure assessed invasively and is widely accepted.

Coronary artery calcium score is an established marker of future CVD, and a coronary calcium score of 0 in asymptomatic individuals indicates a low risk for severe coronary atherosclerosis. Nevertheless, cardiac CT without contrast is limited by a low sensitivity for identifying soft plaques without calcification. A weakness of this study is that we could not compare the amount of coronary calcium found in the JIA patients with matched controls. Because cardiac CT scanning involves small radiation doses, controls were not scanned for ethical reasons.

The author of this thesis was trained at the “echo laboratory” at the Department of Cardiology, OUH, to establish an adequate technique for recording and analysis of echocardiographic data. A more experienced staff member was available to help if imaging was difficult. Several limitations are associated with the echocardiographic technique. Global strain depends on a high image quality in all three apical projections. Small changes in probe and heart position may influence the assessments of velocities and deformation with the tissue Doppler method. All measurements were controlled by experienced cardiologists (ME, SA), and suboptimal images were excluded. For all parameters except for global strain, images from fewer than 7 individuals were excluded. Global strain included 57 of 87 patients and 41 of 46 controls.
Considerations of methods measuring JIA disease activity

Patients were examined by three senior physicians experienced in paediatric rheumatology (AMS, BF, and VL) at the 30-year follow-up, and by four paediatric rheumatologists (including BF) at the 15-year follow-up. At the 15-year follow-up, inter-rater variability was tested, and at the 30-year follow-up, a consensus meeting was held before the study started. Nevertheless, the comparisons of the physician’s global assessment between the 15- and 30-year follow-up may have been influenced by observer variability and the long time gap between the examinations. A strength of our study is that joint status was also assessed by ultrasound at standardised locations in all patients who were examined after 30 years, indicating more reliable assessments of the number of active joints than by the use of clinical examinations only.

JADAS is a relatively new instrument for JIA patients evaluated for children. A limitation of our study is that we used this instrument in adult JIA patients by which not have been evaluated. We found that JADAS3 correlated strongly with categories of disease activity suggesting a good construct validity of this instrument also in adults. On the other hand we discovered that JADAS3 also captured other aspects of the burden of disease, such as damage and overall well-being in adult JIA patients, as some patients in remission had high symptom states (JADAS3 >4.5).

When calculating JADAS, we replaced missing data for the physician’s global assessment of patients without signs of disease activity (the patients who received the questionnaire and were not clinically examined at the 30-year follow-up) with 0 in accordance with the median score for the patients we had examined who were in remission. This replacement is a limitation of our study. Furthermore, a weakness of our study is that we used the cut-off values for acceptable symptom state defined according to JADAS but used the JADAS3 version to measure disease activity in the patients because ESR was missing in
patients not examined clinically. A JADAS score would have been slightly higher than a JADAS3 score in those patients with elevated ESR.

**Statistical limitations**

In papers I and II, multiple comparisons were performed between patients and controls (paper II) and to assess the association between disease variables and markers of subclinical CVD within the patient group (papers I and II). When performing multiple comparisons, there is an inherent risk for type I statistical error, which is a limitation of this study.

**Discussion of main findings**

**Subclinical CVD in JIA patients (papers I and II)**

We found a slightly increased PWV, DBP, and SBP in JIA patients with at least 15 years of active disease compared to controls, and AIx was numerically but not statistically significantly higher in the JIA patients. In addition to the study of Argyropoulou et al., who found increased PWV as assessed by magnetic resonance imaging in 31 children with JIA, two additional studies have investigated arterial properties in JIA patients since we began our work, but the results are conflicting. Vlahos et al. found no difference in PWV in 30 children and adolescents (age range 7-18 years) with JIA compared to controls, while Satija et al. found reduced arterial compliance in 31 children (mean age 10 years) with JIA as compared to controls. Analyses of the blood pressure level in children with juvenile arthritis have also showed conflicting results.

The patients of our study underwent cardiac CT scanning, which showed that the level of coronary artery calcification was not different from the levels reported in a large study including healthy asymptomatic individuals of comparable age.
With echocardiographic examination, we found that systolic function was comparable between patients and controls. These results are in contrast with Oguz et al. and Bharti et al. who reported an impairment of systolic LV function as reflected by decreased EF in children and adolescents with juvenile arthritis.\textsuperscript{93,94} Furthermore, we found a slightly larger interventricular septum thickness in the JIA patients compared to the controls. Concerning diastolic function, a lower mitral deceleration time, a higher E/e´, and a larger LA area were identified in our JIA patients as compared to the controls. Additionally LV e´ tended to be higher in the JIA patients. These results indicate a slightly impaired diastolic function in adult JIA patients. Previous echocardiographic evaluation of cardiac function in 30-50 juvenile arthritis patients with a mean age of 9-15 years suggested diastolic dysfunction, as measured by decreased transmitral E/A ratio, and higher IVRT as compared to controls.\textsuperscript{93;94;140;143;144} In our study, these markers of diastolic function were comparable between patients and controls. However, in line with our study, Lianza et al. and Koca et al. found decreased LV e´ in children with JIA compared to controls,\textsuperscript{144;145} and a higher E/e´ was reported in JIA patients by Koca et al.

**Clinical implications of subclinical CVD**

What is the clinical implication of a slightly higher level of subclinical CVD in adult JIA patients? The mean PWV in the patients was 7.2 m/s, below the value (10 m/s) classified as asymptomatic target organ damage by the European Society of Hypertension and European Society of Cardiology hypertension guidelines.\textsuperscript{146} However, our patients were 25 years younger than the general population that this threshold represents.\textsuperscript{147} The clinical implication of a PWV that is 0.3 m/s higher in JIA patients than controls is unclear. Vlachopoulos et al. found in their meta-analysis that a 1 m/s increase in PWV corresponded to a 15% increased risk in cardiovascular and all-cause mortality after adjusting for age and sex.\textsuperscript{79} In a more
recent meta-analysis, Ben-Shlomo et al. found that after full adjustment for cardiovascular risk factors (smoking, diabetes, anti-hypertensive medication, DBP, and cholesterol) a 1 m/s increase in PWV correlated with a 7% increased risk of cardiovascular events for a 60 year old man. However, PWV was reported to more strongly predict future cardiovascular events in younger versus older people in the study by Ben-Shlomo et al. The difference in PWV between patients and controls in our study was no longer statistically significant when adjusted for DBP, demonstrating that the higher DBP in the patient group contributed to the increased PWV.

The JIA patients had 3.7 mmHg higher SBP and 3 mmHg higher DBP than controls, but the mean levels were within normal limits. In a large meta-analysis including almost 1 million people without previous stroke or heart disease, a lowering of 20 mmHg usual (i.e.: long-term average) SBP and 10 mmHg usual DBP down to at least 115/75 mmHg were identified as correlating with approximately a doubling of stroke and IHD death rates at ages 40-69 years. According to their calculations, a decrease in usual SBP of 2 mmHg would be associated with approximately 10% lower stroke mortality and 7% decreased mortality from IHD, indicating that the findings of our study are of clinical significance.

Our finding of a slightly larger interventricular septum thickness in the JIA patients compared to the controls is in accord with the higher BP measured. The finding of a lower transmitral DT, higher E/e´ ratio, and larger LA area in the patients in this study indicates a higher LV filling pressure in the JIA patients compared to the controls. An increased LV filling pressure correlates with diastolic dysfunction and HF, but the parameters of diastolic function were all within normal levels in our study, suggesting a subclinical increased LV filling pressure in our JIA patients. The clinical implication of a 0.5 higher E/e´ is uncertain, but the deviation from control values concerning several diastolic parameters indicate a marginal but definite impairment of diastolic LV
function in the JIA patients.

Interestingly, the patients had a higher resting heart rate (68 versus 60 beats/minute) than controls as measured by ECG. In a study from 2010 including 28 000 individuals without CVD, a 15 beats/minute increase in resting heart rate corresponded to a hazard ratio for CVD mortality of 1.24 in men and 1.32 in women after adjusting for age, gender, total cholesterol, physical activity, SBP, BMI, and HDL.\textsuperscript{155}

One might speculate whether the higher frequency of daily smokers influenced the slightly higher level of subclinical CVD measured in the patients in our study.\textsuperscript{156} Smoking was tested as a possible confounder for PWV and AIx in multiple linear regression analysis in paper I, but a statistical association was found with AIx only, together with several other CVD risk factors and JIA disease variables.

Based on the evidence presented, we believe that the higher PWV, BP, LV filling pressure, and resting heart rate found in the JIA patients compared to matched controls corresponds to a slightly higher risk of future CVD.

**Traditional cardiovascular risk factors in JIA patients**

Concerning traditional cardiovascular risk factors in JIA patients with at least 15 years of disease activity, we found a higher frequency of daily smokers and arterial hypertension and higher levels of HOMA-IR and hs-CRP as compared to controls.

To our knowledge, only one study has previously investigated smoking habits in juvenile arthritis patients, finding a lower frequency of daily smoking among adolescents with juvenile arthritis than that reported in a survey of the general adolescent population of the same area (the Northwest Ohio Youth Tobacco Survey).\textsuperscript{157} The contrasting finding of a higher frequency of daily smokers in our study may be explained by the differences in age and variations geographically between the two cohorts. Further studies are needed on this
HOMA-IR is a method for assessing insulin resistance, and higher levels may be associated with an increased susceptibility of developing diabetes.\textsuperscript{111} Despite the higher HOMA-IR in the JIA patients, both fasting HbA1c and glucose, diagnostic markers of diabetes mellitus used in clinical practice, were similar to the values found in the controls. No studies have previously looked at the prevalence of insulin resistance in JIA patients.

Interestingly, the JIA patients had lipid profiles that were comparable to the controls. Studies analysing serum cholesterol levels in children with juvenile arthritis have shown contradictory results.\textsuperscript{95-97,141,158} In contrast to our findings, the only previous study looking at cholesterol levels in adult JIA patients reported dyslipidemia in the patient group (mean age 22) compared to controls.\textsuperscript{159}

Hs-CRP concentration is found to have a strong continuous correlation with cardiovascular risk,\textsuperscript{160} and the American Heart Association and Centers for Disease Control suggested in 2003 that hs-CRP levels of <1 mg/L represented low risk, values from 1-3 mg/L average risk, and values >3 represented high vascular risk.\textsuperscript{161} The median hs-CRP value in the patients in our study was double that of controls (1.8 versus 0.9 mg/L) and may suggest a slightly increased cardiovascular risk.

A sedentary lifestyle is a well-known risk factor for CVD, and lower levels of physical activity\textsuperscript{98,162} and physical fitness as measured by VO\textsubscript{2peak}\textsuperscript{99,100} have been reported in children with JIA when compared to healthy children. Interestingly our results were not in agreement with previous reports, as our patients performed more physical activity of moderate intensity than controls, and the average number of hours per week spent on physical activity of vigorous intensity was similar between the groups. Since the 1990s, a “change of advice” has been adopted by the physical therapists and clinicians at the OUH, who started to encourage JIA patients to perform as much physical activity as possible. Our results may reflect a new
“trend” of JIA patients not having a sedentary lifestyle. However, because physical activity was assessed by a questionnaire only, our results should be interpreted with caution.

**Association of JIA disease variables and subclinical CVD**

In papers I and II, comprehensive analyses were performed to investigate the associations between JIA disease variables and subclinical CVD in JIA patients. The JIA disease variables were mainly selected based on “JIA core set outcome variables”.\(^{163}\) We found that parameters reflecting (cumulative) inflammatory burden such as higher platelets-, ESR-, and CRP AUC, and a longer duration of active disease were associated with higher levels of arterial stiffness, DBP, and LV filling pressure. Parameters reflecting disease severity such as several joints with LROM and a polyarticular disease course correlated with higher arterial stiffness and LV filling pressure, and prolonged prednisolone use was associated with higher levels of arterial stiffness, BP, coronary artery calcification, and LV filling pressure.

Similar results have been reported by Provan et al. who found that elevated baseline CRP predicted higher AIx and PWV after 15 years of disease duration in RA patients.\(^ {164}\) Higher CRP has also been identified as correlating with deterioration of myocardial function in individuals without CVD.\(^ {165}\) Elevated levels of the parameter of number of joints with LROM reflects disease damage but may also, together with polyarticular disease course, reflect a high inflammatory burden over many years. Prolonged daily prednisolone use was associated with most markers of subclinical CVD in our study, which corresponds with the reported association between corticosteroids and a higher risk of developing hypertension and cardiovascular events in RA patients.\(^ {102;103;166}\) The use of systemic corticosteroids has greatly decreased with the introduction of biologic therapy and Methotrexate \(^ {167}\) and may not be as important a cardiovascular risk factor for patients diagnosed with JIA today. Yet, in addition to cumulative corticosteroid use, this parameter probably also reflects a high inflammatory
burden in our patients. The identified association between a high inflammatory burden and increased subclinical CVD in adult JIA patients suggests a need for an enhanced awareness of cardiovascular symptoms in patients with severe JIA.

**Disease activity and remission in JIA patients after 30 years (paper III)**

A frequently asked question from newly diagnosed JIA patients and their parents is if JIA is a lifelong disease and what the prognosis is. This question is also central when following JIA patients through the years because disease activity may fluctuate and flares can appear after years of remission.

We found that 59% of JIA patients were in remission (off medication) after 30 years. As discussed earlier, previously reported remission rates have varied greatly between studies (Table 2). Since we started our study, Bertilsson et al. have published an epidemiologic study of 86 JCA patients followed for 17 years, reporting a remission rate lower than ours, at 40%. With an epidemiologic study, one would expect the remission rate to be higher and not lower compared to what we found in our referral-based study. This unexpected outcome may be explained by a low rate of patients who received early treatment with DMARDs in the study by Bertilsson et al., i.e.: 16% of the patients had received DMARDs within the first 2 years, and 15% were on DMARDs at the 5-year follow-up around 1990. In 1997 at the 15-year follow-up of some of the same patients as those included in the present study, 76% had received one or more DMARD. The remission rate in our study was in concordance with that of most long-term studies of juvenile arthritis patients with a disease duration of 21-28 years, reported at around 57-63%. However, this is the first long-term follow-up study using the newly developed remission criteria for JIA. We also found that 46% of the patients had a considerably high symptom state as measured by JADAS >2.1. Our results indicate that JIA lasts into adulthood for about half of the patients.
This study confirmed what was previously known: disease category is of great importance for future remission rates and the severity of the disease. A total of 80% of patients with persistent oligoarticular JIA were in remission in our study. In contrast, 50% of those with extended oligoarthritis or RF-negative polyarthritis at 15 years were in remission at the 30-year follow-up. When diagnosing a child with oligoarthritis, it is difficult to predict the course of the disease. Studies have shown that 30-50% of patients with initial oligoarthritis develop extended oligoarthritis.\textsuperscript{38,168,169} Only one of the patients with polyarticular RF-positive JIA was in remission after median 30 years, confirming that this category is a long-lasting disease similar to that of RA in adults.\textsuperscript{31} Surprisingly, 83% of the 12 patients with systemic JIA were in remission. This category consists of few patients in Scandinavia. The disease course is often severe at diagnosis including fever, rash, arthritis, and involvement of inner organs and may in some cases be difficult to treat.\textsuperscript{170} However, similar remission rates (75-83%) for systemic juvenile arthritis have recently been reported in other Nordic studies.\textsuperscript{128,169} The same pattern according to differences between JIA categories was seen in the levels of JADAS3: patients with systemic JIA or persistent oligoarthritis had lower levels of JADAS3 than those with polyarticular JIA.

An important finding of our study is that 70% of patients were in the same category of disease activity at 15 and 30 years, and 87% of patients in remission off medication after 15 years were still in remission at the 30-year follow-up. This stability of remission is in contrast with the study by Bertilsson et al., who reported a remission rate of 61% after 17 years among those in remission after a 5-year follow-up.\textsuperscript{128} Other previous studies have reported that disease activity alternates greatly in the first years after diagnosis.\textsuperscript{171-173} Our study suggests a higher probability of reaching a state of stable remission in the long-term perspective.
Predictors of long-term active disease

HLA-DRB1*01, physician’s global assessment of disease activity, and a short duration in remission at the 15-year follow-up predicted active disease after 30 years of disease duration in our study. In line with these findings, disease activity measured as a long duration of elevated ESR and a large number of affected joints within the first 6 months were identified as risk factors for persistently active disease in the same cohort at the 15-year follow-up. DR1 has previously been correlated with markers of severe disease course such as joint erosions and polyarticular course type in patients with oligoarticular onset and with RF-positive polyarticular juvenile arthritis.21;35;174 Few studies have looked at early predictors of long-term active disease, but Bertilsson et al. found that remission at the 5-year follow-up was the most important predictor of remission at 17-year follow-up.128

Changes in disease activity and health status from 15- to 30-year follow-up

We found that physician reported data on disease activity and inflammatory markers improved from 15 to 30 years in the patients with persistently active disease, but patient reported health status was stable. This is in contrast with Zak et al. that reported an increase in disability in 63 JCA patients between the 10-year follow-up in 1979/1980 and 26-year follow-up in 1996/1997.41 Older studies have also showed an increase of disability in patients with juvenile arthritis during the years.12;175 An improvement in disease activity and health status but not in pain has previously been reported after 3 years of follow-up in Norwegian children with juvenile arthritis.176 Corresponding to our study, the HAQ values given at the 5-year follow-up (median children HAQ 0.1, range 0.0-1.9) were similar to the values at the 17-year follow-up (median HAQ 0.0, range 0.0-1.5) in the study by Bertilsson et al.128 Our findings of longitudinally improved markers of disease activity and stability in patient reported health status most probably reflect that the patients are more effectively treated now than 15 years
ago. Overall well-being, disability, damage, and psychosocial effects of the disease may, in addition to disease activity, be integrated into the patient’s global assessment and SF-36. Previous reports have described a poorer HRQoL as measured by SF-36 in young adults with juvenile arthritis compared to matched controls from the general population.33;35;37;54 The lack of improvement in the patient reported measures may be caused by permanent damage to the joints. Preliminary analyses of the radiographs taken of ankles, knees, and wrists gave the impression that joint damage and arthrosis were present in a considerable large part of the patients. This needs to be investigated more thoroughly and will be the focus of future work.

**Medication at 30-year follow-up**

After 30 years, only 56% of the 73 patients with active disease were on DMARDs, prednisolone, and/or anti-TNF treatment, indicating that a relatively large portion of the patients were not satisfactorily treated. This finding was surprising but is in accordance with the study by Bertilsson et al. reporting that only 44% of 36 juvenile arthritis patients who were not in remission after 17 years used DMARDs, biologics, or prednisolone.128 Transition from a department of paediatric to adult rheumatology may have influenced the treatment that the JIA patients received. In a Canadian study of 100 JIA patients, a high rate of unsuccessful transfers from paediatric to adult care was found at a 2-year assessment, despite a coordinated transfer process.177 Patients with less active disease at the time of transfer were identified as most likely to be lost to follow-up. Furthermore, a German study including 654 patients showed that health status deteriorated after discharge from paediatric care in patients with long-standing JIA.178 This issue is an important one that needs to be further addressed.
7. MAIN CONCLUSIONS

- Arterial stiffness and blood pressure were slightly higher in adult JIA patients with long-term active disease compared to controls. A total of 26% of patients had detectable coronary artery calcification, and 7% of these had coronary calcification scores above 10, a frequency no higher than that reported in asymptomatic individuals of comparable age.

- The adult JIA patients with long-term active disease had comparable systolic function but differed from controls in having a thicker interventricular septum and altered diastolic parameters indicating a higher LV filling pressure. Additionally, a higher heart rate as measured by ECG was found in the patients.

- Some traditional cardiovascular risk factors were more prevalent in the adult JIA patients with long-term active disease than in controls, including a higher frequency of daily smoking and arterial hypertension, and higher levels of HOMA-IR and hs-CRP, but the lipid profile was comparable between patients and controls.

- A high inflammatory burden, severe disease, and prolonged daily prednisolone use were associated with higher levels of arterial stiffness, DBP, coronary artery calcification, and LV filling pressure in adult JIA patients with long-term active disease.

- A total of 41% of JIA patients were not in remission off medication after 30 years of disease duration, and 28% had a high symptom state (JADAS3 >4.5).

- The overall remission rates after 15 years were comparable to the rates after 30 years of disease duration. Physician’s assessment of disease activity and inflammatory markers were improved, but patient reported health status was not. DR1, elevated CRP, high physician’s global assessment of disease activity, and a short total time in remission at the 15-year follow-up predicted disease activity at the 30-year follow-up.
Concluding remarks and future perspective

Two issues are important to keep in mind when reading the discussion and the conclusion of this thesis. This study is the first to follow JIA patients for 30 years of disease duration. Our results tell us a lot about the disease outcome after 30 years at this point of time, but in 10-20 years, the story may be different because of the big changes in the medical treatment of JIA today compared to the early 1980s. Nevertheless, none of the medications used today cure JIA, they only attenuate the inflammation.

Second, concerning cardiovascular risk, we may have performed this study too early. The patients had a median age of 39 years, and CVD rarely affects individuals at such young ages. In fact, the European (SCORE) and Norwegian (NORRISK) CVD risk scores do not include in the risk calculators parameters for individuals younger than age 40 years. With this in mind, it is tempting to suggest that our study group will see these patients again in 10-15 years. Follow-up plans concerning cardiovascular risk in this cohort have not yet been made, but without doubt, it would be very interesting to investigate the later clinical implications of the slightly higher subclinical CVD found in JIA patients with active disease for at least 15 years after disease onset.
8. REFERENCES


(117) Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; 18(12):1440-63.


(144) Koca B, Demir T, Kasapcopur O. Use of tissue Doppler and its comparison with other pulse Doppler echocardiography in the evaluation of diastolic functions in patients with active juvenile idiopathic arthritis. *Clin Rheumatol* Published Online First: [23. aug 2014]


(151) Appleton CP, Galloway JM, Gonzalez MS, Gaballa M, Basnight MA. Estimation of left ventricular filling pressures using two-dimensional and Doppler echocardiography in adult patients with cardiac disease. Additional value of analyzing left atrial size, left atrial ejection fraction and the difference in duration of pulmonary venous and mitral flow velocity at atrial contraction. *J Am Coll Cardiol* 1993; 22(7):1972-82.


(177) Hazel E, Zhang X, Duffy CM, Campillo S. High rates of unsuccessful transfer to adult care among young adults with juvenile idiopathic arthritis. *Pediatr Rheumatol Online J* 2010; 8:2.
Minden K, Klotsche J, Niewerth M, Zink A, Horneff G. The health status of patients with Juvenile idiopathic arthritis (JIA) significantly worsens after transfer from pediatric to adult care. *Arthritis Rheum* 2014; 66(11), suppl 2902 (abstract).
EXTENDED REPORT

Arterial haemodynamics and coronary artery calcification in adult patients with juvenile idiopathic arthritis

Hanne A Aulie,1 Anne M Selvaag,1 Anne Günther,2 Vibke Lillevy,1 Øyvind Molberg,1,3 Anders Hartmann,3,4 Hallvard Holdaas,4 Berit Flato1,3

ABSTRACT

Objective To compare arterial haemodynamics in adults with long-term juvenile idiopathic arthritis (JIA) to that of healthy controls, and explore the influence of traditional cardiovascular risk factors and disease characteristics on arterial haemodynamics plus coronary artery calcification.

Methods 87 JIA patients (median age 38.4 years) with persistently active disease at least 15 years after disease onset (registered by longitudinal follow-up), were re-examined after median 29 years and compared with 87 matched controls. Arterial haemodynamics were characterised by arterial stiffness and blood pressure. Sphygmocor was used to measure the arterial stiffness markers pulse wave velocity (PWV) and augmentation index (AIx). Coronary calcification was assessed by CT.

Results Compared to controls, patients had significantly higher PWV (7.2 vs 6.9 m/s, p=0.035), and systolic and diastolic blood pressure (SBP, p=0.050 and DBP, p=0.029). AIx was numerically higher in the patients compared to the controls, but no statistically significant difference was found. Coronary calcification was present in 22 (26%) of the patients. Daily smoking was more frequent (p=0.043), and insulin resistance was higher (p=0.034) in patients than controls.

In patients, DBP, but no disease variables were determinants of PWV. Disease variables as well as traditional cardiovascular risk factors were associated with higher AIx, DBP and the presence of coronary calcification.

Conclusions JIA patients with long-term active disease had altered arterial haemodynamics compared with controls in our study. PWV was mainly determined by increased DBP, a parameter that again was associated with JIA disease and treatment variables.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common inflammatory rheumatic disease in childhood with an annual incidence of approximately 15 per 100 000 children.1 2 About 50% of those affected have active disease when they reach adulthood.3 4 Adult-onset chronic inflammatory arthritides have been strongly associated with an increased risk of cardiovascular disease (CVD),6–8 but cardiovascular risk in long-standing JIA has not been explored.

Non-invasive methods may detect vascular dysfunction as surrogate markers of subclinical CVD. Arterial pulse wave velocity (PWV) is a marker of large arterial stiffness and augmentation index (AIx) reflects arterial stiffness by a combination of pulse wave reflection, left ventricular ejection and heart rate.9 Coronary artery calcification is a marker of coronary atherosclerosis and may be quantified by CT.10 These markers are associated with subsequent CVD and all-cause mortality in diverse populations.11–14 Increased blood pressure (BP) is a well-known risk factor of cardiovascular morbidity and mortality.15

Data on arterial properties in JIA are scarce. Vlahos et al16 found impaired endothelial function in 30 children with JIA compared to controls, and Breda et al recently found an increased carotid intima media thickness in 38 JIA children compared to controls.17 Previous studies on BP in JIA have showed contradictory findings.18–19

The aim of the present study was to identify if JIA patients have increased arterial stiffness and BP by comparing arterial haemodynamics in a cohort of well-characterised adult JIA patients with long-term active disease to that of age-matched and gender-matched controls, and to assess coronary artery calcification in the JIA patients. We also wanted to determine a possible influence of traditional cardiovascular risk factors and JIA disease characteristics on the level of arterial haemodynamics and coronary artery calcification.

PATIENTS AND METHODS

Patients and controls

The 87 JIA patients included were selected from a large JIA cohort described in detail elsewhere.5 20 21 This cohort included 254 JIA patients who were, for the first time, referred to Oslo University Hospital (OUH) from 1980 to 1985, and later examined clinically after median 15 years of disease duration (15-year follow-up), and by mailed questionnaires after median 23 years (23-year follow-up).3 20 21 Medical records had been reviewed for information about variables related to disease onset and early disease course.

After median 29 years of disease duration, the patients who did not have active disease at the 15-year and/or 23-year follow-up, received a mailed questionnaire for the interception of possible patients with relapses. The 134 patients in the original cohort still having active disease at the 15-year, 23-year and/or 29-year follow-up, were invited to participate. Ninety (67%) of the 134 eligible JIA patients consented and were enrolled in
Clinical and epidemiological research

an extended clinical examination at OUH, between May 2011 and March 2012 (29-year follow-up). Thirty-six patients did not respond to the invitation and eight chose not to participate. Three patients were excluded from the study after enrolment because of pregnancy. Retrospective analyses of data from the 134 eligible patients at the 15-year follow-up did not show any differences regarding gender, disease duration, or measures of disease activity and severity between the 87 patients included and the 47 eligible but not participating patients (data not shown). However, the non-participants were median 5.1 years younger than the participants.

Age-matched and gender-matched controls (n=87) were randomly selected from the Norwegian population register. Responders with a history of diabetes mellitus or inflammatory arthritis were not included.

The study was approved by the Regional Ethics Committee for Medical Research, and all participants provided written informed consent according to the declaration of Helsinki (2008).

Clinical examination and cardiovascular risk assessment

Clinical examination of the 87 patients was carried out by a specialist in rheumatology (BF, AMS or VL) and included the 71-joint count, general organ status, and physician’s global assessment of disease activity (10 cm VAS). The patients were classified according to the International League of Associations for Rheumatology classification criteria. Active disease was defined as the absence of remission off antirheumatic medication, and included patients with clinically active disease or inactive disease on antirheumatic medication. Clinical examination of the controls was done by the first author (HAA).

Body Mass Index (BMI) and waist circumference were measured in all participants.

Patients and controls were interviewed about comorbidity and family history of premature CVD, defined as a first-degree relative having CVD before the age of 55 in men and 65 in women. Systolic BP (SBP) and diastolic BP (DBP) were obtained in all participants.

Assessment of arterial stiffness and coronary artery calcification

SphygmoCor apparatus (Atcor Medical, Sydney, Australia) was used to measure PWV and AIX in patients and controls. All assessments were done by the first author (HAA). Participants did not eat, drink (except water) or smoke for at least 3 h before the examination.

To measure PWV, pulse wave forms from the right common carotid artery and the left femoral artery were obtained transcutaneously and gated to an electrocardiogram for the assessment of transit time. The PWV was calculated from the surface distance between the two recording sites divided by the time delay between the feet of the two waveforms. Measurements met the automatic quality control (specified by SphygmoCor apparatus) and the mean from two measurements with a difference of <0.5 m/s was used for calculation.

AIX was defined as the difference between the second and first systolic peaks of the central pressure waveform, expressed as a percentage of the pulse pressure and standardised to a heart rate of 75 bpm. The aortic pressure waveform was estimated from recordings of the radial artery waveform by use of a transfer system. The average of three measurements, all having a quality index score >85%, was used for statistical analysis.

Laboratory assessments

Blood was drawn after an overnight fast in patients and controls and analysed for low density lipoprotein (LDL), high density lipoprotein (HDL), and total cholesterol, triglycerides, high sensitivity C-reactive protein (hs-CRP), glucose, glycated haemoglobin (HbA1c), and insulin. The homeostasis model assessment for insulin resistance (HOMA-IR) was derived from the assessments of insulin and glucose. One JIA patient had diabetes type 2 and was not included in analyses concerning glucose, HbA1c and insulin. Area under the curve (AUC) was calculated either from parameters measured at disease onset, 15-year and the current visits (erythrocyte sedimentation rate (ESR) and plantelets), or at the 15-year and the current visits (CRP).

Statistics

Comparisons between JIA patients and matched controls were done by two-tailed paired sample t test for continuous normally distributed variables, Wilcoxon’s rank sum test for continuous not normally distributed values, and McNemar’s test for categorical variables.

Age-adjusted and gender-adjusted linear regression analyses were used to investigate associations between traditional cardiovascular risk factors as well as disease variables and arterial haemodynamics. To identify determinants of PWV and AIX, candidate factors associated with PWV and AIX in the initial analyses (p<0.12), and age and gender, were tested in the subsequent multivariate analyses with backward deletion of possible determinants. Highly intercorrelated (r>0.7) independent variables were avoided in the multivariate analyses. Missing values in the multiple regression analyses were replaced with mean or median values. No variable had more than 5% missing parameters.

Age-adjusted and gender-adjusted logistic regression analyses were used to investigate associations between traditional cardiovascular risk factors and disease variables, and coronary artery calcification. Agatston score dichotomised to Agatston >0 or Agatston=0 was used as the dependent variable. The strength of the associations was given as ORs with 95% CI.

SPSS V20 (SPSS, Chicago, USA) was used for the statistical analyses.

RESULTS

Demographics and traditional cardiovascular risk factors

Table 1 summarises the patient characteristics.

A higher percentage of the JIA patients than the controls were daily smokers (25% vs 13%, p=0.043, table 2). Arterial
hypothesis was present in 11% of the patients and 2% of the controls (p=0.039). The levels of HOMA-IR and hs-CRP were higher in the patients than the controls (p=0.034 and p=0.001, respectively). The JIA patients reported that they performed more physical activity of moderate intensity than the controls (p=0.001).

**Arterial haemodynamics and coronary artery calcification at 29-year follow-up**

PWV was, on average, 7.2 m/s in the patients and 6.9 m/s in the controls (p=0.035, table 3). Als also tended to be higher in the patients than the controls, but not statistically significant difference was found (p=0.154). The SBP and DBP were higher in patients than controls (p=0.050 and p=0.029, respectively). 22 of 84 JIA patients (26%) had a coronary calcification score above zero, including six patients (7%) with a score above 10, and 16 patients (19%) with a score from 1 to 10. The difference in PWV between the patients and controls was no longer statistically significant when adjusted for DBP.

**Associations between traditional cardiovascular risk factors and arterial stiffness in JIA patients at 29-year follow-up**

In age-adjusted and gender-adjusted linear regression analyses, higher SBP and DBP were associated with increased PWV (p<0.001, table 4) in the JIA patients. Higher pulse rate (p=0.003), lower levels of HDL cholesterol (p=0.050) and elevated blood glucose (p=0.001) were also associated with increased PWV. Higher SBP (p=0.001) and DBP (p<0.001) and less vigorous physical activity (p=0.004) were associated with higher AIs.

**Associations between disease variables assessed at 29-year follow-up and arterial haemodynamics**

In linear regression analyses adjusted for age and gender, higher hs-CRP at 29-year follow-up (β=0.662, p=0.004) was associated with higher AIs in the patients. Patients’ global assessment of wellbeing was associated with increased DBP (β=0.125, p=0.043). Current physician’s global assessment of disease activity, numbers of active and mobility-restricted joints, and use of antitumor necrosis factor (anti-TNF) did not correlate with PWV, AIs or DBP (data not shown).

**Longitudinal and cumulative disease variables related to arterial haemodynamics**

In the JIA patients, none of the disease variables assessed cumulatively or at 15-year follow-up showed any statistically significant association with PWV (table 5). Higher physician’s global

**Table 1 Patient characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>JIA patients (n=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Male gender; n (%)</td>
<td>20 (23)</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>38.4 (34.8–40.6)</td>
</tr>
<tr>
<td>Disease duration (years)*</td>
<td>29.2 (28.2–30.6)</td>
</tr>
<tr>
<td>Onset age (years)*</td>
<td>8.8 (4.7–11.7)</td>
</tr>
<tr>
<td>JIA subtype distribution</td>
<td></td>
</tr>
<tr>
<td>Systemic arthritis; n (%)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>RF negative polyarthritis; n (%)</td>
<td>13 (15)</td>
</tr>
<tr>
<td>RF positive polyarthritis; n (%)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Persistent oligoarthritis; n (%)</td>
<td>15 (17)</td>
</tr>
<tr>
<td>Extended oligoarthritis; n (%)</td>
<td>14 (16)</td>
</tr>
<tr>
<td>Enteritis-related arthritis; n (%)</td>
<td>18 (21)</td>
</tr>
<tr>
<td>Psoriatic arthritis; n (%)</td>
<td>15 (17)</td>
</tr>
<tr>
<td>Unclassified; n (%)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Current medication at 29-year follow-up</td>
<td></td>
</tr>
<tr>
<td>Anti-TNF; n (%)</td>
<td>25 (29)</td>
</tr>
<tr>
<td>Methotrexate; n (%)</td>
<td>19 (22)</td>
</tr>
<tr>
<td>NSAIDs daily; n (%)</td>
<td>23 (26)</td>
</tr>
<tr>
<td>Prednisolone; n (%)</td>
<td>6 (7)</td>
</tr>
</tbody>
</table>

*p Median (IQR).

**Table 2 Traditional cardiovascular risk factors in JIA patients and controls**

<table>
<thead>
<tr>
<th>Variable assessed at 29-year follow-up</th>
<th>JIA patients (n=87)</th>
<th>Controls (n=87)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²); mean (SD)</td>
<td>25.7 (5.3)</td>
<td>25.9 (4.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Waist circumference (cm); mean (SD)</td>
<td>92.6 (13.0)</td>
<td>94.2 (11.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Current smokers; n (%)</td>
<td>30 (35)</td>
<td>26 (30)</td>
<td>NS</td>
</tr>
<tr>
<td>Daily smokers; n (%)</td>
<td>22 (25)</td>
<td>11 (13)</td>
<td>0.043</td>
</tr>
<tr>
<td>Ever smokers; n (%)</td>
<td>47 (55)</td>
<td>53 (61)</td>
<td>NS</td>
</tr>
<tr>
<td>Pack-years of smoking (years)*</td>
<td>0.1 (0.0–9.0)</td>
<td>0.1 (0.0–6.2)</td>
<td>NS</td>
</tr>
<tr>
<td>CVD in first degree relative; n (%)</td>
<td>50 (58)</td>
<td>41 (47)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension; n (%)</td>
<td>10 (11)</td>
<td>2 (2)</td>
<td>0.039</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L); mean (SD)</td>
<td>4.8 (1.1)</td>
<td>5.0 (0.9)</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L); mean (SD)</td>
<td>3.0 (1.0)</td>
<td>3.0 (0.9)</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L); mean (SD)</td>
<td>1.5 (0.4)</td>
<td>1.4 (0.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mmol/L); mean (SD)</td>
<td>1.0 (0.7)</td>
<td>1.0 (0.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Glucose (mmol/L); mean (SD)</td>
<td>5.2 (0.5)</td>
<td>5.1 (0.5)</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1c; mean (SD)</td>
<td>5.4 (0.3)</td>
<td>5.4 (0.4)</td>
<td>NS</td>
</tr>
<tr>
<td>HOMA-IR*</td>
<td>0.9 (0.4–1.4)</td>
<td>0.6 (0.4–1.1)</td>
<td>0.034</td>
</tr>
<tr>
<td>hs-CRP (mg/L)*</td>
<td>1.8 (0.8–5.2)</td>
<td>0.9 (0.01–2.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Vigorous physical activity (hours/week)*</td>
<td>2.0 (0.5–4.0)</td>
<td>1.9 (0.3–3.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Moderate physical activity (hours/week)*</td>
<td>2.0 (1.0–4.0)</td>
<td>1.0 (0.1–2.0)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*p Median (IQR).

BMI, Body Mass Index; CVD, cardiovascular disease; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; HOMA-IR, the homeostasis model assessment for insulin resistance; hs-CRP, high sensitivity C-reactive protein; JIA, juvenile idiopathic arthritis; LDL, low density lipoprotein; NS, not statistically significant.

**Table 3 Arterial haemodynamics and coronary artery calcification scores**

<table>
<thead>
<tr>
<th>Variables assessed at 29-year follow-up</th>
<th>N</th>
<th>JIA patients</th>
<th>Controls</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PWV (m/s); mean (SD)</td>
<td>78</td>
<td>7.2 (1.0)</td>
<td>6.9 (0.8)</td>
<td>0.035</td>
</tr>
<tr>
<td>AIs; mean (SD)</td>
<td>79</td>
<td>14.5 (10.8)</td>
<td>12.0 (12.2)</td>
<td>0.154</td>
</tr>
<tr>
<td>Pulse (bpm); mean (SD)</td>
<td>87</td>
<td>62.7 (10.7)</td>
<td>61.8 (9.7)</td>
<td>0.564</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg); mean (SD)</td>
<td>87</td>
<td>119.4 (14.5)</td>
<td>115.7 (9.8)</td>
<td>0.050</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg); mean (SD)</td>
<td>87</td>
<td>75.7 (10.3)</td>
<td>72.7 (8.2)</td>
<td>0.029</td>
</tr>
<tr>
<td>Coronary artery calcification, Agatston score 1–10; n (%)</td>
<td>84</td>
<td>16 (19)</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>Coronary artery calcification, Agatston score &gt;10; n (%)</td>
<td>84</td>
<td>6 (7)</td>
<td>Not assessed</td>
<td></td>
</tr>
</tbody>
</table>

AIs was normalised to a heart rate of 75 bpm.

A, augmentation index; JIA, juvenile idiopathic arthritis; PWV, pulse wave velocity.

Clinical and epidemiological research

Table 4: Associations between traditional cardiovascular risk factors and arterial stiffness in JIA patients

<table>
<thead>
<tr>
<th>Variables assessed at 29-year follow-up</th>
<th>Linear regression analyses*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PWV</td>
</tr>
<tr>
<td></td>
<td>β</td>
</tr>
<tr>
<td>Age (unadjusted)</td>
<td>0.044</td>
</tr>
<tr>
<td>Male gender (unadjusted)</td>
<td>0.677</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>0.017</td>
</tr>
<tr>
<td>BMI</td>
<td>0.042</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.038</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.056</td>
</tr>
<tr>
<td>Pulse</td>
<td>0.033</td>
</tr>
<tr>
<td>CVD in first degree relative</td>
<td>0.381</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>−0.609</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.263</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.105</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.715</td>
</tr>
<tr>
<td>HbA1c</td>
<td>0.650</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.136</td>
</tr>
<tr>
<td>Package years</td>
<td>−0.004</td>
</tr>
<tr>
<td>Daily smoking</td>
<td>−0.081</td>
</tr>
<tr>
<td>Vigorous physical activity</td>
<td>−0.086</td>
</tr>
<tr>
<td>Moderate physical activity</td>
<td>−0.018</td>
</tr>
</tbody>
</table>

*Results of linear regression analyses with Alx and PWV as dependent variables, adjusted for age and gender (unless stated otherwise).

Determinants of arterial stiffness

Determinants of PWV and Alx in the patients were identified by multiple linear regression analyses. Parameters associated with PWV or Alx in the age-adjusted and gender-adjusted regression analyses were assessed (see tables 4 and 5 and online supplementary table S1). DBP was the only determinant of PWV (p=0.001), explaining 36% of the PWV variation (table 6). Determinants of Alx were: age (p=0.002), female gender (p<0.001), DBP (p<0.001), daily smoking (p=0.006), less vigorous physical activity (p=0.001), platelets AUC (p=0.035), number of joints with limited range of motion at 13-year follow-up (p=0.005), and years on prednisolone (p=0.040). These variables explained 58% of the Alx variation.

Factors associated with coronary artery calcification

Logistic age-adjusted and gender-adjusted regression analyses demonstrated that increased levels of waist circumference (OR=1.05; 95% CI 1.00 to 1.10), BMI (OR=1.13; 95% CI 1.01 to 1.26), SBP (OR=1.05; 95%CI 1.01 to 1.10), glucose (OR=3.26; 95%CI 1.08 to 9.79), and years on daily prednisolone (OR=1.14; 95%CI 1.02 to 1.27), were related to coronary calcification (score >0) in the JIA patients.

DISCUSSION

In the present study, JIA patients with long-term active disease had slightly increased arterial stiffness assessed by PWV compared with matched controls. DBP and SBP were also increased in the JIA patients, while Alx was numerically, but not statistically significantly higher. Coronary artery calcifications were

Table 5: The relation between cumulative or longitudinal JIA disease variables and arterial haemodynamics

<table>
<thead>
<tr>
<th>Variables assessed at 15-year follow-up</th>
<th>Linear regression analyses*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PWV</td>
</tr>
<tr>
<td></td>
<td>β</td>
</tr>
<tr>
<td>Physician’s global assessment of disease activity, Likert scale</td>
<td>−0.159</td>
</tr>
<tr>
<td>Patients’ global assessment of wellbeing, Likert scale</td>
<td>−0.127</td>
</tr>
<tr>
<td>Number of active joints</td>
<td>−0.017</td>
</tr>
<tr>
<td>Number of joints with limited range of motion</td>
<td>−0.010</td>
</tr>
<tr>
<td>Joint erosions</td>
<td>−0.313</td>
</tr>
<tr>
<td>Duration of active disease (years)</td>
<td>−0.096</td>
</tr>
<tr>
<td>Cumulative variables assessed during 29 years of disease activity</td>
<td></td>
</tr>
<tr>
<td>CRP, area under the curve</td>
<td>0.001</td>
</tr>
<tr>
<td>Platelets, area under the curve</td>
<td>0.001</td>
</tr>
<tr>
<td>ESR, area under the curve</td>
<td>0.006</td>
</tr>
<tr>
<td>Ever used prednisolone</td>
<td>−0.297</td>
</tr>
<tr>
<td>Years on daily prednisolone</td>
<td>0.008</td>
</tr>
<tr>
<td>Years on daily NSAIDs</td>
<td>−0.001</td>
</tr>
<tr>
<td>Ever used Methotrexate</td>
<td>0.115</td>
</tr>
</tbody>
</table>

*Results of linear regression analyses adjusted for age and gender, with PWV, Alx and DBP as dependent variables.

†Calculated from parameters assessed at 15-year and 29-year follow-up.

‡Calculated from parameters assessed at disease onset, 15-year and 29-year follow-up.
found in 26% of the patients. PWV was mainly determined by increased DBP, a parameter that again was associated with JIA disease and treatment variables. AIx was determined by traditional cardiovascular risk factors, physical activity, inflammatory variables, disease severity, and received antirheumatic medication. To our knowledge, this is the first study presenting data on cardiovascular risk in adults with JIA.

PWV, but not AIx was increased in the JIA patients compared to the controls. AIx and PWV are both indexes of arterial stiffness but cannot be used interchangeably. While carotid-femoral PWV is a direct measure of large arterial stiffness, AIx is an indirect measure of arterial stiffness that quantifies the combination of the amplitude from the reflected peripheral wave, the forward pressure from left ventricular contraction and the heart rate. AIx is found to have predictive value for CVD in selected diseases, but PWV is accepted as the ‘gold standard’ for the assessment of arterial stiffness because of its well-documented ability to predict CVD.

The mean PWV in the patients was 7.2 m/s, a value lower than what has been considered clinically significant (10 m/s) for the prediction of cardiovascular events. However, our patients were only median 38.4 years, 25 years younger than the general population this threshold represents. The difference in mean PWV between patients and controls was 0.3 m/s, and the clinical significance of such a small difference is unclear. Recent data from a meta-analysis showed that a 1 m/s increase of PWV corresponded to a 15% increased risk of cardiovascular and all-cause mortality, suggesting that a 0.3 m/s increase of PWV may be associated with increased cardiovascular risk.

Data on arterial stiffness in JIA have been limited to two studies. Vlahos et al found no difference in PWV in 30 children and adolescents with JIA compared to controls. By contrast, Argyropoulou et al found increased PWV as measured by MRI in 31 children and young adults with JIA. However, the method used by Argyropoulou et al was different from the one used in our study, and both studies were mainly done in children.

Some traditional cardiovascular risk factors, such as daily smoking, arterial hypertension and insulin resistance were increased in the JIA patients compared to the controls. We cannot exclude that these traditional risk factors have influenced the increased PWV measured in the patients. On the other hand, most traditional cardiovascular risk factors, such as BMI, waist circumference, pack-years of smoking, CVD in the family, and serum cholesterol profiles were comparable between the patients and the controls.

Our finding of increased daily smoking is in contrast with an earlier case-control on adolescents with JIA. Studies on serum cholesterol levels in JIA have shown conflicting results, but these studies have mainly been done in children. There are no previous data on insulin resistance in JIA patients.

Interestingly, SBP and DBP at 29-year follow-up were higher in our patients compared to the controls. BP correlated with AIx, PWV and coronary calcification. The difference in PWV between patients and controls was no longer statistically significant when adjusted for DBP demonstrating that the higher DBP in our JIA group has contributed to the increased PWV.

Previous studies on the level of BP in JIA patients have yielded contradictory findings, but these studies included mostly children. Hypertension and BP have been associated with increased arterial stiffness in the general population. On the other hand, aortic stiffness has been identified as a predictor of future hypertension in normotensive individuals indicating a bidirectional relationship of arterial stiffness and hypertension.

This study is the first on coronary artery calcification in JIA. While 26% of the patients had detectable coronary calcification, 7% had coronary calcification scores above 10. This frequency is not different from what has been found in a large study including asymptomatic individuals of comparable age.

Several parameters of cumulative inflammatory burden (duration of active disease, CRP AUC and platelets AUC) were associated with AIx, but not with PWV. ESR AUC was associated with increased DBP. Similar results were found in a recent follow-up study of rheumatoid arthritis (RA) patients. CRP has also been demonstrated to be a strong predictor of CVD in healthy individuals. Our finding is in accordance with the study by Argyropoulou who did not find any association between CRP nor use of antirheumatic medication and PWV.

We found that treatment with prednisolone was a predictor of AIx and a correlate to DBP and coronary calcification. The net effects of antirheumatic medication on CVD risk is not easy to evaluate since the possible cardioprotective effect of reducing

---

Table 6: Determinants of arterial stiffness in adults with JIA

<table>
<thead>
<tr>
<th>Variables assessed at 29-year follow-up</th>
<th>PWV (n=78)</th>
<th>AIx (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>SE</td>
</tr>
<tr>
<td>Constant</td>
<td>1.561</td>
<td>1.142</td>
</tr>
<tr>
<td>Age</td>
<td>0.021</td>
<td>0.025</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.445</td>
<td>0.230</td>
</tr>
<tr>
<td>Variables assessed at 29-year follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.056</td>
<td>0.010</td>
</tr>
<tr>
<td>Daily smoking</td>
<td>5.757</td>
<td>2.700</td>
</tr>
<tr>
<td>Vigorous physical activity</td>
<td>−1.307</td>
<td>0.369</td>
</tr>
<tr>
<td>Cumulative and longitudinally variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets, area under the curve</td>
<td>0.013</td>
<td>0.006</td>
</tr>
<tr>
<td>Number of joints with limited range of motion at 15-year follow-up</td>
<td>0.324</td>
<td>0.112</td>
</tr>
<tr>
<td>Years on daily prednisolone</td>
<td>0.433</td>
<td>0.207</td>
</tr>
</tbody>
</table>

*Final model of multiple linear regression analyses with backward deletion of possible determinants of higher AIx and PWV. Variables associated with PWV and AIx in the age-adjusted and gender-adjusted linear regression analyses (p<0.12, see tables 4 and 5 and online supplementary table S1) as well as age and gender were analysed. R² for PWV=0.364 and for AIx=0.577.

AIx, augmentation index; JIA, juvenile idiopathic arthritis; PWV, pulse wave velocity.
inflammation may be counterbalanced by drug side effects or the possible influence of disease severity as marked by extended medication. Our findings correspond to the literature where use of corticosteroids has been associated with increased risk of hypertension and myocardial infarction in RA patients.36–48

Analyses of self-reported measures of physical activity indicated that vigorous physical activity was associated with decreased AIX in our patients. Although these data should be interpreted with caution, they suggest that performing physical activity may have a preventive cardiovascular effect in JIA patients.

The strength of this study is the thorough collection of comprehensive data in a well-defined cohort of JIA patients presenting new knowledge of arterial haemodynamics and cardiovascular risk profile in adults with JIA. The limitation is the small number of participants and their young age that made the comparison of cardiovascular events and atherosclerosis difficult. In this study, adults with JIA had slightly increased PWV, a marker of large artery stiffness, compared with controls, and 26% had coronary artery calcification. JIA patients had higher BP than controls, and DBP was the most consistent correlate of PWV. None of the disease variables correlated with PWV, but JIA disease and treatment variables were associated with AIX and DBP.

Acknowledgements Torbild Garen for her help with preparation of questionnaires, Cathrine Brunborg for statistical support, Lars Markrid for valuable help obtaining laboratory assessments and Inge-Margrethe Gilboe for administrative support.

Contributors The corresponding author confirms that all the individuals listed as authors fulfill the uniform authorship credit requirements for manuscripts submitted to medical journals, that is, that they all contributed to the manuscript based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published.

Funding The project received financial support from the Norwegian Foundation for Health and Rehabilitation.

Competing interest None.

Patient consent Obtained.

Ethics approval The Regional Ethics Committee for Medical Research (Helse Sør-Øst).

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES


Arterial haemodynamics and coronary artery calcification in adult patients with juvenile idiopathic arthritis

Hanne A Aulie, Anne M Selvaag, Anne Günther, Vibke Lilleby, Øyvind Molberg, Anders Hartmann, Hallvard Holdaas and Berit Flato

Ann Rheum Dis published online April 2, 2014

Updated information and services can be found at:
http://ard.bmj.com/content/early/2014/04/02/annrheumdis-2013-204804

These include:

Supplementary Material
Supplementary material can be found at:
http://ard.bmj.com/content/suppl/2014/04/02/annrheumdis-2013-204804.DC1.html

References
This article cites 47 articles, 22 of which you can access for free at:
http://ard.bmj.com/content/early/2014/04/02/annrheumdis-2013-204804#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections
Connective tissue disease (3871)
Degenerative joint disease (4213)
Immunology (including allergy) (4642)
Musculoskeletal syndromes (4503)
Rheumatoid arthritis (2955)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/
Cardiac function in adult patients with juvenile idiopathic arthritis

Hanne A Aulie, Mette E Estensen, Anne M Selvaag, Vibke Lilleby, Klaus Murbraech, Berit Flatø, Svend Aakhus

Abstract

Objective

To compare cardiac function in adults with long-term juvenile idiopathic arthritis (JIA) with that of healthy controls, and investigate the influence of inflammation, disease severity and use of anti-rheumatic medication on cardiac function.

Methods

85 JIA patients (median age 38.6 years) with active disease for at least 15 years were re-examined median 29 years after disease onset and compared to 46 matched controls. Echocardiography, including tissue Doppler imaging and longitudinal peak-systolic global strain, was used to assess diastolic and systolic myocardial function, and a 12-channel electrocardiography was performed.

Results

The interventricular septum was thicker in patients than controls (mean±SD 0.8±0.2 versus 0.7±0.1 cm, p=0.036). Diastolic function in patients was altered compared to controls characterized by lower mitral E wave deceleration time (165±36 versus 180±40 ms, p=0.029), higher surrogate marker of left ventricular (LV) filling pressure (median lateral E/e´ 5.3, IQR 4.6-6.3, versus 4.8, 3.9-5.7, p=0.036), and larger left atrial area (16.4±2.9 versus 15.1±2.8 cm², p=0.015). Systolic and diastolic blood pressures were higher in patients (120±15 versus...
114±9 mmHg, p=0.021, and 76±10 versus 71±8 mmHg, p=0.009, respectively). QT corrected interval was similar in patients and controls.

High hs-CRP, polyarticular disease course and extended joint affection at 29-year follow-up as well as duration of active disease, cumulative ESR and CRP, and prednisolone use were associated with higher lateral E/e´.

**Conclusion**

Adult JIA patients did not differ from controls in LV systolic function, but had mildly thicker interventricular septum and indications for higher LV filling pressure, and most in patients with a higher disease burden.

**Key Indexing terms:** Juvenile idiopathic arthritis, Cardiovascular diseases, Echocardiography, Inflammation.

**Authors:**

Aulie HA MD, Estensen ME MD PhD, Selvaag AM MD PhD, Lilleby V MD PhD, Murbraech K MD, Flatø B MD PhD, Aakhus S MD PhD

1. Department of Rheumatology, Oslo University Hospital, Rikshospitalet, Oslo, Norway
2. Department of Cardiology, Oslo University Hospital, Rikshospitalet, Oslo, Norway
3. Institute for Clinical Medicine, Medical Faculty, University of Oslo, Oslo, Norway

**Funding statement:** This work was supported by grants from the Norwegian Foundation for Health and Rehabilitation, the Scandinavian Rheumatology Research Foundation, and from Eimar Munthes Minnefond.
Author correspondence (including request for reprints) to:

Hanne Aaserud Aulie, MD, Department of Rheumatology, Oslo University Hospital, Rikshospitalet. Postboks 4950 Nydalen, 0424 Oslo, Norway
Telephone: 0047 91165712
Fax nr: 0047 23072370
Email: hanaul@ous-hf.no

Word count of manuscript: 3051

Conflict of interest: No conflicts of interest.
INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory rheumatic disease that is diagnosed in childhood and has an annual incidence of approximately 15 cases per 100,000 children (1;2). About 50% of the patients have active disease when they reach adulthood (3-5). We have recently reported that 41% of the patients in the present cohort had active disease or used anti-rheumatic medication 30 years after disease onset (6).

Patients with adult-onset rheumatoid arthritis (RA) have an increased risk of congestive heart failure and a higher prevalence of diastolic dysfunction compared to individuals without RA (7-9). Recently, an association between inflammation and a prolonged corrected QT (QTc) interval was found in RA patients, and a higher QTc was correlated with all-cause mortality (10).

Whilst we previously have reported an increased prevalence of hypertension and altered arterial properties in adults with long-standing JIA (11), cardiac function in adults with long-standing JIA has, to the best of our knowledge, not been assessed.

Tissue Doppler imaging (TDI) by echocardiography enables the evaluation of both systolic and diastolic myocardial function in addition to the traditional parameters such as ejection fraction (EF) and mitral flow velocities (12;13). The longitudinal peak-systolic global strain derived from 2-D speckle tracking analysis provides additional information on regional and global myocardial function (14).

The aims of the present study were to compare the cardiac function in adult JIA patients with long-term active disease to that of age- and gender matched controls and to assess whether a larger inflammatory burden, more severe disease or the use of anti-rheumatic medication had an adverse effect on cardiac function.

PATIENTS AND METHODS
Patients and controls

The cohort of 254 patients from which the 85 included patients were selected has previously been described in detail (3;6;15;16). Comprehensive information about the selection criteria for this study has been presented earlier (11). Briefly, the patients were initially referred to Oslo University Hospital (OUH) between 1980 and 1985. Subsequently, they were examined clinically after a median of 15 years of disease duration and by a mailed questionnaire after a median of 23 years. The 134 patients with clinically active disease at the 15-year, 23-year and/or 29-year follow-ups were invited to participate in the present study. Ninety patients (67%) consented and were enrolled in the study between May 2011 and March 2012 (29-year follow-up). Five patients were excluded after inclusion because of pregnancy (n=3), technical complications (n=1) or severe heart disease without relation to JIA (n=1). Retrospective analyses of the data from the 134 eligible patients at the 15-year follow-up did not demonstrate any differences concerning gender, disease duration, or parameters of disease activity and severity between the 85 patients included and the 49 eligible but not participating patients (data not shown). However, the participants were a median of 5.1 years older than the nonparticipants.

Forty-six healthy controls matched for age and gender were randomly selected from the Norwegian population register. Responders with a history of diabetes mellitus, hypertension, previous cardiovascular events, or inflammatory arthritis were not allowed into the control group.

The study was approved by the Regional Ethics Committee for Medical Research, and written informed consent according to the Declaration of Helsinki (2008) was obtained from all the participants.

Clinical examination and cardiovascular risk assessment

Cardiac function in JIA
A specialist in rheumatology (BF, AMS or VL) performed a clinical examination of the 85 patients including the 71 joint count, the physician’s global assessment of disease activity (10 cm visual analogue scale) and general organ status. The International League of Associations for Rheumatology classification criteria was used to classify JIA (17). Active disease was defined as the lack of remission off anti-rheumatic medication (18). For the subgroup analyses, the patients who had cumulatively involvement of more than 4 joints during their disease course were included in the polyarticular course type, and the patients with involvement of 4 joints or less were included in the oligoarticular course type. The controls were clinically examined by one investigator (HAA).

Information regarding comorbidities and a family history of premature cardiovascular disease (CVD), which was defined as a first degree relative having CVD before the age of 65 years in women and 55 years in men, were obtained by interviewing the participants. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured after 5 minutes rest in a supine position. Three measurements with a difference of <5 mmHg were averaged. The presence of arterial hypertension was defined as SBP >140, DBP >90 mmHg, and/or the use of antihypertensive medication. Waist circumference was measured and body mass index was calculated in all the participants.

**Echocardiography**

We performed a standard transthoracic echocardiographic examination of the patients and controls using a Vivid 7 or E9 ultrasound scanner (GE Vingmed Ultrasound, Horten, Norway) as recommended (19). All the recordings were measured after at least 5 minutes rest, and 3 consecutive heart cycles were stored for off-line analyses in dedicated software EchoPAC vs 1.1.12, GE Vingmed Ultrasound). Pulse-wave Doppler with the sample volume at the aortic annulus and the tip of mitral leaflets (apical position) was used to obtain the blood flow
velocity in the left ventricular (LV) outflow tract and mitral inflow, respectively. The LV dimensions were measured after convention from parasternal M-mode registrations (20). The left atrial (LA) area was obtained from the four-chamber view. Pulsed-wave Doppler was used to measure early (E) and late (A) transmitral diastolic flow velocities (supplementary file, figure 2) from which the transmitral E/A ratio was calculated. The E-wave deceleration time (DT) and the isovolumic relaxation time (IVRT) were recorded (21). The LV mitral annular velocities in systole (LV s´) and early diastole (LV e´), were measured in the septal and lateral mitral annulus with colour TDI (supplementary file, figure 2). The E/e´ ratio, a surrogate marker of LV filling pressure, was calculated (22). The LV end-diastolic volume and EF were measured by Simpson’s modified biplane rule (20). The global longitudinal myocardial strain was measured to obtain regional and global myocardial function (14).

All the echocardiographic recordings and analyses were performed by one investigator (HAA) at the echocardiographic laboratory OUH Rikshospitalet. The off-line data reanalyses were blinded for clinical information and patient/control identity. All the parameters were averaged from three heart cycles, except for the global longitudinal strain, which was derived from the analyses of single beat recordings of 3 apical image projections. Intraobserver reproducibility of echocardiographic parameters was assessed by one observer’s analysis of two independent echocardiograms from 25 consecutive patients. Reproducibility was assessed in our laboratory by a technician’s repeat analysis of echocardiograms with >2 weeks interval, expressed as the coefficient of repeatability (CR), (i.e. 1.96 x SD of difference between observers) (23).

Electrocardiography (ECG)

The patients and controls underwent a standard 12-channel ECG recording. The ECG recordings were reviewed for abnormalities such as QTc prolongation, bundle branch
blockage, T wave abnormalities, and chamber enlargement by a reader blinded for patient/control identity. The rhythm, PR-interval, QRS duration, and QTc interval were registered.

**Questionnaire**

A questionnaire including data on smoking habits and physical activity was completed by all the participants. The total work and leisure time physical activity of vigorous and moderate intensities were measured by the short International Physical Activity Questionnaire (24;25).

**Laboratory assessments**

Blood samples were collected after an overnight fast in the patients and controls and were analysed for total cholesterol, triglycerides, high sensitivity C-reactive protein (hs-CRP), glucose, glycated haemoglobin (HbA1c), and prohormone of brain natriuretic peptide. One JIA patient had diabetes type 2 and was excluded from the analyses concerning glucose and HbA1c. The erythrocyte sedimentation rate (ESR) area under the curve (AUC) was calculated from parameters measured at disease onset, 15- and 29-year follow-ups. The CRP AUC was calculated from the parameters assessed at the 15- and 29-year follow-ups.

**Statistics**

The differences between the JIA patients and matched controls and between the 2 patients groups were tested by an independent sample $t$-test for the continuous normally distributed variables, the Mann-Whitney $U$-test for the continuous not normally distributed values, and the $\chi^2$ test for the categorical variables. Central tendencies were presented as the mean±SD for the continuous normally distributed variables, and as the median and interquartile range for the continuous not normally distributed values.
Spearman’s correlation was used to investigate the association between cumulative inflammatory burdens, years on prednisolone, and lateral E/e´ at the 29-year follow-up. To identify the predictors of lateral E/e´, the candidate factors associated with lateral E/e´ in Spearman’s correlation analysis (p<0.05) and age and gender were tested in a subsequent multivariate analysis with the backward deletion of possible determinants. The p values <0.05 (2 tailed) were regarded as statistically significant for all the analyses. SPSS Version 20 (SPSS, Chicago) was used for the statistical analyses.

RESULTS

Demographics and cardiovascular risk factors
The patient characteristics are summarised in table 1. Hypertension was present in 11% of the patients, and the SBP and DBP were higher in the patients than in the controls (p=0.021 and p=0.009, table 2). One of the patients had a previous myocardial infarction. The level of hs-CRP was increased in the patients compared to the controls (p=0.001). The JIA patients reported participating in more physical activity of a moderate intensity than the controls (p=0.046).

LV morphology and function in patients and controls
Of the 85 JIA patients, one had a moderate aortic regurgitation, and one had a moderate tricuspid regurgitation. Of the 46 controls, 3 had a mild to moderate mitral regurgitation. No other abnormalities were found.

In general, the patients and controls were comparable concerning the parameters of systolic function (table 3). However, the interventricular septum diameter (IVSd) was thicker in the patients than in the controls (p=0.036). The echocardiographic parameters of diastolic function were within the normal range for the patients (table 4). Seventy-five patients had

Cardiac function in JIA
normal E/e´ values (<8), 8 patients had borderline elevated values (8-12), and none of the patients had values above 12. However, compared to the controls, the mitral E wave DT was lower (p=0.029), and the lateral E/e´ and LA area were higher (p=0.036 and p=0.015) in the patients.

Intra-observer reproducibility for echocardiographic parameters was good with CR for IVSd: 0.2 cm, LVIDd: 0.3 cm, FS: 5,7%, e´ septal: 3 cm/s, E: 0.2 m/s, E/A: 0,9, E/e´: 0,2, DT: 61 ms, EF: 7,2%, EDV: 21,2 mL.

The influence of the inflammatory burden and disease severity on LV diastolic function
Lateral E/e´ was higher in the patients with hs-CRP ≥2 mg/L, a polyarticular disease course and/or ≥3 joints with a limited range of motion (LROM) at the 29-year follow-up than in patients with less severe disease (p=0.004, p=0.050 and p=0.016 respectively, figure 1).

A longer duration of active disease was positively correlated with the E/A ratio and the lateral E/e´ in the patients (p=0.011 and p=0.023, table 5). Additionally, higher ESR AUC and CRP AUC, and more years on daily prednisolone correlated with a higher lateral E/e´ (p=0.042, p=0.033 and p=0.021 respectively).

The predictors of lateral E/e´ in the patients were identified by multiple linear regression analyses. The parameters significantly associated with lateral E/e´ in Spearman’s correlation analysis (see table 5) and age and gender were analysed. Age (p=0.010) and the duration of active disease (p=0.046) were identified as predictors of lateral E/e´ (data not shown).

ECG findings in patients and controls
ECGs were recorded from 73 patients and 46 controls. Two patients had pathologic ECGs, i.e. Wolff-Parkinson-White syndrome (1 patient) and LV hypertrophy (1 patient). Four patients
had borderline ECGs (unspecific STT alterations). All the controls had normal ECGs. There was no difference in the QTc interval between the patients and the controls (418±20 versus 415±17 ms, p=0.409). The heart rate was higher in the patients than in the controls (68±13 versus 60±8 beats/minute, p=0.001).

DISCUSSION
In the present follow-up study of JIA patients with long-term active disease, we found that the patients had a slightly altered LV morphology and diastolic function but similar systolic function compared to the matched controls. The diastolic function was more impaired in the patients with a higher disease burden, i.e. high hs-CRP, a polyarticular disease course, and/or numerous joints with LROM. Additionally, disease variables reflecting the cumulative inflammatory burden such as a long duration of active disease, CRP and ESR AUC, and long-term prednisolone use were significantly correlated with a higher lateral E/e´. To our knowledge, this is the first study evaluating cardiac function in adults with long-term JIA.

The finding of a comparable LV systolic function in patients and controls contrasts reports from Oguz et al. and Bharti et al. who found an impairment of LV systolic function, which was reflected by a decreased EF, in children and adolescents with JIA (26;27). Furthermore, Bharti et al. and Alkady et al. have reported a larger end-diastolic diameter in children with JIA compared to controls (26;28). All the values were within normal limits in these studies (26-28).

The interventricular septum was slightly thicker in the patients than in the controls in our study, which might be associated with the mildly higher BP in the patient group (29).

Diastolic function is mainly dependent on myocardial relaxation and LV load (30). The similar transmural E and A velocities, and IVRT in the patients and controls indicate that LV relaxation was not affected in the JIA patients (21). However, the lower mitral DT

Cardiac function in JIA
combined with the higher (lateral) E/e´ ratio and the larger LA area indicate that the JIA patients had higher LV filling pressures than the controls (22;31;32). An increased LV filling pressure is usually associated with diastolic dysfunction and heart failure (33;34). Although the diastolic parameters in the JIA patients were all within normal limits, the deviation from the control values indicates a marginal but definite impairment of diastolic LV function.

Previous studies in children and adolescents with JIA have reported an impairment of diastolic function expressed by a decreased transmitral E/A ratio and a longer IVRT, which usually indicates an alteration in LV relaxation properties (26;28;35;36). Our study confirms the finding of an increased E/e´ in JIA children compared to controls from the latest study by Koca et al. (36). However, most of the previous studies were conducted in children (mean age 9-15 years), and in the studies by Bharti et al. and Alkady et al., more than 20% of the patients were in the systemic JIA category. This compared to our data with a frequency of 5%, which is representative of the prevalence of systemic JIA in Scandinavia.

The data on the pathogenesis linking inflammation and diastolic dysfunction are limited. Recently, it has been proposed that systemic inflammation may induce oxidative stress in the coronary microvascular endothelium, causing stiffening and hypertrophy of the cardiomyocytes, which leads to increased LV diastolic stiffness (37). Small vessel ischemic disease could also have contributed to the findings of a higher LV filling pressure in our study. However, the definite mechanism for diastolic dysfunction in JIA remains elusive and calls for further study.

The ECG evaluation showed that the QTc interval was equal in both the patients and the controls. The higher heart rate found in the patients causes less time for myocardial relaxation and may be explained by inflammation. Our study confirms the findings of Koca et al. who did not find any difference in the QTc interval in 50 children and adolescents with JIA compared to controls (35).
Interestingly we observed that the diastolic function was more impaired in the patients who had experienced a larger burden of inflammation, more severe disease and prolonged daily prednisolone use compared to the patients with less severe disease. This suggests a relationship between immune dysregulation and subclinical diastolic dysfunction in JIA, and one might speculate whether today’s aggressive treatment approach for the suppression of systemic inflammation in JIA is also instrumental for the prevention of cardiovascular disease in these patients.

The results found in the present study correspond to the previously reported associations between JIA disease and treatment variables and markers of arterial stiffness and DBP found in the same patient cohort (11). Prior studies have evaluated the association between inflammation and cardiac function. Liang et al. found a correlation between interleukin-6 and diastolic dysfunction in RA patients in a large echocardiographic study (38), and an elevated CRP has been shown to be an independent predictor for the deterioration of myocardial function in asymptomatic adult individuals without cardiovascular disease (39). The association between corticosteroids and CVD is difficult to measure because treatment with corticosteroids increases the risk of hypertension and myocardial infarction in RA patients (40-42), but functions cardio-protectively by reducing inflammation.

Strengths and limitations of the study

The strengths of this study are the long-term follow-up of a well-defined cohort of JIA patients and the presentation of novel data on cardiac function obtained by the blinded evaluation of comprehensive echocardiographic recordings. However, there are several limitations. Because multiple comparisons were performed, there is an inherent risk for type I statistical error. Nevertheless, the consistent difference from the controls in the echocardiographic parameters of diastolic dysfunction in the patients supports the validity of

Cardiac function in JIA
the findings. The number of patients included in our study was relatively small. However, the present study remains the largest on cardiac function in JIA patients. Because a cross-sectional study design was used for this cohort, the statistical relationships found indicate associations between parameters and not necessarily any causal relationships.

The reproducibility for echocardiographic data is representative for the laboratory responsible for all echocardiographic data in the present study. Although recording and analysis of echocardiograms were obtained by one observer (HAA), this observer complied with the laboratory standards and was supervised in this context. Thus, we think the reproducibility data given are valid for the present study.

In conclusion, adult JIA patients with long-term active disease have comparable systolic function, but differ from controls in that they have a thicker interventricular septum and their diastolic parameters indicate a higher LV filling pressure. However, because the parameters for cardiac morphology and diastolic function in JIA patients are all within the normal range, the alterations are subclinical and do not infer specific treatment. There was an indication of higher LV filling pressures in the JIA patients with a large inflammatory burden, severe disease and prolonged daily prednisolone use compared to the patients with less severe disease. These results point to a relationship between immune dysregulation and subclinical diastolic dysfunction in JIA and suggest the necessity of increased awareness for cardiovascular symptoms in patients with severe JIA.
Acknowledgements: The authors would like to thank Pia Elisabeth Bryde, Richard Massey and Lene Annette Rustad for their valuable assistance with the echocardiographic recordings, Torhild Garen for her help with preparation of questionnaires, Cathrine Brunborg for statistical support, Lars Mørkrid for valuable help obtaining laboratory assessments, and Inge-Margrethe Gilboe for administrative support.

Competing Interest: The authors have declared no conflicts of interest.
Reference List


Cardiac function in JIA


(20) Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-63.


Cardiac function in JIA


(36) Koca B, Demir T, Kasapcopur O. Use of tissue Doppler and its comparison with other pulse Doppler echocardiography in the evaluation of diastolic functions in patients with active juvenile idiopathic arthritis. Clin Rheumatol Published Online First: [23. aug 2014]


Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>JIA Patients (n=85)</th>
<th>Controls (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender; n (%)</td>
<td>20 (25)</td>
<td>9 (20)</td>
</tr>
<tr>
<td>Age (years); median (IQR)</td>
<td>38.6 (35.0 – 40.6)</td>
<td>37.7 (34.6 – 40.4)</td>
</tr>
<tr>
<td>Disease duration (years); median (IQR)</td>
<td>29.2 (28.2 – 30.6)</td>
<td>-</td>
</tr>
<tr>
<td>Onset age (years); median (IQR)</td>
<td>8.9 (5.2 – 11.6)</td>
<td>-</td>
</tr>
</tbody>
</table>

**JIA category distribution**

<table>
<thead>
<tr>
<th>JIA category</th>
<th>JIA Patients (n=85)</th>
<th>Controls (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic arthritis; n (%)</td>
<td>4 (5)</td>
<td></td>
</tr>
<tr>
<td>RF negative polyarthritis; n (%)</td>
<td>12 (14)</td>
<td></td>
</tr>
<tr>
<td>RF positive polyarthritis; n (%)</td>
<td>5 (6)</td>
<td></td>
</tr>
<tr>
<td>Persistent oligoarthritis; n (%)</td>
<td>15 (18)</td>
<td></td>
</tr>
<tr>
<td>Extended oligoarthritis; n (%)</td>
<td>14 (17)</td>
<td></td>
</tr>
<tr>
<td>Enthesitis related arthritis; n (%)</td>
<td>18 (21)</td>
<td></td>
</tr>
<tr>
<td>Psoriatic arthritis; n (%)</td>
<td>15 (18)</td>
<td></td>
</tr>
<tr>
<td>Undifferentiated arthritis; n (%)</td>
<td>2 (2)</td>
<td></td>
</tr>
</tbody>
</table>

**Current medication at 29-year follow-up**

<table>
<thead>
<tr>
<th>Medication</th>
<th>JIA Patients (n=85)</th>
<th>Controls (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF; n (%)</td>
<td>25 (29)</td>
<td></td>
</tr>
<tr>
<td>Methotrexate; n (%)</td>
<td>19 (22)</td>
<td></td>
</tr>
<tr>
<td>NSAIDs daily; n (%)</td>
<td>23 (27)</td>
<td></td>
</tr>
<tr>
<td>Prednisolone; n (%)</td>
<td>5 (6)</td>
<td></td>
</tr>
</tbody>
</table>

**Health status in the JIA patients at 29-year follow-up**

<table>
<thead>
<tr>
<th>Status</th>
<th>JIA Patients (n=85)</th>
<th>Controls (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician´s global (10-cm VAS ); median (IQR)</td>
<td>1.5 (0.5 – 2.4)</td>
<td></td>
</tr>
<tr>
<td>Number of active joints; median (IQR)</td>
<td>1 (0 – 2)</td>
<td></td>
</tr>
<tr>
<td>Number of joints LROM; median (IQR)</td>
<td>3 (1 – 7)</td>
<td></td>
</tr>
<tr>
<td>Patient´s global (10-cm VAS ); median (IQR)</td>
<td>1.8 (0.7 – 2.8)</td>
<td></td>
</tr>
</tbody>
</table>
IQR = interquartile range, RF = rheumatoid factor, anti-TNF = anti-tumor necrosis factor, NSAIDs = nonsteroidal anti-inflammatory drug, LROM = limited range of motion.
<table>
<thead>
<tr>
<th>Variable assessed at 29-year follow-up</th>
<th>JIA Patients (n=85)</th>
<th>Controls (n=46)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²); mean (SD)</td>
<td>25.7 (5.3)</td>
<td>25.3 (4.2)</td>
<td>0.629</td>
</tr>
<tr>
<td>Waist circumference (cm); mean (SD)</td>
<td>92.6 (13.0)</td>
<td>93.0 (10.2)</td>
<td>0.849</td>
</tr>
<tr>
<td>Daily smokers; n (%)</td>
<td>20 (24)</td>
<td>5 (11)</td>
<td>0.077</td>
</tr>
<tr>
<td>Pack-years of smoking (years)*</td>
<td>0.01 (0.0 – 8.6)</td>
<td>0.1 (0.0 – 2.9)</td>
<td>0.469</td>
</tr>
<tr>
<td>CVD in first degree relative; n (%)</td>
<td>48 (57)</td>
<td>21 (46)</td>
<td>0.260</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg); mean (SD)</td>
<td>120 (15)</td>
<td>114 (9)</td>
<td>0.021</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg); mean (SD)</td>
<td>76 (10)</td>
<td>71 (8)</td>
<td>0.009</td>
</tr>
<tr>
<td>Hypertension; n (%)</td>
<td>9 (11)</td>
<td>0 (0)</td>
<td>0.026</td>
</tr>
<tr>
<td>Myocardial infarction; n (%)</td>
<td>1 (1.2)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/L); mean (SD)</td>
<td>4.8 (1.1)</td>
<td>4.9 (0.8)</td>
<td>0.732</td>
</tr>
<tr>
<td>Triglycerides (mmol/L); mean (SD)</td>
<td>1.0 (0.7)</td>
<td>1.0 (0.5)</td>
<td>0.968</td>
</tr>
<tr>
<td>Glucose (mmol/L); mean (SD)</td>
<td>5.2 (0.5)</td>
<td>5.1 (0.5)</td>
<td>0.621</td>
</tr>
<tr>
<td>HbA1c (%); mean (SD)</td>
<td>5.4 (0.3)</td>
<td>5.4 (0.4)</td>
<td>0.372</td>
</tr>
<tr>
<td>hs-CRP (mg/L)*</td>
<td>1.8 (0.7 – 4.9)</td>
<td>0.7 (0.01 – 1.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Pro-BNP (pmol/L)*</td>
<td>3.7 (1.7 – 6.9)</td>
<td>4.8 (3.0 – 7.0)</td>
<td>0.107</td>
</tr>
<tr>
<td>Vigorous physical activity (hours/week)*</td>
<td>2.0 (0.4 – 3.8)</td>
<td>2.0 (0.0 – 3.3)</td>
<td>0.602</td>
</tr>
<tr>
<td>Moderate physical activity (hours/week)*</td>
<td>2.0 (1.0 – 4.0)</td>
<td>1.0 (0.5 – 2.6)</td>
<td>0.046</td>
</tr>
</tbody>
</table>

*Median (interquartile range).

BMI = body mass index, CVD = cardiovascular disease, HbA1c = glycated haemoglobin, hs-CRP = high sensitivity C-reactive protein, Pro-BNP = prohormone of brain natriuretic peptide.
Table 3 Left ventricular dimensions and systolic function

<table>
<thead>
<tr>
<th>Variable assessed at 29-year follow-up</th>
<th>JIA Patients (n=85)</th>
<th>Controls (n=46)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/minute)</td>
<td>66.3 (10.9)</td>
<td>63.1 (9.7)</td>
<td>0.095</td>
</tr>
<tr>
<td>LV IDd (cm)</td>
<td>5.1 (0.4)</td>
<td>5.1 (0.4)</td>
<td>0.459</td>
</tr>
<tr>
<td>LV PWd (cm)</td>
<td>0.7 (0.1)</td>
<td>0.7 (0.1)</td>
<td>0.782</td>
</tr>
<tr>
<td>IVSd (cm)</td>
<td>0.8 (0.2)</td>
<td>0.7 (0.1)</td>
<td>0.036</td>
</tr>
<tr>
<td>LV EDV (mL)</td>
<td>90.8 (19.3)</td>
<td>91.9 (20.0)</td>
<td>0.774</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>59.6 (3.6)</td>
<td>60.2 (3.3)</td>
<td>0.341</td>
</tr>
<tr>
<td>LV FS (%)</td>
<td>33.6 (5.5)</td>
<td>33.1 (5.1)</td>
<td>0.599</td>
</tr>
<tr>
<td>LV Global Strain (%)</td>
<td>-18.2 (2.5)</td>
<td>-18.7 (2.0)</td>
<td>0.281</td>
</tr>
<tr>
<td>LV s´ septal (cm/s)</td>
<td>8.2 (1.3)</td>
<td>8.4 (1.4)</td>
<td>0.668</td>
</tr>
<tr>
<td>LV SV (mL)</td>
<td>67.9 (12.1)</td>
<td>68.0 (12.2)</td>
<td>0.970</td>
</tr>
<tr>
<td>LV CI (L/min/m²)</td>
<td>2.4 (0.5)</td>
<td>2.3 (0.3)</td>
<td>0.144</td>
</tr>
</tbody>
</table>

Values are the mean (SD).

LV = left ventricle, IDd = internal diameter in end-diastole, PWd = posterior wall diameter in end-diastole, IVSd = septum diameter in end-diastole, EDV = end-diastolic volume, EF = ejection fraction, FS = fractional shortening, s´ = mitral annular velocity in systole, SV = stroke volume, CI = cardiac index.
Table 4: Left ventricular diastolic function and left atrial dimensions

<table>
<thead>
<tr>
<th>Variable assessed at 29-year follow-up</th>
<th>Patients (n=85)</th>
<th>Controls (n=46)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV E (m/s)</td>
<td>0.7 (0.1)</td>
<td>0.7 (0.1)</td>
<td>0.272</td>
</tr>
<tr>
<td>LV A (m/s)</td>
<td>0.5 (0.1)</td>
<td>0.5 (0.1)</td>
<td>0.616</td>
</tr>
<tr>
<td>LV E/A ratio</td>
<td>1.5 (0.4)</td>
<td>1.4 (0.4)</td>
<td>0.926</td>
</tr>
<tr>
<td>LV DT (ms)</td>
<td>165 (36)</td>
<td>180 (40)</td>
<td>0.029</td>
</tr>
<tr>
<td>LV IVRT (ms)</td>
<td>101 (14)</td>
<td>99 (13)</td>
<td>0.517</td>
</tr>
<tr>
<td>LV e´ septal (cm/s)</td>
<td>10.1 (2.2)</td>
<td>10.1 (1.8)</td>
<td>0.942</td>
</tr>
<tr>
<td>LV e´ lateral (cm/s)</td>
<td>13.5 (3.2)</td>
<td>14.2 (2.7)</td>
<td>0.208</td>
</tr>
<tr>
<td>LV E/e´ septal</td>
<td>7.4 (1.6)</td>
<td>7.2 (2.1)</td>
<td>0.651</td>
</tr>
<tr>
<td>LV E/e´ lateral*</td>
<td>5.3 (4.6 – 6.3)</td>
<td>4.8 (3.9 – 5.7)</td>
<td>0.036</td>
</tr>
<tr>
<td>LA area (cm²)</td>
<td>16.4 (2.9)</td>
<td>15.1 (2.8)</td>
<td>0.015</td>
</tr>
<tr>
<td>LA area index (cm²/m²)</td>
<td>8.9 (1.4)</td>
<td>8.2 (1.3)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Values are the mean (SD) unless stated otherwise.

*Median (inter-quartile range).

LV = Left ventricle, E = peak early transmitral flow velocity, A = peak late transmitral flow velocity, E/A ratio = peak early-to-late ratio mitral flow velocity, DT = E-wave deceleration time, IVRT = isovolumetric relaxation time, e´ = mitral annular velocity in diastole, LA = left atrium.
Table 5 The relation between cumulative inflammatory burdens and LV diastolic function at 29-year follow-up in JIA patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (IQR)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of active disease*</td>
<td>12.1 (7.0 – 14.4)</td>
<td>0.277 †</td>
<td>0.019</td>
<td>0.018</td>
<td>-0.125</td>
<td>0.141</td>
<td>0.249 †</td>
</tr>
<tr>
<td>ESR AUC</td>
<td>33.5 (22.5 – 51.0)</td>
<td>-0.004</td>
<td>-0.117</td>
<td>-0.052</td>
<td>-0.109</td>
<td>0.179</td>
<td>0.229 †</td>
</tr>
<tr>
<td>CRP AUC</td>
<td>8.5 (5.0 – 18.8)</td>
<td>0.070</td>
<td>-0.038</td>
<td>0.081</td>
<td>-0.014</td>
<td>0.133</td>
<td>0.236 †</td>
</tr>
<tr>
<td>Years on prednisolone</td>
<td>0.04 (0.0 – 1.1)</td>
<td>0.123</td>
<td>-0.171</td>
<td>0.049</td>
<td>-0.126</td>
<td>0.108</td>
<td>0.253 †</td>
</tr>
</tbody>
</table>

*assessed at 15-year follow-up

†p<0.05

LV = left ventricle, E/A ratio = peak early-to-late ratio mitral flow velocity, DT = E-wave deceleration time, E = peak early transmural flow velocity, e´ = mitral annular velocity in diastole, LA = Left area, ESR = erythrocyte sedimentation rate, AUC = area under the curve, CRP = C-reactive protein.
Figure 1 LV E/e’ according to disease status assessed at 29-year follow-up

LV = Left ventricular, E/e’ = filling pressure, hs-CRP = high sensitivity C-reactive protein, LROM = limited range of motion.
Figure 2 Diastolic function as measured by echocardiography

Above: Left ventricular transmitral recordings of early (E) and late (A) diastolic flow velocities from which the transmitral E/A ratio was calculated. Transmitral recordings of E wave deceleration time.

Below: Left ventricular mitral annular velocities in systole (LV s’) and early diastole (LV e’), measured in the septal and lateral mitral annulus with colour Tissue Doppler imaging.
EXTENDED REPORT

Disease progression into adulthood and predictors of long-term active disease in juvenile idiopathic arthritis

Anne M Selvaag,1 Hanne A Aulie,1 Vibke Lilleby,1 Berit Flato1,2

ABSTRACT

Objectives To describe disease activity 30 years after disease onset in a previously studied cohort of patients with juvenile idiopathic arthritis (JIA) and reveal predictors of long-term active disease.

Methods Patients with JIA, first referred 1980–1985 and re-examined 15 and 23 years after onset, were invited to attend. All 176 patients were assessed by questionnaires. Patients with signs of active disease at 15 years or later also came to a clinical re-examination (n=90). Disease activity was assessed by the clinical juvenile arthritis disease activity score (JADAS3) and by the criteria for remission in JIA, and health status by Health Assessment Questionnaire (HAQ) and Medical Outcome Study 36-item Short Form Health Survey (SF-36).

Results At 30-year follow-up, 59% of the patients were in clinical remission off medication, 7% were in remission on medication and 34% had active disease. 70% of the patients were in the same category of disease activity at 15 and 30 years. The JADAS3 was ≤2.0 in 54%, 2.1–4.5 in 18% and >4.5 in 28%. HLA-DRB1*01, physician’s global assessment and a short total time in remission at 15 years, predicted active disease. Physician’s global assessment also predicted a JADAS3 >4.5. From 15 to 30 years (n=90), physician’s global assessment, number of active joints, erythrocyte sedimentation rate and C reactive protein improved significantly, but patient’s global assessment, HAQ and SF-36 did not.

Conclusions 41% of the patients with JIA had active disease or were on medication after 15 years and 28% had a high symptom state. Remission rates and patient-reported health status at 15 years were comparable with rates at 30 years.

INTRODUCTION

The disease activity in juvenile idiopathic arthritis (JIA) can persist for many years, even through adult life, but may also go into remission with minimal sequelae before the patient reaches adulthood.

Follow-up studies of patients with JIA of more than 20 years are scarce, and previous long-term studies of JIA are difficult to compare due to different definitions of remission and disability.1–4 Few long-term studies have included the recently developed criteria for remission in JIA and longitudinal assessments of health status.5

In adult rheumatology, pooling of disease activity measures into composite scores has resulted in scores like the Disease Activity Score in 28 Joints.6 Recently, a similar instrument, the Juvenile Arthritis Disease Activity Score (JADAS), was evaluated for JIA.7 Several studies have implemented this instrument, but it has not previously been used in a long-term follow-up study.

The aim of this study was to assess disease activity and health status in a previously studied cohort of patients with JIA 30 years after disease onset, to compare disease activity after 15 and 30 years and to reveal predictors of long-term active disease.

MATERIALS AND METHODS

Patients and controls

A total of 260 patients with JIA, first time referred to Oslo University Hospital, Rikshospitalet, from 1980 to 1985, were re-examined clinically after median 15 years of disease duration and by mailed questionnaires after median 23 years.8 9 Six patients had died, thus 254 patients were invited to take part in the present study. All patients were assessed by questionnaires and those with signs of active disease and/or on antirheumatic medication after 15, 23 and/or 30 years were invited to an extended clinical examination.

The patients were classified according to the International League of Associations for Rheumatology (ILAR) criteria for JIA after 15 years of disease duration.10 11 Disease onset was defined as the day the physician diagnosed the arthritis.

Informed consent was obtained from all the participants.

Clinical examination

The patients were examined by one of the three rheumatologists at follow-up (BF, VL and AMS). The clinical examination included registration of number of joints with swelling, tenderness and limited range of motion (LROM), number of active joints (swelling or both tenderness and LROM) and physician’s global assessment of disease activity (on a five-point Likert scale, where one means inactive and five very severe disease activity, and on a 10 cm visual analogue scale (VAS), where 0 means no disease activity and 10 means very severe disease activity).

Remission, medication and health status

Inactive disease was defined according to the preliminary criteria for clinical remission in JIA, as having no active arthritis; no fever, rash, serositis, splenomegaly or generalised lymphadenopathy attributable to JIA; no active uveitis; normal erythrocyte sedimentation rate (ESR) or C reactive
protein (CRP); and a physician’s global assessment of disease activity rated at the best score possible for the instrument used, except that for patients in remission off medication after 15 years, inactive disease was defined as no history of flare after 23 and 30 years. Clinical remission on medication was defined as minimum six continuous months of inactive disease on medication. Clinical remission off medication was defined as minimum 12 months of inactive disease off all antiarthritic and antiuveitis medication. All the patients received a questionnaire about antirheumatic and antiuveitis medication, history of joint injections, presence of uveitis, quality of life according to the Medical Outcome Study 36-item Short Form Health Survey (SF-36) and physical disability and discomfort assessed by the Health Assessment Questionnaire (HAQ).13

Disease activity was assessed by the JADAS which is computed from the number of active joints, the physician’s global assessment of disease activity measured on a 10 cm VAS, patient’s global assessment of well-being measured on a 10 cm VAS, where 0 means doing very well, and normalised ESR.7 A JADAS3 developed to calculate a score without ESR has recently been evaluated.14 We used the JADAS3 version to calculate a score that also included patients who were in remission. Missing data for the physician’s global assessment of patients without signs of disease activity or off antirheumatic medication were replaced by zero, in accordance with the median score for the patients we had examined who were in remission. The range of the JADAS3 for a 71 joint evaluation was 0–91. A cut-off value for an acceptable symptom state has been found to correspond to a JADAS <4.5 for children with JIA.15 We, therefore, chose a JADAS3 >4.5 as a level of a high symptom state.

Statistical analyses

The differences between participants and non-participants and between two patient groups were analysed by t tests for continuous data and by χ² tests for categorical data and frequencies. Because of non-normality distribution we used Kruskal–Wallis test to analyse differences in the JADAS3 across the JIA categories and Mann–Whitney U tests to reveal differences between two independent groups (results with a p<0.01 were reported because of multiple comparisons). Spearman’s correlation coefficient was used to assess the relationship between the JADAS3 and categories of disease activity.

We used Wilcoxon signed-rank test for comparisons between continuous non-normality distributed data from 15-year and 30-year follow-up, and Friedman’s two-way analysis of variance for more than two comparisons.

Logistical regression analyses were used to assess predictors of active disease and a JADAS3 >4.5 (see online supplementary text).

For all analyses, p values <0.05 (two-tailed tests) were considered statistically significant. All analyses were performed on the SPSS software programme (SPSS, Chicago, Illinois, USA) V18.0.

RESULTS

Patient characteristics

Out of 254 eligible patients, 176 (69%) were assessed by questionnaires after median 29.6 years (range 20.6–39.9) of disease duration. The median age was 38.8 years (range 27.8–45.1) and 74% were women. Ninety patients also came to a clinical examination.

The 176 participants were comparable with the 84 non-participants (including six deceased patients) with regard to gender, disease category and disease duration, as well as physician’s global assessment of disease activity, number of active joints, remission rate, HAQ and SF-36 after 15 years, but the non-participants were slightly younger at onset than the participants (6.9±4.7 vs 8.2±4.1 years; p=0.032). After 30 years, the 86 patients who were not examined had lower levels of HAQ and higher levels of well-being and SF-36 Physical Component Score (PCS) than the 90 examined patients (all p<0.001; data not shown).

Remission and medication

After median 30 years, 73 patients (41%) had active disease (n=60) or were in remission on medication (n=13), and 103 patients (59%) were in clinical remission off medication (table 1).

Out of 61 patients with active disease at 15-year follow-up, 39 (64%) had active disease after 30 years. Out of 98 patients in remission off medication at 15 years, 85 (87%) were still in remission at 30-year follow-up. In total, 124/176 patients (70%) had an unchanged category of disease activity from 15-year to 30-year follow-up, whereas 52 patients (30%) changed category of disease activity.

During the first 15 years of disease, 123 patients (70%) had received disease-modifying antirheumatic drugs (DMARDs), including 46 patients (26%) treated with methotrexate. Out of the 73 patients who were not in remission off medication at 30 years, 41 patients (56%) used DMARDs (26 patients), biological immunosuppressants (27 patients) and/or prednisolone (six patients). Thirty-two patients (44%) used no medication or non-steroidal anti-inflammatory drugs only, but they had higher physician’s global assessment, number of active joints and reduced well-being compared with those who used DMARDs, biological medicine and/or prednisolone (all p<0.05). The patients in remission off medication had significantly lower levels of HAQ and higher levels of well-being and SF-36 PCS than those with active disease (all p<0.001, data not shown). Nine (5%) patients reported uveitis during the last 12 months and 16% ever had uveitis.

JADAS3

Table 2 shows the remission rates and median JADAS3 values after median 30 years according to the ILAR JIA classification categories.

There was a statistically significant difference in remission rates with the highest rates in those with persistent oligoarticular and systemic JIA (80% and 83%, respectively), and the lowest in those with polyarticular rheumatoid factor (RF)-positive JIA (17%) and enthesitis-related arthritis (ERA; 37%, p=0.001). The JADAS3 was median 1.9 (range 0.2–23.1) for the total

Table 1 Changes in disease activity categories from 15-year to 30-year follow-up in patients with juvenile idiopathic arthritis (JIA)

<table>
<thead>
<tr>
<th>Disease activity at 15-year follow-up*</th>
<th>Disease activity at 30-year follow-up*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active disease</td>
<td>Remission on medication</td>
</tr>
<tr>
<td>Total</td>
<td>Active disease</td>
</tr>
<tr>
<td>61 (35)</td>
<td>39 (64)</td>
</tr>
<tr>
<td>17 (10)</td>
<td>9 (53)</td>
</tr>
<tr>
<td>98 (56)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Total</td>
<td>176 (100)</td>
</tr>
</tbody>
</table>
| Values refer to the number of subjects (%). *According to preliminary criteria for clinical remission in JIA.3 

study group. There were differences in the JADAS3 across JIA categories (p=0.019). Patients with systemic JIA or persistent oligoarthritis had lower levels of JADAS3 than those with polyarticular RF-positive JIA (all p<0.01).

The JADAS3 was median 6.0 (range 1.1–23.1) for patients with active disease, 2.2 (range 0.2–11.7) for patients in remission on medication and 0.5 (range 0.2–7.7) for patients in remission off medication (p<0.001) at 30 years. Seventy-two (41%) of the 176 patients had JADAS3 ≤1.0, 23 (13%) had JADAS3 between 1.1 and 2.0, 31 (18%) had JADAS3 between 2.1 and 4.5 and 30 (28%) had JADAS3 >4.5 (figure 1). All the patients with a JADAS3 ≤1.0 were in remission (97% off medication and 3% on medication). Of the patients with a JADAS3 >4.5, 80% had active disease and 20% were in remission (16% off medication and 4% on medication, median JADAS3 6.5). The JADAS3 had a strong correlation to disease activity categories (active disease, remission off medication), Spearman’s correlation coefficient 0.73 (p<0.001).

Predictors of active disease
Predictors of active disease were analysed by multiple logistical regression analyses. All the core set variables at 15 years were associated with active disease at 30-year follow-up. Predictors of ‘active disease or being in remission on medication’ at 30 years were: HLA-DRB1*01 (DR1) positivity (OR 8.5, 95% CI 2.6 to 28.1), physician’s global assessment of disease activity at 15-year follow-up (OR 5.7, 95% CI 2.7 to 12.2) and a short duration of total time in remission at 15 years (OR 7.9, 95% CI 2.8 to 22.6) (table 3).

The same variables were identified when the dependent variable was exchanged with ‘having active disease’ (not being in remission on/off medication, data not shown), except that CRP at 15 years came out as an additional predictor (OR 3.2, 95% CI 1.3 to 7.9).

Physician’s global assessment of disease activity at 15 years was a predictor of a high symptom state (JADAS3 >4.5) at 30-year follow-up (OR 2.4, 95% CI 1.7 to 3.5).

Comparing health status at 15-year and 30-year follow-up
After 30 years, 79 (45%) of the 176 patients had a HAQ disability index >0. We compared health status and disease activity at 15 years with that of 30-year follow-up in 90 patients who had active disease or needed medication at 15 years or later (table 4). There were significant improvements in physician’s global assessment of disease activity, number of active joints, ESR and CRP (all p<0.05), but not in number of joints with LROM, patient’s global assessment, HAQ and SF 36 (table 4).

DISCUSSION
The present study shows that 41% of the patients with JIA were not in remission off medication after 30 years of disease duration, 46% had a JADAS3 >2 and 28% had a high symptom state. The overall remission rates at 15 years were comparable with rates at 30 years, physician’s assessment of disease activity and inflammatory markers were improved, but patient-reported health status was not. DR1, elevated CRP, high physician’s global assessment of disease activity and a short total time in remission at 15 years predicted disease activity at 30-year follow-up.

The finding that 41% of the patients had persistently active disease or were on antirheumatic medication after 30 years is in accordance with several long-term studies which have reported active disease in 37%–43% of patients after 21–28 years of disease duration. However, Peterson et al found self-reported...
active disease in 67% of the patients after 25 years, and studies of patients with a disease duration of 10–17 years reported high rates of disease activity (50%–67%), but different definitions of remission were used.16–20 During the first years of disease, a higher percentage of our patients received DMARDs than those in studies with lower remission rates.8 16 21 22 After 30 years, only 56% of the 73 patients with active disease were on DMARDs, prednisolone and/or anti-tumour necrosis factor treatment, suggesting that a considerable part of the patients were not satisfactorily treated. Our results support that JIA is not a self-limiting disease for a substantial proportion of the patients.

The remission rates for the categories of JIA showed the same trend as in studies with shorter follow-up.11 16 23–25 Most patients with persistent oligoarticular JIA were in remission (80%), in contrast to patients with polyarticular RF-positive JIA where only one patient was in remission. Interestingly, 83% of the 12 patients with systemic JIA were in remission. In Scandinavia this patient group is small, and other studies have reported similar remission rates (75%–83%) in systemic JIA.20 24

The overall disease course seemed to be stable in 70% of the patients between 15-year and 30-year follow-up. Eighty-seven per cent of the patients in remission off medication were in the same category at 30 years, and the disease remained active in 64% of those with active disease at 15 years. This is in contrast to a recent study where only 61% of the patients with juvenile chronic arthritis who were in remission at 5-year follow-up were in remission at 17-year follow-up. Studies of patients with JIA with disease duration <10 years have reported cyclic episodes of remission and active disease,23 20–26 and Wallace et al20 found that patients with other JIA categories than

### Table 3  Predictors of persistent disease activity and a high symptom state at 30-year follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multivariate analysis†</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligoarticular onset‡</td>
<td>8.5 (2.6 to 28.1)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Polyarticular course¶</td>
<td>5.7 (2.7 to 12.2)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>PGA at 15 years</td>
<td>4.0 (1.8 to 8.8)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>CRP &gt; 5 mg/L at 15 years</td>
<td>3.3 (1.7 to 6.5)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Patient’s global ≥ 3 at 15 years</td>
<td>5.4 (2.4 to 12.1)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>HAQ &gt; 0 at 15 years</td>
<td>5.1 (2.7 to 10.0)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Total time in remission &lt;8 years at 15-year follow-up</td>
<td>7.9 (2.8 to 22.6)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

†Logistical regression analyses.
‡Nagelkerke R²=63%.
§Oligoarticular onset: ≤4 active joints first 6 months, from all JIA categories except polyarticular JIA.
¶Polyarticular course: having in total ≥5 active joints after 6 months of disease, from all JIA categories except persistent oligoarticular JIA.
**Nagelkerke R²=21%.

CRP, C reactive protein; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; JADAS3, Juvenile Arthritis Disease Activity Score, clinical version; JIA, juvenile idiopathic arthritis; LROM, limited range of motion; PGA, physician’s global assessment of disease activity.

### Table 4  Longitudinal data on health status in 90 patients with JIA with signs of active disease after at least 15 years of disease duration

<table>
<thead>
<tr>
<th>Variable</th>
<th>15 years</th>
<th>23 years</th>
<th>30 years</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician’s global, Likert</td>
<td>2.3 (1.1)</td>
<td>na</td>
<td>1.8 (0.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>No. of active joints</td>
<td>3.0 (5.4)</td>
<td>na</td>
<td>1.5 (2.7)</td>
<td>0.028</td>
</tr>
<tr>
<td>No. of joints LROM</td>
<td>6.3 (8.8)</td>
<td>na</td>
<td>7.8 (11.7)</td>
<td>0.104</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>14.3 (15.5)</td>
<td>na</td>
<td>10.8 (11.1)</td>
<td>0.015</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>9.7 (13.7)</td>
<td>na</td>
<td>4.2 (6.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patient’s global, Likert</td>
<td>2.7 (0.9)</td>
<td>2.8 (1.0)</td>
<td>2.9 (0.9)</td>
<td>0.359</td>
</tr>
<tr>
<td>HAQ</td>
<td>0.4 (0.5)</td>
<td>0.4 (0.5)</td>
<td>0.5 (0.5)</td>
<td>0.184</td>
</tr>
<tr>
<td>SF-36 PCS</td>
<td>45.2 (10.3)</td>
<td>45.3 (10.1)</td>
<td>44.5 (9.9)</td>
<td>0.580</td>
</tr>
<tr>
<td>SF-36 MCS</td>
<td>51.9 (8.6)</td>
<td>49.8 (10.9)</td>
<td>50.5 (10.1)</td>
<td>0.291</td>
</tr>
</tbody>
</table>

Numbers are mean values (SD). CRP, C reactive protein; ESR, erythrocyte sedimentation rate; JIA, juvenile idiopathic arthritis; HAQ, Health Assessment Questionnaire; LROM, limited range of motion; na, not applicable; SF-36 PCS, Medical Outcomes Study Short Form-36 Physical Component Score; SF-36 MCS, Medical Outcomes Study Short Form-36 Mental Component Score.
persistent oligoarthritis spent minimum two-thirds of their disease course in a state of active disease. We did few examinations during the disease course, and some variation of disease activity and medication may have been lost. Our results suggest that although the disease activity may vary considerably during the first years, it seems to get more stable in adults with JIA.

In the 90 patients with signs of active disease after at least 15 years, physician reported data on disease activity improved over time, but patient-reported health status did not. In addition to disease activity, patient’s global assessment, HAQ and SF-36 may incorporate overall well-being, disability, damage and psychosocial effects of the disease. There are a limited number of studies of more than 20 years of follow-up in patients with JIA, and only one of them used repeated evaluations of the patients.1–4 19 The fact that disability did not increase significantly over time is in contrast to older studies.1 20 However, these studies were performed three to five decades ago and factors like new treatment modalities may have influenced our results.

We found that physician’s global assessment of disease activity at 15 years predicted disease activity at 30 years, also when measured as a JADAS3 >4.5. CRP and less time in remission during the first 15 years also predicted active disease. Few studies have looked for predictors of more than 20 years outcome. In a Swedish study remission at 5-year follow-up predicted remission at 17-year follow-up.20 Magnani et al30 found that patients with JIA who had one or more episodes of inactive disease during the first 5 years had better outcomes at 7-year follow-up than those who had continuous disease activity. Flato et al35 found that persistently elevated ESR the first 6 months of the disease predicted active disease at 15-year follow-up in the present patient cohort.

DR1 was also a predictor of persistent disease activity. DR1 has previously been associated with a polyarticular course in patients with oligoarticular onset and with RF-positive polyarticular JIA.31 32

JADAS is a relatively new instrument for patients with JIA. Several studies on patients with short disease duration have used it.33–37 The JADAS has been evaluated for children with JIA. We have used JADAS in adult patients. One previous study applied JADAS in adults.34 We found that JADAS3 correlated strongly with categories of disease activity in our adult patients, but experienced that JADAS3 additionally may capture other aspects of the burden of disease like damage and overall well-being, as some patients in remission had high symptom states (JADAS3 >4.5). The study has some limitations. We chose to use the JADAS3 version, even though the cut-off values for acceptable symptom state were defined according to JADAS. In those patients who had elevated ESR, a JADAS score would have been slightly higher than a JADAS3 score, and thus our results should be interpreted with this in mind. Patients in remission off medication after 15 years were clinically re-examined only if they reported signs of disease activity by questionnaires after 23 or 30 years. However, the non-examined patients had significantly better health status after 30 years than those examined, supporting that their disease was in remission. Another limitation of the study is that we used the preliminary criteria for remission in patients with ERA, psoriatic arthritis and undifferentiated JIA.3 The criteria have not been evaluated for these categories, but other studies have nevertheless applied them to comprise their total patient groups.23 30

The strength of this study is the long follow-up time of 30 years, with repeated assessments of clinical data and questionnaires. It is also the first long-term study that includes the remission criteria for JIA and the JADAS. Our patient cohort has previously been described with characteristics comparable with those in epidemiological studies. However, the non-participants were significantly younger at disease onset than the participants. This is probably of minor importance for the results, as the disease activity in these two groups was not significantly different at 15 years. Since the 15-year follow-up, six patients had died. We have not examined their cause of death, this will be the focus of future work, but none of the six patients had systemic JIA. It is possible that severe disease could have influenced their deaths, thus eliminating some patients with active disease from this follow-up.

In this long-term study we have reported that the overall remission rates were similar at 15-year and 30-year follow-up. After 30 years, 41% of the patients were not in remission off medication and 28% had a high symptom state. Physician’s assessment of disease activity and inflammatory markers improved over the years, but patient-reported disability and health status did not. Treatment and rehabilitation of patients with JIA have improved during the last decades. More long-term studies into adulthood are needed to reveal the consequences of the present treatment regimes.

Acknowledgements Torhild Garen for her help with the preparation of questionnaires and Inge-Margrethe Gilboe for administrative support.

Contributors The corresponding author confirms that all the individuals listed as authors fulfil the uniform authorship credit requirements for manuscripts submitted to medical journals, that is, that they all contributed to the manuscript based on (1) substantial contributions to conception and design, acquisition of data or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding The study was funded by the Norwegian Women’s Public Health Association.

Competing interests None.

Ethics approval The Regional Ethics Committee for Medical Research, REK South-East.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

Clinical and epidemiological research


