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PERSPECTIVES ON WALKING IN INDIVIDUALS WITH RHEUMATOID ARTHRITIS AND JUVENILE IDIOPATHIC ARTHRITIS

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Perspectives on walking in individuals with rheumatoid arthritis and juvenile idiopathic arthritis

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To each and every one who contributed to this thesis,
keep on walking!
ABSTRACT

Background and aim: Gait deviations in individuals with Rheumatoid Arthritis (RA) and Juvenile Idiopathic Arthritis (JIA) have previously been demonstrated as a consequence of active disease. During the last decade, pharmacological treatments have dramatically improved outcomes but the effect on gait dynamics is not fully understood. The overall aim of this thesis was to enhance the understanding of the effect of pharmacological interventions on gait dynamics in individuals with RA and JIA. Moreover, we aimed to evaluate the usability of measures of overall gait quality which could facilitate future comparisons between groups and after interventions. In Study I the aim was to evaluate the usability of the Gait Deviation Index (GDI) as a measure of overall gait quality in adults with RA. The aim of Study II was to determine the effects of anti-Tumor Necrosis Factor Alpha (TNF-α) treatment on gait dynamics in individuals with RA. Study III aimed to evaluate the occurrence, clinical characteristics and prognostic factors associated with ankle arthritis in children with JIA. The aim of Study IV was to evaluate the effects of Intra-Articular Corticosteroid Injections (IACI) in the foot on gait dynamics and patient-relevant outcomes in children with JIA.

Participants and methods: In Study I, 63 adults with RA and 59 healthy controls were included in a retrospective and cross-sectional study. Gait dynamics, obtained by three dimensional (3D) gait analysis and represented by the GDI, were analyzed and related to walking speed, physical disability and pain. In Study II, 16 adults with RA were included, and gait dynamics, obtained by 3D gait analysis, and disease characteristics were analyzed at baseline and three months after anti-TNF-α treatment. In Study III, 440 children with JIA were followed for the first eight years of disease in a population based cohort. The occurrence of ankle arthritis was assessed and related to clinical characteristics, and to disease outcome. In Study IV, 43 children with JIA were included and followed for three months after foot IACI treatment. Gait dynamics and disease characteristics were assessed at baseline, and at three weeks and three months after treatment.

Results: In Study I, the GDI was found to be a useful measure of overall gait quality in individuals with RA. In Study II, treatment with anti-TNF-α improved gait dynamics in adults with RA, but significant gait deviations were still present after treatment. In Study III, ankle arthritis was found to be common in JIA, related to a polyarticular disease course in young children, and was associated with failure to achieve remission. In Study IV, as a result of IACI treatment improvements were identified in foot-related disability and inflammatory joint symptoms, but gait dynamics were unchanged.

Conclusion: We recommend the use of measures of overall gait quality, such as the GDI, to quantify gait deviations in individuals with RA and JIA. This measure adds an aspect of dynamic function to arthritis care and facilitates comparisons of gait dynamics between groups or over time and between gait dynamics and other types of outcome measures. Gait deviations persist despite pharmacological treatment, indicating that the biomechanical perspective is important when evaluating walking disability. Ankle arthritis is common in JIA, predicts a polyarticular disease course in young children and is associated with failure to achieve remission. We suggest that ankle arthritis should be taken into account in the assessment of prognosis and choice of treatment strategy in JIA.
LIST OF SCIENTIFIC PAPERS

The thesis is based on the following original articles and manuscripts. Every paper will be referred to in the text by its Roman numerals.


<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>3D GA</td>
<td>Three Dimensional Gait Analysis</td>
</tr>
<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
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<tr>
<td>ANA</td>
<td>Anti-nuclear antibody</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
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<tr>
<td>CHAQ</td>
<td>Child Health Assessment Questionnaire</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CRP</td>
<td>C - Reactive Protein</td>
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<tr>
<td>DAS28</td>
<td>Disease Activity Score 28 joint count</td>
</tr>
<tr>
<td>DMARD</td>
<td>Disease-Modifying AntiRheumatic Drugs</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-Linked ImmunoSorbent Assay</td>
</tr>
<tr>
<td>ESR</td>
<td>Erythrocyte Sedimentation Rate</td>
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<tr>
<td>GDI</td>
<td>Gait Deviation Index</td>
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<tr>
<td>GDI-k</td>
<td>Gait Deviation Index- Kinetic</td>
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<tr>
<td>HAQ</td>
<td>Health Assessments Questionnaire Disability Index</td>
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<tr>
<td>HLA-B27</td>
<td>Human Leucocyte Antigen B27</td>
</tr>
<tr>
<td>IACI</td>
<td>Intra-Articular Corticosteroid Injections</td>
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<tr>
<td>ICC</td>
<td>Intraclass Correlation Coefficient</td>
</tr>
<tr>
<td>ICF</td>
<td>International Classification of Functioning, Disability and Health</td>
</tr>
<tr>
<td>ILAR</td>
<td>International League of Associations for Rheumatology</td>
</tr>
<tr>
<td>JAFI</td>
<td>Juvenile Arthritis Foot disability Index</td>
</tr>
<tr>
<td>Nd</td>
<td>Non-Dimensional, Dimensionless</td>
</tr>
<tr>
<td>NoSPeR</td>
<td>Nordic Study group of Pediatric Rheumatology</td>
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<tr>
<td>RA</td>
<td>Rheumatoid Arthritis</td>
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<td>RF</td>
<td>Rheumatoid Factor</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SEM</td>
<td>Standard Error of Measurement</td>
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<tr>
<td>TNF-α</td>
<td>Tumor Necrosis Factor-alpha</td>
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<tr>
<td>US</td>
<td>Ultra Sound</td>
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<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
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## THESIS AT A GLANCE

<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Method</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>To evaluate the usability of the GDI as a measure of overall gait quality in adults with RA.</td>
<td>Retrospective case-control analysis of 63 adults with RA and 59 healthy controls. Using 3D gait analysis, gait deviations, represented by the GDI, were analyzed relative to typical gait patterns, walking speed, physical disability and pain.</td>
<td>Adults with RA showed gait deviations as compared to healthy controls with a mean GDI about 1.3 SD away from normal gait. A change of 5 GDI units was required to account for natural variation in gait on an individual level. Level of gait deviations was to some extent related to walking speed but not to physical disability or pain.</td>
<td>GDI appears to be a useful measure of overall gait quality in adults with RA and may help clinicians understand the relationship between RA, gait deviations and walking disability.</td>
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<td>II</td>
<td>To determine the effects of anti-TNF-α treatment on gait dynamics in individual with RA.</td>
<td>A pre-post design study including 16 adults with RA. Gait dynamics were analyzed after 3 month of anti-TNF-α treatment relative to disease characteristics.</td>
<td>As a result of treatment both the GDI and GDI-kinetic improved on average by about 4 GDI units. Disease activity, physical disability (HAQ) and pain during walking improved significantly after treatment.</td>
<td>Treatment with anti-TNF-α improved gait dynamics in adults with RA but significant gait deviations were still present after treatment. Thus, gait dynamics is an important aspect to consider in treatment evaluations.</td>
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<tr>
<td>III</td>
<td>To evaluate the occurrence, clinical characteristics and prognostic factors associated with ankle arthritis in children with JIA.</td>
<td>440 children with JIA, all ILAR categories, were followed for eight years of disease in a longitudinal population based cohort (NoSPeR). Occurrence of ankle arthritis was assessed and related to clinical characteristics, and outcome of diseases.</td>
<td>251 (57%) children experienced ankle arthritis during the first eight years of disease. Ankle arthritis was least common in the persistent oligoarticular category (25%) and most common in polyarticular categories (83-85%). Children who developed ankle arthritis early were younger at disease onset and had an increased risk of a higher number of cumulative involved joints and for not achieving remission.</td>
<td>Ankle arthritis is common in JIA. Early ankle arthritis predicts a polyarticular disease course in young children and is associated with failure to achieve remission eight years after disease onset. We suggest that ankle arthritis should be recognized in the assessment of prognosis and choice of treatment strategy in JIA.</td>
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<tr>
<td>IV</td>
<td>To evaluate the effects of IACI treatment on overall gait dynamics and patient-relevant outcomes after 3 weeks and 3 months in children with JIA with foot and ankle synovitis.</td>
<td>43 children with JIA were followed over 3 months in a prospective intervention study. Using 3D gait analysis gait dynamics and self-reported physical (CHAQ) and foot-related (JAFI) disability were analyzed.</td>
<td>Foot-related disability and inflammatory joint symptoms improved following treatment. Gait dynamics were compromised before treatment and did not improve following treatment. The ability to generate ankle power during walking and ankle/hip power ratio was reduced, indicating a power shift from the ankle to the hips, more prominent in children with polyarthritis.</td>
<td>Improvements in foot-related disability and inflammatory joint symptoms but not in gait dynamics were identified as a result of IACI treatment. Children with polyarticular disease and those scoring more difficulties with walking prior to treatment had the worst outcome and should be monitored carefully following intervention.</td>
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</table>
1 INTRODUCTION

During the last decade, pharmacological treatments have dramatically improved outcomes in individuals with Rheumatoid Arthritis (RA) and Juvenile Idiopathic Arthritis (JIA); reduced disease activity and clinical remission are the paramount goals. Reduced disease activity facilitates an active lifestyle that is vital for individuals with inflammatory joint disease, both to reduce the impact of arthritis-associated comorbidities and to benefit from the positive effects of physical activity on general health and fitness. A common, easy accessible, low-cost way of being physically active is to walk. However, walking disability is common among individuals with RA and JIA and is rated as a disability that is very important to improve.

The main focus of this thesis is on gait dynamics, one of several perspectives on walking. According to the International Classification of Functioning, disability and health (ICF) a clear distinction between walking and gait can be drawn. In their definition, which is the definition also used in this thesis, “walking” refers to mobility or the ability to move around and is a component of activity (Figure 1). As the title of this thesis implies, walking is multifaceted and several factors contribute to walking ability. One of these factors is gait pattern function. In this thesis focus is on gait patterns measured in a motion analysis laboratory. The word “gait” refers to the “quality of walking” and is classified as a component of body function.
Figure 1. The international classification of functioning, disability and health (ICF) provides a framework for the description of health and health-related states within which measures of gait and walking can be identified and sorted.

1.1 GAIT DEVIATIONS IN INDIVIDUALS WITH JUVENILE IDIOPATHIC ARTHRITIS AND RHEUMATOID ARTHRITIS

In individuals with RA approximately 60% experience walking disability at disease onset, and after the initial years of disease, walking disability stabilizes with a prevalence of around 40%. Walking ability is complex, and several components contribute to walking disability such as: pain, pathology, psychology, and environmental factors. Studies of gait dynamics have the potential to reveal insights into factors contributing to walking disability. Gait deviations in RA and JIA have been associated with disease activity, deformity and pain. In adults with knee osteoarthritis the quality of waking itself has been related to the progression of disease. Despite a growing body of studies evaluating gait quality in individuals with RA and JIA, the association between gait deviations, disease progression and walking disability is unclear.

Gait deviation is a common finding in individuals with RA and JIA and both inflammatory (swelling, pain, and stiffness) and mechanical (joint destruction and deformity) factors are known to lead to primary and compensatory gait deviations. To avoid loading painful joints, individuals with RA and JIA typically adapt a gait pattern characterized by reduced walking speed, cadence and stride length. Other common gait deviations seen in individuals with RA and JIA are longer weight bearing periods on both feet and a reduced range of motion, joint moment and joint power (Figure 2).
Figure 2. Example of gait deviations at the ankle joint from a child with JIA and bilateral foot involvement. Each graph represents a gait cycle with the first 60% representing stance phase and last 40% swing phase. In the graphs, stance and swing are visually separated by a vertical black line. The shadowed areas represent the mean and 1 SD of healthy controls. Solid line; left side, dashed line; right side. Impairments are seen with reduced dorsiflexion on the left side at the second half of the stance phase, possibly due to knee arthritis (A), with corresponding reduction in plantar flexion moment (B). Plantarflexion on the right side is reduced in the transition phase from stance to swing (A) with corresponding reduction in ankle power (C). Also note the prolonged stance phase time, represented by the later peak values in the child with JIA compared to healthy controls.

There is limited knowledge of the possible effects of today’s potent medical treatments on gait dynamics in individuals with RA and JIA. The effect of pharmacological intervention on gait dynamics was analyzed as early as 1983 but despite recent advances in pharmacological therapy, only a few studies have evaluated gait dynamics following pharmacological interventions in RA and JIA since then. Two of these studies were first published in 2013 and evaluated the effect of anti-Tumor Necrosis Factor alpha (TNF-α) treatment on gait dynamics in adults with RA, one of them being Study II in this thesis. In both studies, reduction of disease activity was accompanied by improvements in gait dynamics including increased walking speed, stride length, ranges of motion and ability to load the joints. However, gait deviations persisted despite treatment with anti-TNF-α.

Previous work has identified improved gait dynamics as a result of Intra-Articular Corticosteroid Injections (IACI) treatment in adults with RA and in children with JIA. The effects of IACI on gait dynamics have also been documented in adults with osteoarthritis in the knee. Broström and co-workers evaluated the effect of IACI treatment in any lower extremity joint in children with JIA. In their study gait dynamics in both treated and untreated joints improved as a result of treatment. Their study was conducted at the very beginning of the era of biologic therapy and included a small sample size with a three week follow-up. To expand on the results from Broström’s study, we chose a longer follow-up period for our study and evaluated gait dynamics over a period of three months following foot IACI in a pharmacologically well-managed cohort (Study IV).
The relationship between gait deviations and walking disability in RA and JIA is not fully understood and several components contribute to walking disability. The goals of this thesis are to evaluate whether gait deviations persist after pharmacological treatments and to evaluate the usability of measures of overall gait quality in individuals with RA and JIA. The relation between gait deviations and walking disability is considered and discussed but was not the main focus of this thesis.

1.2 JUVENILE IDIOPATHIC ARTHRITIS AND RHEUMATOID ARTHRITIS

RA and JIA are two different diseases with several common features. RA and JIA are inflammatory diseases mainly affecting the joints. The hallmark of RA and JIA is arthritis with inflammation of the synovial membrane (synovitis), characterized by swelling, tenderness and restricted ranges of motion. Most joints in the body are at potential risk of arthritis-associated inflammation. In children with JIA, large joints, such as the knee, ankle and wrist, are most commonly involved whereas in adults with RA, peripheral joints in the hand or foot are predominantly affected. Disease pathophysiology is characterized by infiltration of immune cells such as B cells, T cells, inflammatory macrophages, neutrophils and mast cells, eventually leading to joint tissue destruction with bone erosion by osteoclasts and degradation of cartilage by proteases. The definition of active arthritis as defined by the pediatric association of the International League of Associations for Rheumatology (ILAR), is based on clinical findings of joint swelling, or a limited range of joint mobility with pain or tenderness. Whereas in the American College of Rheumatology (ACR) from 1987, the criterion for arthritis is based on joint swelling.

Pain is the most common symptom of RA as well as JIA, and has been associated with sleep disturbances, functional disability, and psychosocial distress and may continue despite inactive disease. Both JIA and RA commonly follow an unpredictable disease course fluctuating between phases of active disease and remission. Remission criteria have varied over time as have the percentages of individuals achieving remission. It is estimated that about 50% of children with JIA achieve remission within five years and about 40% have continued disease activity 30 years after disease onset. In adults with RA, the percentage of patients achieving remission is lower, but it is concluded that it is easier to achieve sustained remission today than it was a decade ago.

JIA and RA have a profound effect on an individual's situation and affect both physical and emotional aspects of functioning as well as health-related quality of life. Both JIA and RA are associated with comorbidities. In children with JIA, comorbidities such as low bone mass, increased risk of fractures, early onset of osteoporosis, bone growth disturbances, uveitis and fatigue have been reported. Furthermore, there is an elevated cardiovascular disease risk, especially for those children with continued disease into adulthood. In adults with RA, an increased risk of fatigue, as well as hypertension, osteoporosis, osteoarthritis, hyperlipidemia, and mortality from cardiovascular disease are reported. In both RA and JIA, inflammation around affected joints leads to muscular weakness, which may even persist when the disease is inactive. In adults with RA the combination of progressive joint damage and continuing functional decline may lead to activity limitations and participation restrictions in daily life. Thus, there are many reasons for individuals with JIA and RA to stay physically active. Given the high frequency of
individuals with RA reporting walking disability, it is imperative to explore contributing factors, such as gait deviations.

1.2.1 Juvenile Idiopathic Arthritis

JIA is the most common rheumatic disease of childhood and is a major cause of short term and long term disability. JIA does not refer to a single disease, but to all forms of arthritis that begin before 16 years of age, persist for more than six weeks and are of unknown etiology. Both genetic and environmental factors are thought to contribute to disease onset. The annual incidence of JIA in Sweden is estimated to be 11-15 per 100,000 children/year, which means that about 200-250 new children develop JIA annually. In total, there are about 1,200-1,700 children with JIA under the age of 18 in Sweden. Girls are more frequently affected than boys with a gender ratio of about 2:3:1. For girls there is a peak onset at 1-3 years of age whereas the age of onset among boys is more evenly distributed throughout childhood. In pediatric rheumatology, the classification criteria have varied between countries and over time making population comparisons difficult. The most recent classification criteria, and the criteria used in this thesis, is the ILAR classification which classifies JIA into seven different categories. This classification criteria has been stated to be a “work in progress” rather than a static framework (Table I).

Ankle arthritis in JIA

Study III evaluates the occurrence, clinical characteristics and prognostic factors associated with ankle arthritis in children with JIA. The ankle joint is described as the second most frequently involved joint, after the knee, and is estimated to affect 21-60% of children with JIA. In recent reports, foot-related disability has been associated with increased disease activity, and the need for improved foot care programs has been highlighted. Furthermore, occurrence of ankle arthritis has been associated with more progressive disease and with reduced physical activity, as assessed by accelerometry. The ankle and the elbow joints have also been shown to be more prone to ultrasound verified subclinical activity in patients in remission. However, the designs of existing studies reduce generalizability of the result. Therefore the occurrence, clinical characteristics and prognostic factors associated with ankle arthritis were evaluated in a prospective, longitudinal and population-based cohort including 440 children with JIA (Study III).
<table>
<thead>
<tr>
<th>Table I. Adopted from ILAR classification criteria, definitions and exclusions 34.</th>
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</table>

**Systemic Arthritis**  
*Definition:* Arthritis in one or more joints with or preceded by fever of at least 2 weeks’ duration that is documented to be daily (“quotidian”) for at least 3 days, and accompanied by one or more of the following:  
1. Evanescent (nonfixed) erythematous rash  
2. Generalized lymph node enlargement  
3. Hepatomegaly and/or splenomegaly  
4. Serositis  
*Exclusions:* a, b, c, d.

**Oligoarthritis**  
*Definition:* Arthritis affecting one to 4 joints during the first 6 months of disease. Two subcategories are recognized:  
1. Persistent oligoarthritis: Affecting not more than 4 joints throughout the disease course  
2. Extended oligoarthritis: Affecting a total of more than 4 joints after the first 6 months of disease  
*Exclusions:* a, b, c, d, e.

**Polyarthritis (Rheumatoid Factor Negative)**  
*Definition:* Arthritis affecting 5 or more joints during the first 6 months of disease; a test for RF is negative.  
*Exclusions:* a, b, c, d, e.

**Polyarthritis (Rheumatoid Factor Positive)**  
*Definition:* Arthritis affecting 5 or more joints during the first 6 months of disease; 2 or more tests for RF at least 3 months apart during the first 6 months of disease are positive  
*Exclusions:* a, b, c, e.

**Psoriatic Arthritis**  
*Definition:* Arthritis and psoriasis, or arthritis and at least 2 of the following:  
1. Dactylitis  
2. Nail pitting or onycholysis  
3. Psoriasis in a first degree relative  
*Exclusions:* b, c, d, e.

**Enthesitis Related Arthritis**  
*Definition:* Arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following:  
1. The presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain  
2. The presence of HLA-B27 antigen  
3. Onset of arthritis in a male over 6 years of age  
4. Acute (symptomatic) anterior uveitis  
5. History of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter’s syndrome, or acute anterior uveitis in a first-degree relative  
*Exclusions:* a, d, e.

**Undifferentiated Arthritis**  
*Definition:* Arthritis that fulfills criteria in no category or in 2 or more of the above categories

Exclusions a: Psoriasis or a history of psoriasis in the patient or first degree relative. b: Arthritis in an HLA-B27 positive male beginning after the 6th birthday. c: Ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter’s syndrome, or acute anterior uveitis, or a history of one of these disorders in a first-degree relative. d: The presence of IgM rheumatoid factor on at least 2 occasions at least 3 months apart. e: The presence of systemic JIA in the patient.  
Abbreviations: ILAR, International League of Associations for Rheumatology.
1.2.2 Rheumatoid Arthritis

RA is a chronic, inflammatory, autoimmune, systemic disease and is the most common rheumatic disease in adults. The etiology of RA is unknown but both genetic and environmental factors are thought to contribute to disease onset. Population based studies demonstrate that RA affects about 0.5-1% of the general population in developed countries and in Sweden 0.5-0.7%. The peak age of onset is between 55 and 60 years and women are affected to a larger extent with a gender ratio of 3:1. In 2010 a new classification criterion was established in order to optimize diagnosis. In this thesis adults with RA were, however, diagnosed using the ACR criterion from 1987 (Table II).

Table II. Adopted from the 1987 ACR classification criteria for RA

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Morning stiffness</td>
<td>Morning stiffness in and around the joints, lasting at least one hour before maximal improvement.</td>
</tr>
<tr>
<td>Arthritis in at least three joints</td>
<td>At least three joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left proximal interphalangeal (PIP), metacarpophalangeal (MCP), wrist, elbow, knee, ankle, and metatarsophalangeal (MTP) joints.</td>
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<tr>
<td>Arthritis in hand joints</td>
<td>At least one area swollen (as defined above) in a wrist, MCP, or PIP joint.</td>
</tr>
<tr>
<td>Symmetric arthritis</td>
<td>Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPS, MCPs, or MTPs is acceptable without absolute symmetry)</td>
</tr>
<tr>
<td>Rheumatoid nodules</td>
<td>Subcutaneous nodules, over bony prominences, extensor surfaces, or in juxta-articular regions, observed by a physician</td>
</tr>
<tr>
<td>Rheumatoid Factor (RF)</td>
<td>Demonstration of abnormal serum of rheumatoid factor by any method for which the result has been positive in less than 5% of normal control subjects.</td>
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<tr>
<td>Radiographic changes</td>
<td>Radiographic changes typical of RA on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)</td>
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</table>

4/7 variables need to be fulfilled for classification as RA. Criteria 1 through 4 must have been present for at least 6 weeks. Abbreviations: RA, Rheumatoid arthritis; ACR, American College of Rheumatology.
1.3 TREATMENT MANAGEMENT

Treatment management in individuals with RA and JIA is based on a combination of pharmacological therapy, physical and occupational therapy, and psychosocial support, often provided by an inter-professional rheumatology team.

Pharmacological treatment

The primary focus of pharmacological therapy is the prompt resolution of inflammation in order to prevent joint destruction and systemic disease effects, to reduce disability and to improve health-related quality of life. Presently, there is no treatment that cures arthritis; still, recent advances in pharmacological treatment have changed the expectations of treatment over time, with sustained remission as the paramount goal. Nowadays a wide range of effective medication is available ranging from Non-Steroidal Anti-Inflammatory (NSAID) drugs and steroidal Intra-Articular corticosteroid injections (IACI) to Disease-Modifying Anti-Rheumatic Drugs (DMARDS) like methotrexate, and biological agents directed towards specific disease modulators, such as anti-Tumor Necrosis Factor-alpha (TNF-α). Both in children with JIA and in adults with RA there is evidence of a window of opportunity during which early pharmacological treatment can change the disease course in a milder direction and diminish destruction and deformity of the joints.

TNF is a cytokine that plays a key role in the inflammatory and immune responses. Treatment with anti-TNF-α aims to reduce disease activity and joint damage progression. Symptom relieving effects appear rapidly, often within days or weeks and produce both a local effect on inflammatory joint symptoms as well as a global effect on pain, stiffness and well-being. Multiple studies have evaluated the effect of anti-TNF-α treatment on disease activity in adults with RA and, with some variation in estimates, about 40% of patients have a good effect, 30% have a moderate effect and 30% have little or no effect. Anti-TNF-α treatment has a positive effect on the degenerative process particularly when combined with DMARDS such as methotrexate.

IACIs are an important therapeutic option to relieve the symptoms of active synovitis even though the effectiveness in joints in the lower extremities has been discussed. The symptom relieving effect appears rapidly with most effects during the first three weeks. This mode of therapy is generally considered for treatment in individuals with arthritis in a small number of joints, particularly large joints, or with a polyarticular disease with the aim of inducing prompt remission of synovitis, while simultaneously continuing/initiating therapy with DMARDS and/or biologic agents. IACI also plays an important role in the prevention of deformities. In children with JIA, ankle arthritis has proven to be more resistant to treatment with IACI than the knee, with relapse occurring in 55% of ankle vs. 27% of knee joints, and the risk of relapse has been estimated higher in the ankle and subtalar joints than in other joints, e.g. knee and wrist.

Non pharmacological treatment

Physical inactivity remains common in both adults with RA and children with JIA despite numerous studies having shown positive effects of physical activity on disease activity. Maintenance of an active lifestyle is vital for individuals with inflammatory joint disease, both to reduce the impact of arthritis-associated comorbidities and to benefit
from the positive effects of physical activity on general health and fitness \(^2, 98, 99\). Thus, the main goals for physical therapy interventions are to facilitate physical activity and to reduce the impact of disease by encouraging individuals to regularly undertake in exercises to improve or maintain: joint motion, balance, coordination, cardiovascular fitness and muscular strength. To gain benefits for general health and fitness, general recommendations by the World Health Organization (WHO) were stated for both adults and children \(^6\). The recommendations for physical activity for individuals with rheumatic disease are the same as for healthy individuals. However, the level and choice of activity needs to be carefully adapted to the individual’s capacity, disease severity, and fluctuations of the disease \(^100\). To gain health benefits, moderate and high intensity activities are recommended; however, walking is an important component of total physical activity and is an accessible and low-cost way of being physically active.

### 1.4 MEASURING GAIT DYNAMICS

Walking has long fascinated humans, and documentation on the subject exists from the time of Aristoteles, 384-322 BC. In the middle of the 19th century, along with the advances in photography, the first scientific attempts to understand walking took place. An increase in interest in instrumental clinical gait analysis followed at the beginning of the 20th century, with the need to rehabilitate adults returning from war with amputations. But the real breakthrough came with the invention of powerful computers in the 1980s \(^101\). Walking is a fundamental function and the most natural and convenient way of moving short distances, and often, only requiring a pair of comfortable shoes.

In clinical settings, walking function is commonly measured using walking speed \(^17\), the six-minute walk test \(^102\), or self-reported questionnaires, such as the Health Assessment Questionnaire (HAQ) \(^103\), Child HAQ (CHAQ) \(^104\) and Rheumatoid Arthritis Quality of Life Scale \(^105\). Performance based measures, such as the timed up-and-go and the six-minute walk test, etc., are useful to quantify functional improvements or to classify function in a clinical setting but are not informative about movement quality. Performance based tests are informative in determining if walking function is impaired and by how much (in seconds or distance), but are not helpful in answering questions about the “which and why” of abnormal walking patterns. Both inflammatory and mechanical processes contribute to the development of pain and deformities and eventually disability in individuals with arthritis \(^16\). In order to enhance the understanding of how these processes impact gait dynamics the combination of advanced measures such as three dimensional (3D) gait analysis and ultrasound (US) has been recommended \(^12,106\).

#### 1.4.1 Three dimensional gait analysis

3D gait analysis provides detailed information about normal and pathological gait and is useful in clinical practice and for research purposes \(^101\). Information about joint rotation and forces are obtained to further outline the relationship between joint disease, joint impairments and compensatory gait strategies \(^16\). The predominant focus in studies using 3D gait analysis in adults with RA has been on the foot, with fewer studies examining the influence of the larger joints in the lower extremities \(^17,18\). This is reasonable since the foot and ankle complex is highly involved in the disease process, both in adults with RA and children with JIA \(^67,107\). A few studies have evaluated gait in children with JIA \(^10,20,21,108-112\). Most studies including 3D gait analysis in RA and JIA are observational or evaluate
orthopedic interventions \textsuperscript{18, 20, 21} and, as previously discussed, there are only few studies evaluating the effect of pharmacological intervention on gait dynamics.

A motion analysis laboratory contains specialized equipment operated by a team of multidisciplinary personnel, including physiotherapists, podiatrists, engineers and medical doctors such as orthopedic surgeons, neurologists and rheumatologists \textsuperscript{101}. Motion analysis begins with physical examination including assessments of joint range of motion, muscular contracture, muscle strength, bony deformity and examination of the neurological system. Gait analysis can be performed either barefoot or with footwear and with or without walking aids. During 3D gait analysis an individual is instructed to walk back and forth on an established pathway, approximately 10 meters in length, while measures of kinematics and kinetics are obtained using 3-D cameras and force-plates \textsuperscript{114}.

### Areas of potential use for 3D gait analysis within rheumatology

- Explain the relationship between joint disease, joint impairments, compensatory gait strategies and walking disability
- Establish as a baseline before treatment
- Evaluate interventions e.g. pharmacological, surgical and conservative (orthotics, and physiotherapy)
- Patient educational purposes
- Complement information obtained through self-reported and performance based outcomes

From 3D gait analysis, measures of kinematics, kinetics and spatiotemporal parameters can be obtained to enhance our understanding of specific gait pathology \textsuperscript{18}. Kinematics is defined as bone motion or the relative motion between two adjacent bones, but does not account for the cause of that motion. Thus, kinematics includes joint rotations, velocities and acceleration and answer questions about \textit{which} gait deviations are occurring. Kinetics includes the study of forces, moments and powers and may answer questions about \textit{why} a specific gait deviation occurs \textsuperscript{101, 114}. These forces, not visible to the eye, are measured through the use of force plates. A movement of the body can be generated by moments. Moments are the effect of a force acting at a distance from the joint axis, and may cause the segment to rotate or to stop rotating. Moments are described either as internal (the forces from muscles, ligaments and tendons that act on a joint) or external (gravitational, inertial, and contact forces acting on the body) \textsuperscript{101, 114}. Joint power provides information regarding muscle action, such as whether the muscles are performing eccentric or concentric contractions and is estimated by multiplying the joint moments and angular velocity. Joint powers are classified as either absorbing power (eccentric contraction) or generating power (concentric contraction) \textsuperscript{101, 114}. Simultaneously during the 3D gait analysis, information about spatiotemporal parameters, e.g. walking speed, stride length, step length and limb support time can be obtained. These measures are important, not only to provide a description of an individual’s walking function but also to interpret measures of kinematics and kinetics \textsuperscript{115}. Moreover, spatiotemporal parameters are commonly normalized to height,
and moment and powers to body weight, in order to allow comparisons between individuals and over time.\textsuperscript{116}

A standardized terminology is adopted to analyze gait dynamics. Analyses are based on a gait cycle, also referred to as a stride, which starts when the foot strikes the ground and ends when the same foot strikes the ground again. A gait cycle is subdivided into a stance phase, the first 60\% and a swing phase, the last 40\% of the gait cycle. The stance and swing phases are further subdivided to enhance communication and understanding of gait deviations\textsuperscript{101}.

**Measures of gait dynamics**

Gait variables obtained with 3D gait analysis are often reported as single values, such as minima or maxima, or ranges of motion, e.g. max knee flexion in swing or max dorsiflexion in stance.\textsuperscript{11} However, interpretation of an individual’s level of overall gait quality may be difficult due to the complexity and interdependence of gait data and the volume of variables generated. During the last decade, several statistical methods, indexes and classifications based on data from 3D gait analysis were developed in order to create scores indicating overall gait quality, well summarized by Cimolin & Galli (2014)\textsuperscript{117}. In this thesis only the Gait Deviation Index (GDI) published in 2008, and the GDI-kinetic from 2011 are considered\textsuperscript{118,119}. The GDI scores are generic, thus they quantify gait deviations in any individual and generate a unique score for the left and right sides. The GDI is a measure of overall gait quality and is informative of the level of deviance in an individual’s gait pattern compared to the average gait pattern of healthy controls. Thus, the GDI score itself is not informative of which joint rotations or anatomical planes are most effected. The GDI is based on kinematics from the pelvis and hip in all three anatomical planes, the knee and ankle in the sagittal plane and foot progression in the transversal plane\textsuperscript{119} and the GDI-kinetic includes frontal and sagittal plane moments and joint powers from the hip, knee and ankles\textsuperscript{118}. A GDI score of 100 or higher indicates typical gait pattern, while each 10 point decrement below 100 indicates 1 SD from normal gait, e.g. a GDI score of 89 indicates 1.1 SD from normal gait. GDI scores incorporate the entire variability across the gait cycle and take both deviations in timing and amplitude into account.

Using the GDI as a measure of overall gait quality in individuals with RA and JIA was novel with Studies I, II and IV. The GDI is used for populations with cerebral palsy to improve the understanding of the overall gait deviations, and to follow individuals over time or after interventions\textsuperscript{119-124}. We believe this could also be true within rheumatology and doing so would enhance the understanding of the relationship between mechanical and inflammatory processes and gait deviations, and their interplay over time and following interventions. Moreover, relating measures of gait quality to measures of walking disability would add to the understanding of the association between them.

Reduced walking speed and cadence, shorter stride and step length, and prolonged double limb support time are common findings in individuals with RA and JIA\textsuperscript{18,21}. In healthy individuals reduced walking speed has been linked to reduced movements and moments\textsuperscript{115}, not unlike the specific gait patterns noted in RA and JIA\textsuperscript{11}. Thus, a current debate focuses on whether speed or pathology, or a combination of both, are the main cause of gait deviations\textsuperscript{13,125,126}. A combination is most likely the cause, however, the impact of walking speed on gait dynamics varies with the actual speed and pathologies involved.
Joint power is informative of the type of muscle contraction and the rate at which the muscles are contracting. Adequate ability to generate and absorb joint power is necessary for activities of daily living such as walking and stair-climbing. Joint power can be compromised for many reasons such as reduced speed, reduced range of motion, stiffness and muscular weakness. In healthy individuals, the ability to generate power in both the ankle and the hip has been identified as an important factor in increasing walking speed. In older healthy adults and in individuals with neurological disabilities a distal-to-proximal shift in muscle function has been demonstrated when ankle power has been impaired. In Study IV in this thesis, the ability to generate ankle and hip joint power was evaluated after treatment with foot IACI in children with JIA. Since ankle arthritis has been associated with reduced muscular strength, we hypothesized that ankle power would be impaired in relation to healthy controls. Furthermore we hypothesized that the ability to generate ankle power would improve with treatment.

1.5 RATIONALE FOR THIS THESIS

Gait deviations in individuals with RA and JIA have previously been demonstrated as a consequence of active disease. Within the current era of new and potent medications, it is important to determine whether gait dynamics are impaired despite pharmacological interventions. It is also important to identify usable measures of overall gait quality that facilitate comparisons between groups and following interventions, in order to enable future longitudinal analyses. The studies in this thesis extend the knowledge and understanding of changes in gait dynamics following pharmacological interventions in individuals with RA and JIA. Moreover, the implication of ankle arthritis on disease progression and on gait dynamics is demonstrated and discussed. The findings from this thesis could, together with future research in this field, make important contributions to improving clinical guidelines and treatment recommendations for improved walking ability in individuals with RA and JIA.
1.6 AIMS

The aims of this thesis were to evaluate the usability of measures of overall gait quality and the effect of pharmacological interventions on gait dynamics in individuals with RA and JIA.

The specific aims of the studies were:

Study I

To evaluate the usability of the GDI in adults with RA. The specific aims were: a) to evaluate the ability of the GDI to identify gait deviations b) to evaluate the inter-trial repeatability and c) to examine the relationship between GDI and walking speed, physical disability and pain.

Study II

To determine the effects of anti-TNF-α treatment on gait dynamics in adults with RA.

Study III

To evaluate the occurrence, clinical characteristics and prognostic factors associated with ankle arthritis in children with JIA. The specific aims were: a) to describe clinical characteristics in children with early ankle arthritis and b) to assess associations between early ankle arthritis and disease progression and remission status eight years after disease onset.

Study IV

To evaluate short (3 weeks) and long-term (3 months) effects of IACI treatment on overall gait dynamics and patient-relevant outcomes in children with JIA who had foot and ankle arthritis. The specific aims of this study were: a) to evaluate gait dynamics and self-reported physical disability before and following treatment with IACI and b) to determine whether children with polyarthritis and oligoarthritis respond similarly to IACI treatment.
2 METHODS

Several outcome measures were used in the four studies (Table III). A brief summary of the study outlines are presented below, followed by a more detailed description in tables and text regarding participants, data collection, evaluation methods, and data analysis.

2.1 STUDY OUTLINES

Study I

A retrospective case-control analysis was performed to evaluate the usability of the GDI in adults with RA. Sixty-three adults with RA and 59 healthy controls without walking difficulties participated in the study. All subjects with RA who had performed a gait analysis at the Motion Analysis Laboratory at the Karolinska Hospital, Stockholm between 2002 and 2010 were considered for inclusion. Included data were obtained at gait analysis, from the Swedish Rheumatology Quality Register\textsuperscript{130} or from the patient’s medical record.

Study II

A prospective pre-post design study was conducted to quantify the impact of anti-TNF-α treatment on gait dynamics in adults with RA. Sixteen adults with RA who started treatment with anti-TNF-α between 2004 and 2010 were included. Gait dynamics, pain, disease activity and self-reported physical disability were evaluated before introduction of anti-TNF-α treatment and after three months of treatment.

Study III

The occurrence of ankle arthritis and associations with polyarticular disease and failure to achieve remission was assessed in a prospective population based cohort study. Four hundred forty children with JIA, including all ILAR categories, from four Nordic countries
Methods were included over an eight year interval. Relevant data was retrieved from the Nordic Study group of Pediatric Rheumatology (NoSPeR) database.

Study IV

A prospective pre-post design study was conducted to evaluate the effect of foot IACI on gait dynamics using 3D gait analysis and clinical outcome measures. Forty-three children with JIA undergoing treatment with IACI due to foot synovitis between 2008 and 2013 were included together with 40 healthy controls matched by age and gender. Gait dynamics, pain and foot-related disability were evaluated before treatment, and three weeks and three months after treatment.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Outcome measures</th>
<th>Data analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Retrospective, cross-sectional, case-control study</td>
<td>n=122</td>
<td>Gait dynamics, Pain, Physical disability</td>
<td>Descriptive statistics, ICC 2.1, One-way ANOVA, Student’s t-test</td>
</tr>
<tr>
<td>II</td>
<td>Prospective pre-post design study</td>
<td>n=16 adults with RA</td>
<td>Gait dynamics, Pain, Physical disability</td>
<td>Descriptive statistics, Sample size calculation, Spearman’s rank correlations, Wilcoxon’s signed rank test</td>
</tr>
<tr>
<td>III</td>
<td>Prospective population based cohort study</td>
<td>n=440 children with JIA, all ILAR categories</td>
<td>Ankle arthritis, Pain, Physical disability, Disease characteristics</td>
<td>Descriptive statistics, Chi-square (χ²), Logistic regression, Mann Whitney U test</td>
</tr>
<tr>
<td>IV</td>
<td>Prospective pre-post design study</td>
<td>n=83 adults with RA, 40 healthy children</td>
<td>Gait dynamics, Pain, Physical disability, Foot-related disability, Disease characteristics</td>
<td>Descriptive statistics, Friedman’s Two-Way ANOVA, Linear mixed model, Student’s t-test, Wilcoxon’s signed rank test</td>
</tr>
</tbody>
</table>

Table III. Overview of design, participation, outcome measures and data analysis in the thesis.

Abbreviations: RA, Rheumatoid Arthritis; JIA, Juvenile Idiopathic Arthritis; ILAR, International League of Associations for Rheumatology; ICC, Intraclass Correlation Coefficient; ANOVA, Analysis of Variance

2.2 PARTICIPANTS AND DATA COLLECTION

A total sample of 645 individuals participated in the present thesis. Two studies (Study I and II) included adults and two studies (Study III and IV) included children. The pre-treatment gait analysis evaluation for participants in Study II was included in Study I. Healthy participants were included in Study I and IV (n=99, Study I: 59 adults and Study IV: 40 children) (Table IV). In this thesis, healthy participants are defined as individuals without any condition known to affect walking function such as: musculoskeletal disease, inflammatory joint disorder, neurological disorder, or gross motor delay.
Table IV. Overview of participants in Studies I-IV. Details of participants characteristics are described in each paper.

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Gender (number female/male)</th>
<th>Age at inclusion (years min-max)</th>
<th>Disease duration (years min-max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>63 adults with RA</td>
<td>54/9</td>
<td>25-82</td>
<td>1-46</td>
</tr>
<tr>
<td></td>
<td>59 healthy adults</td>
<td>38/21</td>
<td>25-86</td>
<td>n.a</td>
</tr>
<tr>
<td>II</td>
<td>16 adults with RA (overlapping with Study I)</td>
<td>11/5</td>
<td>35-74</td>
<td>1-39</td>
</tr>
<tr>
<td>III</td>
<td>440 children with JIA</td>
<td>291/149</td>
<td>1-16*</td>
<td>n.a</td>
</tr>
<tr>
<td>IV</td>
<td>43 children with JIA</td>
<td>35/8</td>
<td>5-18</td>
<td>0.5-14</td>
</tr>
<tr>
<td></td>
<td>40 healthy children</td>
<td>28/12</td>
<td>5-20</td>
<td>n.a</td>
</tr>
</tbody>
</table>

Abbreviations: RA, Rheumatoid Arthritis; JIA, Juvenile Idiopathic Arthritis; n.a, not applicable. * Age at disease onset.

Study I

In Study I, 63 adults with physician-diagnosed RA, and 59 healthy adults, matched by age, were included from the Motion Analysis Laboratory database at the Karolinska University Hospital, Stockholm. Participants had completed a 3D gait analysis between 2002 and 2010. All individuals with RA fulfilled the 1987 revised ACR criterion, had lower extremity involvement, and did not use walking aids. Exclusion criteria were: a history of major joint surgery, such as total joint arthroplasty or arthrodesis of the hip, knee, or ankle, or IACI less than four weeks prior to examination. Individuals with a neurological disorder or gross motor delay were excluded, as were those with a HAQ score registered more than one month from the date of the gait analysis. Of the 86 patients identified in our database with inflammatory joint disease, 23 did not meet the inclusion criteria or met the exclusion criteria, yielding a cohort of 63 participants.

Data from one gait analysis session for each included individual were used in the analysis. If individuals with RA had done multiple gait analysis evaluations, the first analysis was used. Measures of demographics, medical treatment, physical disability, and pain were obtained either at the gait analysis session, from the patient’s records or from the Swedish Rheumatology Quality Register, a national database of health information. Data registered within one month of the gait analysis session were included. Two clinical researchers (ACE, EWB), experienced in gait analysis, collected the data using a standardized procedure.

Study II

Sixteen adults with RA were included. Patients were recruited between 2004 and 2010 from the rheumatology outpatient clinic at Karolinska University Hospital, Stockholm and from one private rheumatology outpatient clinic in Stockholm. All patients were selected on the basis of availability and willingness to participate and were scheduled to start anti-TNF-α treatment, either of Etanercept (38%), Infliximab (31%), Adalimumab (25%) or Golimumab (6%). To be included in the study, participants had to meet the following criteria: (i)
Methods

physician-confirmed RA, meeting the 1987 ACR criterion for RA \(^{35}\), (ii) lower extremity involvement but no use of walking aids, (iii) initiation of treatment with anti-TNF-\(\alpha\) after performing the gait analysis, (iv) no history of joint surgery (arthroplasty and/or arthrodesis of the hip/ knee and/or ankle), and (v) no intra-articular steroid injections within four weeks before the gait analysis. Eighteen patients were included but two patients were excluded from the analysis because of technical data acquisition issues.

Participants conducted two 3D gait analyses, one prior to the start of their anti-TNF-\(\alpha\) treatment and one after three months of treatment. The analyses were conducted by either of two investigators (EWB, ACE). GDI and GDI-kinetic scores were calculated based on data from the 3D gait analysis \(^{118, 119}\). Measures of pain, physical disability and disease activity were collected at baseline and at the 3-months follow-up, either at the gait analysis session or retrieved from the Swedish Rheumatology Quality Register \(^{130}\).

Study III

The population-based approach Nordic JIA cohort consists of 500 children; among these, 440 were followed prospectively for a median of 97 months (IQR 95–105) and classified according to the ILAR criteria. Consecutive incident cases of newly diagnosed JIA from defined geographic areas of Denmark, Finland, Norway and Sweden were included. The inclusion period was from January 1 1997 to June 30 2000 (3.5 yrs. in Norway, 3.0 yrs. in Sweden, Finland and Copenhagen, Denmark and for 1.5 yrs. in Århus, Denmark). During the study period, pediatric rheumatologists from twelve participating centers registered all children with JIA. ILAR category was determined for the majority of patients, separately by two of the authors (LB and EN), and based on all available information that was registered at each visit during the study period \(^{34}\). The study design and disease characteristics of the participants are extensively described elsewhere \(^{131}\).

Data included in Study III were retrieved from the Nordic JIA cohort database by two researchers (LB, ACE). Number of active joints in the lower extremity over the first eight years of disease was analyzed in relation to data of disease characteristics, level of physical disability and disease outcome.

Study IV

Forty-three children diagnosed with JIA, according to the ILAR criteria \(^{34}\), and 40 healthy children matched by age participated in the study. Children with JIA were included consecutively between October 2008 and January 2011 and between November 2011 and March, 2013 from the Astrid Lindgrens Children’s Hospital. Inclusion criteria were: i) active arthritis in any foot joint ii) scheduled for IACI iii) aged between 5 and 18 years, iv) typically developing otherwise and v) able to understand written and spoken Swedish. Additional joint injections in knees, hips and upper extremities were allowed. Exclusion criteria included IACI less than four weeks prior to the assessment and any history of major surgery in lower extremity such as ankle arthrodesis. Children were placed under general anesthesia and injected in subtalar and midtarsal joints using fluoroscopy and contrast (Omnipaque 300 TM) to ensure an optimal needle placement and treatment effect. Triamcinolone hexacetonide (Lederspan®) was used in all joints except for distal and proximal phalangeal joints which were injected with methylprednisolone (Depo-Medrol®). Participants were instructed not to walk on the treated side/s for 24 hrs in accordance with the standard clinic protocol.
Gait dynamics, physical disability and disease characteristics in children with JIA were evaluated at three time points (Figure 3): prior to IACI treatment (mean (SD) = 5(7) days), three weeks after treatment (mean (SD) = 22(6) days) and three months (mean (SD) = 96(10) days) after treatment with IACI. Two clinical researchers (SH, ACE) experienced in childhood rheumatic disorders extracted demographic and medical data from the patient’s medical record according to a standardized procedure to reduce the potential for misclassification bias. The following measures were collected: demographics, treated joints and baseline medications, joint impairments, pain, self-reported foot-related disability and gait dynamics.

**Figure 3.** Overview of included children; study design and methods in Study IV. Note that three of the five children not participating in the 3 weeks evaluation did participate in the three months evaluation.
2.3 EVALUATION METHODS AND OUTCOMES

Methods for data collection are summarized in Table V and described in details in the following section.

<table>
<thead>
<tr>
<th>Objective</th>
<th>Method</th>
<th>Study</th>
<th>ICF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gait dynamics</td>
<td>3D Gait analysis</td>
<td>I, II, IV</td>
<td>Body function</td>
</tr>
<tr>
<td>Pain</td>
<td>VAS</td>
<td>I, II, IV</td>
<td>Body function</td>
</tr>
<tr>
<td></td>
<td>Faces pain scale</td>
<td></td>
<td>Body function</td>
</tr>
<tr>
<td>Physical disability</td>
<td>CHAQ/HAQ</td>
<td>I-IV</td>
<td>Activity &amp; Participation</td>
</tr>
<tr>
<td>Foot-related disability</td>
<td>JAFI</td>
<td>IV</td>
<td>Body function/Activity &amp; Participation</td>
</tr>
<tr>
<td>Disease characteristics</td>
<td>28- joint count, occurrence of arthritis, Joint Score</td>
<td>II-IV</td>
<td>Body function/structure</td>
</tr>
<tr>
<td></td>
<td>DAS28-CRP, ESR, CRP, ANA, HLA-B27, Uveitis</td>
<td>II, III</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ICF, International Classification of Functioning, Disability and Health; 3D, three dimensional; VAS, Visual Analog Scale; HAQ, Health Assessments Questionnaire; CHAQ, Child HAQ; DAS-28, Disease Activity Score; ESR, Erythrocyte sedimentation Rate; CRP, C-Reactive Protein; ANA, Anti-nuclear antibody; HLA-B27, Human leucocyte antigen B27

2.3.1 Measuring gait dynamics

Three dimensional gait analysis

3D gait analysis was conducted to assess deviations in gait patterns. All 3D gait analyses were conducted at the Motion Analysis Laboratory at the Karolinska University Hospital, Stockholm between 2002 and 2013. In most cases gait analyses were conducted in the afternoon to avoid morning stiffness, though some individuals did not report morning stiffness and preferred to come in the morning. At all sessions participants walked barefoot and at a self-selected comfortable speed.

An eight-camera motion analysis system with passive markers (Vicon MX40, Oxford, UK) was used to measure kinematics and two staggered force plates (Kistler Type 9281C, Winterthur, Switzerland) were used to simultaneously measure ground reaction forces. Joint reaction moments and powers were computed through inverse dynamics. All moments in this thesis are presented as internal moments. Subjects walked on a 10 meter walkway and repeated the task up to 15 times in an effort to acquire kinematic and kinetic data from at least five gait cycles on each side. Effort was made to direct the subjects to strike the force plates cleanly and consecutively. Of the available gait cycles, three representative cycles were chosen for left and right side (leg) individually. All subjects were tested using a full-body model (34 markers, 15 segments) marker set. Markers were placed by experienced physiotherapists (EWB and ACE) on well-defined anatomical landmarks.
The lower body was modeled as seven segments (pelvis, two thighs, two shanks and two feet) according to Vicon’s Plug-In-Gait model. Measurements from the upper body (trunk, head and arms) are not included in the present thesis. Pelvis angles in all planes and foot progression (transverse plane) angles are described in global coordinates whereas all other hip, knee and ankle angles are described relative to the proximal segment. Each foot was considered as one rigid body, articulating with the tibia in plantar/dorsiflexion.

Figure 4. Marker placement during 3D gait analysis.

Spatiotemporal parameters, such as walking speed, stride and step length, were normalized according to Hof to generate dimensionless (nd), and thereby comparable, numbers. In Study IV, joint power generation was defined as the joint moment multiplied by the joint angular velocity divided by body weight (W/kg) and was calculated in pre-swing/early swing.

Gait Deviation Index (GDI), GDI-kinetic and speed-matched GDI

The Gait Deviation Index (GDI) is a measure of overall gait quality in the lower extremity and is based on kinematics from the pelvis and hip in all three anatomical planes, the knee and ankle in the sagittal plane and foot progression in the transversal plane (Figure 5). The GDI-kinetic includes frontal and sagittal plane moments and joint powers from the hip, knee and ankles. Thus, GDI scores are based on gait parameters that can only be obtained by 3D gait analysis. GDIs, both for the individuals with RA/ JIA and the healthy controls, were calculated using MATLAB and the calculations were based on a reference set walking at a self-selected speed and consisted of one representative stride from right and left side in 83 healthy children (Study I), 59 healthy adults (Study II) and 40 healthy children (Study IV). GDI-kinetic scores in Study II were based on a reference set of 56 adults. Two GDI scores are generated from each stride, for left and right side (leg) independently. GDI scores are interpreted as follows: a value of 100 or higher indicates a typical gait pattern; while each 10-point decrement below 100 indicates one standard deviation (SD) from typical gait (e.g. a GDI score of 85 indicates 1.5 SD from normal gait).
GDI scores do not control for the effects of walking speed, thus healthy individuals walking at slower speeds have GDI scores of less than 100. To evaluate the effect of speed on the GDI in individuals with RA, GDI scores were additionally calculated using a speed-matched reference set (Study I) \(^{133}\). These speed-matched GDI scores (SMGDI) are described in detail in Study I \(^{134}\).

**Figure 5.** Reflective markers are placed on anatomical landmarks (A). Body parts are simplified to segments (B) and movements are displayed in three planes (C). Solid lines represent left side and dashed lines represent right side (C). The Gait Deviation Index (GDI) (D), a measure of overall gait quality, is based on 9 gait curves from 3 planes and 4 joints. A GDI score of 100 or higher indicates normal gait pattern, while each 10 point decrement below 100 indicates 1 SD from normal gait (e.g. GDI = 85 means 1.5 SD from normal gait).
2.3.2 Measuring pain

Visual Analogue Scale and the Faces Pain Scale

In Study I and II, a Visual Analog Scale (VAS) ranging from 0 (no pain) to 100 (worst pain) was used to assess pain during walking at the gait analysis session. In Study IV, the faces pain scale-revised was used for children younger than eight years of age. The faces pain scale uses six pictures to illustrate pain ranging from “no pain” to “worst pain”. The pain scales were rigorously explained using an interactive procedure. Directly after performing the walking task, the participants were asked to rate their perceived pain during walking as follows “Please rate how much pain you perceived during walking?” and “Where did it hurt?” In Study I, to assess the relationship between pain and gait dynamics, pain scores (VAS) were dichotomized into “no/low” pain (VAS 0 mm-30 mm) and “moderate/high” (VAS >30 mm) according to the proposed cut-point from Collins et al.

2.3.3 Measuring physical disability

The (Child) Health Assessment Questionnaire disability index

The Health Assessment Questionnaire disability index (HAQ) and the Child-HAQ (CHAQ) are 20-item questionnaires providing information about self-assessed physical disability. They are shown to be valid and reliable tools for assessment in adults with RA and children with JIA. Both HAQ and CHAQ contain eight domains addressing activities of daily living in the preceding week and include: walking, rising, hygiene, reach, dressing, handgrip eating and activities. Each item is scored on a four-point ordinal scale: 0 (without any difficulty), 1 (with some difficulty), 2 (with much difficulty) and 3 (unable to do). The eight domains together make a disability index that is also complemented by two VAS scores, one for disease-related pain and one for disease-related overall well-being. In Study I, to study the relationship between physical disability and gait dynamics, HAQ scores were dichotomized into “no/low” physical disability (HAQ 0-1) and “moderate/high” (HAQ 1.1-3). In Study III, the rising, walking and activities domains were compiled into a disability index representing disability from the lower extremity by adding the scores from each domain and dividing by three. In Study IV the walking scale from the CHAQ (CHAQ walk) completed before injections was used to group children with JIA in three groups with: “no”, “some” and “much” reported walking disability. In Study III and IV a proxy version of the CHAQ was used for children under the age of nine and ten respectively.

2.3.4 Measuring foot-related disability

Juvenile Arthritis Foot disability Index

The Juvenile Arthritis Foot disability Index (JAFI) was used to assess foot-related disability in the most involved foot over the preceding week (Study IV). JAFI is a 27-question survey and is divided into three subscales: impairments (9 questions), activity (14 questions) and participation (4 questions). Each item is scored on a five-point ordinal scale: 0 (never), 1 (occasionally), 2 (sometimes), 3 (frequently), and 4 (always). The JAFI has good content and construct validity and has demonstrated good reliability for assessing foot-related disability in children with JIA and preliminary results indicate good responsiveness. Median score and minimum and maximum values are reported for each subscale individually.
2.3.5 Measuring disease characteristics

Joint Score, 28-joint count and occurrence of arthritis

Joint involvement was assessed differently in the studies comprising the thesis. In Study II, the number of swollen and tender joints was derived retrospectively from the Swedish Rheumatology Quality Register and based on a 28-joint count \(^1^{141}\). In Study III, the cumulative number of joints with arthritis, as defined according to the ILAR criteria, was totaled \(^3^{34}\). In study IV, findings from clinical examination were compiled into a score called “the Joint Score” \(^1^{142}\). Hips, knees, ankles, hind/mid foot, and forefoot were assessed for: 1) capsular swelling or effusion (not for the hips or hind/mid foot), 2) tenderness and pain, and 3) loss of motion. A total score ranging from 0 (no impairment) to 26 (maximal impairment) was derived by adding the score from each joint \(^1^{142}\). By using the “Joint Score” all the joints in the foot were included, which was not feasible with standard scores.

Measures of disease activity and biomarkers

In Study II, the 28-joint Disease Activity Score based on C-reactive protein (DAS28-CRP) \(^1^{143}\), Erythrocyte Sedimentation Rate (ESR), and C-Reactive Protein (CRP) levels were analyzed before and three months after medical treatment. In Study III, the maximum values of ESR and CRP assessed during the first six months of disease were collected.

In Study III, the following data were derived from the Nordic JIA cohort database and analyzed in relation to presence of ankle arthritis: remission status at the final visit as determined according to the preliminary criteria published by Wallace \(^1^{144}\); uveitis, registered as present when confirmed by an ophthalmologist; Human Leukocyte Antigen B27 (HLA-B27); AntiNuclear Antibody (ANA), performed twice, at least three months apart and cumulative numbers of affected joints. ANAs included in analysis were measured using immunofluorescence on HEp-2 cells and were interpreted as positive or negative according to the reference values used by the local laboratory in each country.

2.4 STATISTICAL METHODS AND DATA ANALYSIS

Statistical methods and data analyses used are presented in detail below. A summary of the statistical approaches can be found in Table VI. Statistical analyses were performed using Statistica Software 10.0 (StatSoft Inc., Tulsa, OK, USA) (Studies I and II), Statistical Package for Social Sciences (SPSS), version 22 (SPSS Inc., Chicago, IL, USA) (Studies III, IV), Statistical Analysis Software version 9.3 (SAS Institute Inc., Cary, NC, USA) (Study IV) or G*power 3.1.9.2 (In Study II, sample size calculations) \(^1^{145}\). Differences were considered statistically significant for p-values < 0.05.

Measures of kinematics, kinetics and spatiotemporal gait parameters obtained from 3D gait analyses were averaged over the three gait cycles per side to account for natural variation in gait pattern. In all analyses except for in the linear mixed model used in Study IV, kinematic, kinetic and spatiotemporal gait parameters were averaged over left and right sides and then used in statistical analysis. Statistical methods were chosen and analyses were performed based on type of data, e.g. categorical or interval data, data distribution and sample sizes.
### Table VI. Overview of statistical methods used in Studies I-IV.

<table>
<thead>
<tr>
<th>Statistical method</th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chi-square</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
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<tr>
<td>Descriptive statistics</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Friedman’s two-way ANOVA</td>
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<td></td>
<td>X</td>
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<tr>
<td>Intra-class Correlation Coefficient (ICC&lt;sub&gt;2,1&lt;/sub&gt;)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Linear mixed model</td>
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<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Logistic regression</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Mann-Whitney U test</td>
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<td></td>
<td></td>
<td>X</td>
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<tr>
<td>One-way ANOVA</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sample size calculation</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Spearman’s rank correlation coefficient</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Student’s t-test</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Wilcoxon’s signed rank test</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Abbreviations: ANOVA, Analysis of Variance

### Descriptive statistics (Study I-IV)

Data types obtained in the different studies were ratio/interval, ordinal and categorical data. Ratio/interval data, e.g. gait analysis parameters, were presented using mean and standard deviation (SD) or median and minimum - maximum value or interquartile range (IQR, 25th to 75th percentile) depending on distribution of the data and the size of the sample. Ordinal data, e.g. from questionnaires, and VAS scales were presented by median and IQR or minimum and maximum values. Categorical data, e.g. presence of arthritis, were represented using total number and percent.

### Analysis of effect of pharmacological intervention

In Study II, the effect of anti-TNF-α treatment on gait dynamics was assessed using Wilcoxon’s signed rank test due to skewed distribution and reduced sample size. Spearman’s rank correlation coefficient was used to evaluate if improvement following treatment was related to baseline values in GDI, GDI-Kinetic and spatiotemporal parameters. Improvement was calculated as a percentage as follows: (variable after anti-TNF-α – variable before anti-TNF-α) / (variable before anti-TNF-α)*100. Correlations were interpreted according to Portney and Watkins: 0-0.25 (little or no relationship); 0.25–0.50 (fair); 0.50–0.75 (moderate to good) and 0.75–1 (good to excellent) 146.

Study IV: Effect of IACI treatment on VAS scores and Joint Score was estimated using a Friedman’s Two-Way Analysis of Variance (ANOVA) and on JAFI using Wilcoxon’s signed rank test. Differences gait dynamics over time in within children with JIA in relation to healthy children were calculated using a linear mixed model with two within effects; time, three time points (compound symmetry) and side left and right (unstructured).
Analysis of difference between individuals with JIA/RA and healthy controls

In Study I, differences in demographic variables, GDI scores and spatiotemporal parameters between adults with RA and healthy adults were evaluated using a Student’s t-test. In Study IV, differences between the children with JIA and controls were estimated with a Chi-squared test for the proportion females and males and with the Student’s t-test for age, weight and height. Differences in gait parameters between controls and children with JIA before treatment and three weeks after treatment were calculated using Student’s t-test. Differences between controls and polyarthritis and oligoarthritis respectively were analyzed with the Mann-Whitney U test due to skewed distribution and reduced sample size.

Gait dynamics in relation to physical disability and pain

In Study I, a one-way ANOVA was used to evaluate differences in GDI scores between individuals with RA when grouped according to level of physical disability (HAQ) and pain (VAS).

Sample size recommendations

In Study II, sample size recommendations for future studies were made based on the change in GDI, GDI-kinetic, dimensionless walking speed and stride length after anti-TNF-α treatment. In these calculations the following assumption was made: the differences following treatment could be considered a relevant difference between two different groups in a Randomized Control Study. The effect size was calculated by dividing the mean difference by the SD of difference for GDI, GDI-Kinetic, dimensionless walking speed, and stride length before and after anti-TNF-α treatment. Sample size calculations were based on an α-value of 0.05, a beta value of 0.8 and effect sizes.

Reliability of the gait deviation index

In Study I, the natural variation in GDI between strides at the same evaluation session the inter-trial (stride) repeatability was calculated with an Intra-class Correlation Coefficient (ICC_{2,1})^{147}, calculated from the mean square values derived from a one-way repeated-measures ANOVA. Calculations were based on three strides, and for each stride left and right side were averaged. ICC_{2,1} was interpreted according to the recommendations of Landis and Koch^{148}. ICC gives no information about the size of disagreement between the included strides, and should be complemented by the Standard Error of Measurement (SEM). This was calculated by adding the variances between the repeated measures for each subject, dividing the sum of the variances by the number of the subjects (n), and taking the square root (vmean square-within targets). To determine the size of the variation in gait, the repeatability coefficient was calculated (SEM x 1.96 x √2)^{149}. However, the repeatability coefficient, also called the smallest detectable change (SDC) can be interpreted as “the magnitude of change below which there is more than a 95% chance that no real change has occurred”^{150}. The repeatability coefficient refers to individual levels and should not be used to interpret the average change for a group of individuals^{149}.
Analysis of impact of ankle arthritis

In Study III, statistical analysis of differences in disease characteristics between children with and without ankle arthritis were estimated using Chi-square test (Fisher’s exact test 2-sided) for comparison of dichotomous variables and the Mann Whitney U test for comparison of non-parametric interval data. A multiple logistic regression analysis was performed in order to identify the association between early ankle arthritis and failure to achieve remission eight years after disease onset. The dichotomized variable remission (remission without medication) versus not being in remission (remission with medication and not in remission) was used as dependent variable in the regression model. The following independent variables were included; presence of ankle, knee and hip arthritis during the first year of disease, presence of HLA-B27, gender, and age at disease onset. A forward step-wise inclusion of variables was performed and the independent variables associated with the dependent variable (p<0.05 in the univariate analysis) were included in the multiple regression analysis. Results of the regression models are shown as odds ratio (OR) and 95% confidence interval (95% CI). The level of significance was set at 5% (p < 0.05).

2.5 ETHICAL CONSIDERATIONS

Studies I,II and IV were approved by the regional ethical board of Stockholm, Sweden. In Study III, The Research Ethical Committees in each country, Sweden, Norway, Finland and Denmark, gave their approval in accordance with national practice and legislation. All studies were conducted in accordance with the Declaration of Helsinki. Participation was voluntary and all participants were given oral and written information about the studies. Consent to participate in the study was obtained from all adults, and by parents or legal guardian where applicable in the pediatric population.
3 RESULTS AND DISCUSSION

3.1 GENERAL

In adults with RA the strongest predictor of walking disability eight years after disease onset is walking disability two years after disease onset $^{151}$. This result underpins the importance of identifying walking disability in early disease and revealing contributing factors. For example, there is evidence that gait deviations due to painful deformities in the foot may be improved by orthotic treatment when detected in early disease $^{152}$. Walking disability is complex, and in a study by van der Leeden et al. disease activity and pain were related to walking disability while joint deformities were not $^{151}$. Both disease activity and joint deformities have, however, been related to gait deviations $^{16}$. Within rheumatology the link between biomechanics of gait and walking disability has been identified as an important but under-researched area $^{16}$. The integration of biomechanics of gait into studies of patient subjective experience has the potential to yield new insights into factors contributing to walking disability $^{8}$. Within the current era of new and potent medications, it is important to ascertain whether gait dynamics are impaired despite pharmacological treatment. It is also important to identify usable measures of overall gait quality in order to facilitate comparisons between groups in future interventional or longitudinal analyses $^{18}$.

The main findings in this thesis reveal that gait deviations persist despite pharmacological interventions. We suggest that the biomechanical perspective should be considered when evaluating walking disability in arthritis care. This can be facilitated by the use of measures of overall gait quality, such as the GDI. GDI scores add an aspect of dynamic function, facilitate longitudinal analysis and enable comparisons between groups or following interventions. Furthermore, ankle arthritis and foot-related disability are common in children with JIA and are related to failure to achieve remission. Based on these findings we suggest that ankle arthritis should be taken into consideration in the assessment of prognosis and choice of treatment strategy in JIA.

In the following sections, main findings from the four studies in the thesis will be briefly presented and discussed followed by a discussion of methodologies and limitations. A
detailed description of results together with tables and figures are found in the original articles at the end of the thesis.

3.2 RESULTS

3.2.1 Ankle arthritis in JIA

The occurrence, clinical characteristics and prognostic factors associated with ankle arthritis in children with JIA from the first eight years of disease were analyzed (Study III). This population-based cohort has the advantage of being representative of the whole disease spectrum and its diverse clinical phenotypes, facilitating generalizability of the results. We hypothesized, and later concluded, that ankle arthritis was common and related to worse outcome.

The ankle was the second most frequently involved joint and was involved in 57% of the children with JIA (Study III) (Figure 6). The ankle presented early in the disease course with a median of seven months (IQR 6-13) after disease onset. Ankle arthritis was least common in the persistent oligoarticular category (25%) and most common in children with the extended oligoarticular (83%) and polyarticular RF negative disease (85%). The common occurrence of ankle arthritis must be seen in the light of existing literature pointing at diagnostic and treatment challenges, such as resistance to treatment with IACI, increased risk of relapse, and subclinical activity. Thus, it is important to diagnose ankle arthritis early in order to optimize treatment.

![Figure 6. Arthritis in the lower extremity during the first eight years of disease (n=440, Study III)](image-url)
In contrast to adult rheumatology, involvement of the ankle seemed to represent involvement of the whole foot. We found that in the 94 children with subtalar arthritis, 83 (88%) had additional ankle arthritis and for the 75 children with tarsal involvement 81% had ankle arthritis. A similar pattern was seen between ankle joint and MetaTarsoPhalangeal (MTP) joints and toe arthritis (Study III).

Children with occurrence of ankle arthritis during the first year of disease differed from those without early ankle arthritis in several aspects (Table VII). They were younger at disease onset and had higher levels of ESR and CRP during the first six months of disease after disease onset. Moreover, occurrence of ankle arthritis during the first year was associated with higher physical disability, with polyarticular disease course, and with failure to achieve remission eight years after disease onset. There was no difference between children with and without occurrence of early ankle arthritis during the first year regarding presence of ANA, HLA-B27 or uveitis.

In a multiple regression model, occurrence of ankle arthritis within the first year of disease was associated with failure to achieve remission eight years after disease onset, OR 2.0 (95% CI 1.3-3.0) when adjustments were made for: knee and hip arthritis during the first year, age at disease onset, presence of HLA-B27 and gender.

The common occurrence of ankle and foot arthritis in children with JIA reported from Study III is in conformity with existing research. The strengths of our study were the population-based approach and the inclusion of all ILAR categories, which facilitate generalization of the results. The most important findings were probably the high frequency of ankle arthritis and the fact that early occurrence of ankle arthritis was associated with a polyarticular disease course in young children and with failure to achieve remission.

Two clinical implications can be drawn from this study: first, an increased awareness of risk of extension to polyarticular disease course in children presenting with ankle arthritis and oligoarticular pattern; second, we suggest that occurrence of ankle arthritis should be taken into account in the assessment of prognosis and choice of treatment strategy in JIA. This could be achieved in clinical practice by including image-guided assessment, in order to detect arthritis extension early, as well as shorter follow-up intervals.
Table VII. Clinical characteristics for children with and without occurrence of ankle arthritis during first year of disease

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total group</th>
<th>Ankle arthritis first year of disease</th>
<th>No ankle arthritis first year of disease</th>
<th>Ankle vs. no ankle p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at disease onset, median (IQR)</td>
<td>440</td>
<td>4.9 (2.1-8.8)</td>
<td>6.6 (2.8-10.1)</td>
<td><strong>0.003</strong> ^b</td>
</tr>
<tr>
<td>Gender, female n (%)</td>
<td>440</td>
<td>127 (68)</td>
<td>164 (65)</td>
<td>0.475 ^a</td>
</tr>
<tr>
<td>ANA positive, n (%)</td>
<td>391</td>
<td>46 (29)</td>
<td>61 (26)</td>
<td>0.645 ^a</td>
</tr>
<tr>
<td>HLA-B27 positive, n (%)</td>
<td>410</td>
<td>33 (19)</td>
<td>53 (22)</td>
<td>0.462 ^a</td>
</tr>
</tbody>
</table>

**Assessments, first six months of disease**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total group</th>
<th>Ankle arthritis first year of disease</th>
<th>No ankle arthritis first year of disease</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR mm/hour, median (IQR)</td>
<td>333</td>
<td>45 (26-77)</td>
<td>24 (12-48)</td>
<td>&lt;0.001 ^b</td>
</tr>
<tr>
<td>CRP mg/liter, median (IQR)</td>
<td>332</td>
<td>28 (10-56)</td>
<td>10 (0-23)</td>
<td>&lt;0.001 ^b</td>
</tr>
</tbody>
</table>

**Assessments, first eight years of disease**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total group</th>
<th>Ankle arthritis first year of disease</th>
<th>No ankle arthritis first year of disease</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative joints, median (IQR)*</td>
<td>440</td>
<td>10 (6-16)</td>
<td>3 (2-9)</td>
<td>&lt;0.001 ^b</td>
</tr>
<tr>
<td>Remission at eight years follow-up, n (%)</td>
<td>427</td>
<td>63 (34)</td>
<td>118 (48)</td>
<td><strong>0.004</strong> ^a</td>
</tr>
<tr>
<td>Uveitis, n (%)</td>
<td>425</td>
<td>36 (20)</td>
<td>53 (22)</td>
<td>0.809 ^a</td>
</tr>
<tr>
<td>CHAQlow/HAQlow, n (%) &gt;0</td>
<td>358</td>
<td>18 (12)</td>
<td>17 (8)</td>
<td>0.279 ^a</td>
</tr>
<tr>
<td>CHAQ/HAQ, n (%) &gt;0</td>
<td>359</td>
<td>56 (38)</td>
<td>54 (26)</td>
<td><strong>0.020</strong> ^a</td>
</tr>
</tbody>
</table>

^aFisher’s exact test 2-sided, ^bMann-Whitney U test. n; number, ANA; Antinuclear antibody, HLA-B27; Human Leukocyte Antigen B27, (C)HAQ; (Child) Health Assessment Questionnaire. Values for the C-reactive protein (CRP) level and the erythrocyte sedimentation rate (ESR) are the maximum values reported during the first 6 months after disease onset, CHAQlow, Child Health Assessment Questionnaire lower extremity; percent of children rating > 0, indicating physical disability related to the lower extremities at the eight year follow-up. *Cumulative number of arthritis in specific joints that have been active during the first eight years of disease.
3.2.2 Measures of gait dynamics

Gait deviation index scores

While subjective evaluation of dynamic function after treatment in individuals with musculoskeletal disorders has been done for many years, valid objective measurements of dynamic function have been lacking. A novel aspect of this thesis was the use of the GDI scores, measures of overall gait quality, in individuals with RA and JIA.

GDI scores add an aspect of movement quality during dynamic function and were shown to be useful facilitating comparisons between groups and following interventions (Study I, II and IV) (Figure 7). Individuals with RA and JIA show gait deviations as compared with healthy controls. Moreover, adults with RA (Study I and II) had more pronounced gait deviations than the children with JIA (Study IV) (Figure 7). The average GDI score for children with JIA was slightly lower compared to healthy controls but was not statistically different (Study IV).

Figure 7. Overall lower extremity kinematics represented by GDI scores from Studies I, II and IV. * indicate level of statistical difference between groups. Using measures of gait quality facilitates comparisons between groups and after interventions.
The first discussions within our research group about developing a gait index for individuals with arthritis took place in 2008, the same year as the GDI was published. The GDI is, in contrast to its forerunners, a generic index and was proven valid to quantify gait deviations in any individual. Thus, we decided to evaluate the usability of the GDI as a measure of gait quality in adults with RA. The primary hypothesis was that the GDI would be a useful measure of overall gait quality within this group of patients.

The results from Study I showed that gait deviations in adults with RA were evident and the mean GDI score was 87 (SD 9), which is about 1.3 SD below a GDI score of normal gait pattern (p< 0.001) (Figure 1, Study I). Among our sample many subjects had established disease, and did not have access to current medical therapy at disease onset. Thus, the gait deviations they exhibited may also reflect, apart from impairments due to arthritis, joint deformities and/or compensatory walking strategies adopted to avoid loading of painful joints. In the children with JIA in Study IV, who had access to today’s more potent pharmacological treatment from disease onset, the level of gait deviation was minor with respect to kinematics (GDI score pretreatment 97 (SD 11) and did not differ statistically from healthy controls (Study IV). Moreover, this result could also be influenced by disease duration which was significantly shorter for children in Study IV (4.5 years (SD 3.6) compared to the participants with RA in Study I (15 years (SD 11). Another factor known to impact gait dynamics is pain but, interestingly; levels of pain were equivalent between the two samples.

When using GDI scores in clinical and in research settings, it is useful to estimate how much difference is required for a meaningful clinical change. In Study I, the size of the natural variation in gait between strides assessed at the same session was estimated to be 5.4 GDI units. Thus, individual differences in GDI for a person with RA should be above five GDI units to account for natural variation in gait. Therefore we consider this the minimal change in GDI required to be clinically meaningful for an individual with RA. Importantly, this number should not be confused with Minimal Clinical Important Difference (MCID) which requires comparison with accepted clinical standard outcomes measuring walking function, and preferably includes the patient’s own perspective. Thus, the MCIDs for GDI in RA and JIA are still to be determined. Our result is based on a within-session analysis using several strides from one 3D gait analysis session per included individual (Study I). Variation due to marker placement, skin movement artifacts, time of the day, and the experience of the assessor/s was not taken into account. Subsequently, we would expect a greater difference from a between-session analysis.

In conclusion, we recommend the use of GDI, or an equivalent measure, in future studies of gait dynamics in individuals with RA and JIA. The GDI provides an overall impression of gait quality and may, in combination with other measures, help to understand the relationship between RA/JIA, gait deviations and walking disability. It was estimated that on an individual basis a change of five GDI units or more was required to account for the natural variation in gait.

Walking speed

Clinical impression and previous literature conclude that individuals with RA and JIA commonly walk with reduced walking speed and cadence, shorter stride and step length and prolonged double limb support time. This was also true for the participants with arthritis included in this thesis (Study I, II, and IV). Walking speed is related to height,
meaning that tall people walk faster than people of short stature. Moreover, growing children may appear to walk faster over time but this may be an effect of skeletal growth. To overcome the problem with comparing walking speed in individuals of different height, spatiotemporal parameters obtained in this thesis were made dimensionless (normalized) according to the recommendations by Hof. Normalization of walking speed within rheumatology studies is uncommon and a detailed comparison with other studies is difficult. Individuals with RA and JIA included in this thesis (Study I, II and IV) walked with significantly reduced walking speed as compared to healthy controls (Figure 8). An important finding when comparing the walking speed from the RA and JIA populations in this thesis to healthy controls was that mean speed was still reasonably fast and, for most groups, within normal speeds of healthy controls (Figure 8). We, and others, relate this positive result to today’s treatment paradigm resulting in reduced disease activity and joint destruction.

**Figure 8.** Dimensionless self-selected walking speed summarized from Studies I, II and IV. Reference values on the x-axis are adopted from a reference set of 86 children walking at different speeds and the vertical lines indicate different speed intervals. Free = self-selected speed and at “slow” and “fast” speeds participants have been encouraged to slow or quicken their preferred walking velocity. * indicate level of statistical difference between groups.
Joint power

In children with JIA ankle power was reduced as compared to healthy children both before and after foot IACI treatment, \( p<0.001 \) (Figure 9) (Table 4 in Study IV). Adequate joint power is necessary for activities of daily living such as walking and stair-climbing. Joint power can be compromised due to reduced walking speed and reduced ranges of motion, both documented features in children with JIA (Table 4 in Study IV). It could also be possible that reduced generating ankle power is related to reduced muscle strength of the plantarflexors \(^{55, 56}\), which is a common finding in clinical practice. McKay et al. (2013) evaluated the effect of knee IACI treatment on muscle strength and concluded that muscular weakness was related to factors other than active arthritis, including pain, muscle atrophy due to inactivity, as well as the effect of cytokines and inflammatory myopathy \(^{56}\). Other possible causes of reduced ankle power during walking could be compensatory stiffening of the ankle joint in order to reduce pain and increase stability \(^{156}\).

![Ankle and hip power](image)

**Figure 9.** Ankle and hip joint power graphs for healthy controls (black) and in children with JIA (grey) (Study IV). Generating ankle power is significantly reduced between healthy controls and JIA \( p=0.001 \) while generating hip joint power does not differ between the groups.
An important finding in Study IV was that the ability to generate hip power in individuals with RA and JIA did not differ from healthy controls (Figure 9). This finding indicates that hip flexors were compensating for weaker plantarflexors. This is in contrast to healthy individuals in whom slower walking speed is associated with an increase in ankle power in relation to hip power (Figure 10)\textsuperscript{115}. The children with JIA in our sample had ankle and foot impairments which most likely restricted the ability to generate more ankle power. That hip muscles compensate for weaker ankle muscles has previously been described as an age-related mechanism in older healthy adults\textsuperscript{127} and as a compensatory mechanism in individuals with osteoarthritis\textsuperscript{157} and neurological disabilities\textsuperscript{158}. This could possibly explain the slower walking speed seen in the children with JIA, since it has been suggested that to increase walking speed, increased generation of both hip and ankle power is required\textsuperscript{128, 157}. The possible consequences on pain and function of this power shift toward the hips are not known and warrant further investigation. Importantly, joint moments and powers can only be obtained through 3D gait analysis including force plates recording. Thus, this technique is needed to evaluate these aspects in future studies and in clinical settings. In future studies the consequence of reduced ankle power on walking ability and sport participation for children with JIA would also be of interest to consider.

![Figure 10](image)

**Figure 10.** Black horizontal line represents the ankle/hip power ratio in 86 healthy children walking at five different speeds, data adopted from Schwartz et al 2008\textsuperscript{115}. The vertical black bar represents the healthy controls in Study IV and the grey vertical bar represents the children with JIA. Free= self-selected walking speed.

### 3.2.3 Effect of pharmacological treatment on gait dynamics

The effect of reduced disease activity through pharmacological treatment on gait dynamics is not fully understood and is therefore an important aspect to evaluate in order to improve walking ability. In Study II, the effect of anti-Tumor Necrosis Factor-alpha (TNF-\(\alpha\)) treatment was evaluated and in Study IV the effect of Intra-articular corticosteroid injection (IACI) in the foot and ankle was explored.
Results and discussion

Effect of anti-tumor necrosis factor -α therapy

Improvements in disease activity following anti-TNF-α treatment due to the fast-acting effects of these drugs are well known. The novel aspect of Study II was the evaluation of the effect of reduced disease activity, following anti-TNF-α treatment, on gait dynamics. In this pilot study we aimed to determine the effects of anti-TNF-α treatment on gait dynamics in individuals with RA. We hypothesized that gait dynamics would improve three months following treatment with anti-TNF-α, a hypothesis that was confirmed since gait dynamics improved as a result of treatment, however not to the levels of healthy controls.

As commonly shown in studies evaluating the effect of biologic therapy, significant improvements in Study II were seen in measures of disease characteristics such as; HAQ, HAQ Pain, HAQ Global, DAS28-CRP, ESR, CRP,28 joint count following treatment with anti-TNF-α (Study II). Moreover, participants reported less pain during walking after anti-TNF-α treatment: VAS median difference (IQR) =11 (0–21) (p = 0.05).

Gait dynamics, both with respect to kinematics (GDI p= 0.04), kinetics (GDI-k p=0.05) and spatiotemporal parameters, improved following therapy (Study II). However, despite improvements in gait dynamics as a result of treatment gait deviations persisted three months after anti-TNF-α treatment (three months scores: mean GDI 91 (SD 12), mean GDI-k 93 (SD 19). A meaningful change in GDI (>5 GDI units) was evident in only five out of 16 patients. Of these five patients, four had a baseline GDI score below 90 and there was a moderate to good negative correlation between percentages of improvement in GDI after anti-TNF-α compared to GDI before treatment (rs = –0.71, p = 0.002). This result indicated that those with lower baseline value improve the most.

As a result of anti-TNF-α treatment a majority of the patients increased their walking speed, with a mean increase of 8% (Study II). This increase in walking speed was in accordance with other studies which evaluated the effect of pharmacological treatment on gait dynamics. Oda et al. (2014) evaluated gait dynamics six months following treatment with anti-TNF-α, and reported an increase in walking speed of 22% . This more pronounced improvement in speed could be due to the longer follow-up time and the lower baseline scores compared to Study II. Both studies were e-published in 2013, and no prior studies evaluating the effect of anti-TNF-α treatment were identified. The results from both studies are based on data from small sample sizes and conclusions should be drawn cautiously. Moreover, many participants had established disease with disease durations that extend to before the introduction of biologic therapy. Together, the two studies touch on an important aspect; on average, gait deviations persist despite treatment with advanced pharmacological therapy. Future studies are needed which include longitudinal analysis of gait dynamics in individuals starting treatment with biologic therapy in early disease and should preferably combine gait dynamics with ultrasound and x-rays to identify those at greater risk of gait deviations despite good response in disease activity. Moreover, measures of walking disability should be obtained simultaneously to further outline the relationship between gait dynamics and walking ability.
Effect of intra articular corticosteroid injections

The aim of Study IV was to evaluate the effect of IACI on gait dynamics and patient-relevant outcomes in children with JIA with foot and ankle synovitis. The novel aspect of this study was the evaluation of gait dynamics and foot-related disability after IACI treatment in the era of biologic therapy, not previously evaluated. We hypothesized that gait dynamics was compromised in children with JIA who had foot involvements and that gait dynamics would improve with treatment, but not to the level of controls. However, we found that, as a result of IACI treatment, improvements were identified in foot-related disability and inflammatory joint symptoms but gait dynamics were unchanged.

As expected due to the proven effect of IACI, the number of joints with active arthritis improved significantly (p<0.001) (Study IV). Foot-related disability improved in the JAFI_{impairment} (p=0.001) and JAFI_{activity} subscales (p=0.023) following treatment, but not in the JAFI_{participation} subscale (p=0.278) (Table 3, Study IV). Importantly, despite improvements, 70% of the included children experienced continued foot-related disability at three months following treatment. These findings are in accordance with others who have highlighted the need for improved foot care in children with JIA. Given the high occurrence of children with ankle and foot involvement (Study III) and the persistent problems following medical treatment (Study IV) we recommend that foot-related disability is routinely assessed in clinical practice. The CHAQ walking scale may be used to identify walking disability but might not be sufficient to detect foot disability, and therefore, to address this, the CHAQ might be complemented by the JAFI.

Following treatment, there was no statistically significant improvement in self-rated pain during walking over the three evaluations (p=0.135) (Study III). This was surprising and in contrast to Broström and co-workers (2004) who found that pain significantly decreased as a result of IACI treatment. Our results could be influenced by general scoring difficulties among our sample and the rating by one individual who rated highly increased pain following treatment. Effort was made to only include pain in lower extremity while walking, thus, pain in hands and shoulders should not be reported. However, we still acknowledge that generalized pain could have influenced this result.

We find that the most important result from Study IV was that gait dynamics did not change following treatment. Most aspects of gait dynamics were, however, deviant compared to healthy controls following IACI treatment (Table 4, Study IV). This finding was in contrast to a study by Broström and co-workers (2004) where pain, walking velocity and joint moments improved as a result of IACI treatment. Importantly, gait deviations were more prominent after IACI treatment in their study as compared to baseline scores in Study IV. The two cohorts are interesting to compare since they were recruited from the same hospital but data collection was separated by ten years. We speculate that this improved general level of gait dynamics seen in our study was related to improved therapeutic options and strategies. An important strength with Study IV was that the included children were under general anesthesia during the IACI, and fluoroscopy and contrast enhancements were used to ensure an optimal needle placement and treatment effect. In future studies it would be of interest to evaluate the impact of gait dynamics on more demanding activities, such as jumping, running and sport participation.
3.2.4 Gait quality in relation to walking speed, pain, disease activity, and physical disability

Integrating gait dynamics into studies of patient’s experiences of walking could expose factors contributing to walking disability. In Study IV, presence of gait deviations was related to walking disability in children with JIA. In adults with RA, gait deviations was somewhat related to walking speed but not to physical disability, pain and disease activity (Study I) (Figure 11). In the following section relationships between GDI and other outcome measures will be discussed.

Figure 11. Schematic overview of results from Studies I, II and IV. Relationships within individuals with RA and JIA between GDI and other outcome measures using an ICF context.

In adults with RA, the GDI was partly influenced by walking speed. However, RA-related pathology was a greater contributor to the lower GDI scores than speed (Study I). It has previously been shown that the GDI score drops in healthy individuals who walk slowly. As individuals with arthritis commonly walk with reduced speed, the question regarding how much of the assessed gait deviations that were primarily related to speed has been raised. In order to evaluate the effect of walking speed on GDI in adults with RA (Study I), we calculated the GDI scores twice. In relation first to healthy controls walking at a self-selected speed and second to healthy controls walking at a speed matched to the speed of the adults with RA. Our results showed a significant improvement in average GDI of approximately 4 GDI units after speed matching, from 88 (SD 9) to 92 (SD 9) (p=0.017). As illustrated (Figure 2 in Study I) this difference was most obvious for adults with RA walking at very slow speed, which included about 40% of the actual sample. However, since the speed-matched GDI scores for the RA group remained significantly reduced (mean GDI 92 (SD 9) as compared to controls (mean GDI 100 (SD 10))), factors other than speed, such as...
pain, deformities, and compensatory walking strategies may contribute to impaired gait quality 17, 18.

In Study I, we concluded that the GDI scores were not related to pain. This result was surprising since others have demonstrated relationships between deviant gait patterns and pain 160, 161. Generalized pain has also been strongly associated with walking disability in individuals with RA 151. In our study self-reported pain in the lower extremities during walking was analyzed while other studies have used assessments of global pain, also including upper extremities. Even though painful joints may lead to altered gait characteristics, gait patterns are probably also influenced by muscular weakness, feelings of instability and deformities 22, 162. The results in Study I could also be influenced by our approach in dividing pain scores into two groups containing low and high levels of pain respectively or by using a measure of overall gait quality, as both approaches reduced the variability in the parameters.

We found that gait deviations and disease activity were not related to one another (Study II). The relationship was evaluated by a correlation analysis between GDI and DAS28-CRP before (r_s = 0.09, p = 0.75) and approximately three months after treatment with anti TNF-α treatment (r_s = 0.07, p = 0.8) (Study II). The finding was unexpected since increased disease activity has been related to both gait deviations 9, 12 and walking disability 151 in previous studies. The participants in Study II had established disease and a median disease duration of 9.5 years (interquartile range: 4.6-20.6) with potential joint destructions and deformities affecting gait patterns. Joint destruction and deformities are a consequence of increased disease activity but was not assessed in this thesis. It is, however, strongly recommended to consider this in future studies, since associations between structural deformities and gait dynamics have been identified previously 12.

While the main focus of this thesis was on the presence of gait deviations, the link to walking or physical disability was considered (Study I and IV). An important finding was that the CHAQ walking subscale has the potential to be used to identify children with gait deviations (Study IV). Children reporting much difficulty with walking (CHAQ walking subscale) at baseline had more gait deviations as compared to children reporting less walking difficulty (Figure 9A and B) (Study IV). In the group reporting much difficulty with walking at baseline both GDI (p= 0.009) and ankle/hip power ratio (p= 0.004) differed from healthy controls. Three weeks following treatment the GDI and ankle/hip ratio did not differ from healthy controls, however, at the three months follow-up GDI returned to a significantly lower score, p=0.02. This improvement at three weeks, although not significant, could be attributed to the fast treatment effect of IACI 91. Importantly, we found that children reporting “no difficulty” with walking before IACI treatment had similar level of gait quality as healthy controls (Figure 12 A and B). Thus, the CHAQ walking subscale has the potential to be used to identify children with gait deviations (Study IV). Moreover, this result points to gait dynamics being an important factor to consider when assessing walking disability in individuals with arthritis. Future research including greater sample sizes is warranted to confirm this result.

No association was found between gait quality (GDI) and physical disability, as assessed by the HAQ (Study I). This result strengthens what was already known from a study by Weiss et al. who correlated gait parameters (e.g. max knee flexion, max ankle plantarflexion) to the HAQ and found mostly weak correlations 11.
Results and discussion

There are several reasons for this difference in results found in Studies I and IV of associations between gait dynamics and disability. In Study I the sample was dichotomized and in Study IV the sample was divided into three groups. Study I had a cross-sectional design while in Study IV, GDI scores following treatment were related to baseline scores. In Study I the total HAQ score was used and in Study IV the walking dimension from the CHAQ was used. While the HAQ and CHAQ are considered a gold standard for assessing physical disability in RA/JIA, and are widely used, it should be noted that the HAQ and CHAQ include both upper and lower extremity activities. Thus, HAQ and CHAQ-scores are influenced by upper extremity activities not incorporated into the GDI. Study I was a retrospective analysis and therefore only the total HAQ scores were accessible. The advantage of using the HAQ and CHAQ walking subscale as a measure of walking disability is facilitated by the common use and good acceptance of the HAQ and CHAQ in clinical settings. Both the HAQ and the CHAQ have, however, been criticized for having ceiling effects, and the HAQ walking scale for low validity. Given the high level of gait function found in the children with JIA in Study IV, this could have influenced the results and the validity of using the CHAQ walking subscale as a measure of walking disability may be questioned. In future analysis, the use of other questionnaires specifically designed to assess walking disability in individuals with arthritis may be considered.
Figure 12. GDI (A) and ankle/hip power ratio (B) grouped according to reported walking difficulty (CHAQ walking dimension) before IACI treatment (Study IV). Pretreatment = white boxes, post 3 weeks = grey boxes, post 3 months = dashed/grey boxes. Number of participants represented in boxes in figure A(B) pre/3weeks/3months; “no difficulty” = 13/13/13, “some difficulty” = 19/15/17, “much difficulty” = 11/9/9. The horizontal line represents the median value for healthy children for (A) GDI and (B) ankle/hip power ratio. * Statistical difference from healthy control.
3.3 METHODOLOGICAL CONSIDERATIONS

3.3.1 Samples and study designs

The use of already existing data, such as the retrospective analysis in Study I, has advantages – such as being less time consuming – but it also has disadvantages: missing data, inability to include additional data and uncertainty of how data have been gathered. Our decision to exclude those with an outdated HAQ score resulted in reduced number participants which could have affected the results. Individuals with RA in the database at the Karolinska University Hospital, Stockholm were included when they completed a 3D gait analysis for a cross-sectional or a pre/post- treatment study 11, 129. Moreover the participants are heterogeneous in terms of disease duration and pharmacological therapy, which, taken all together, restricts generalization.

Study II and IV evaluated the effect of well-established pharmacological interventions on gait dynamics in prospective pre-post studies. To evaluate the true effect of pharmacological intervention on gait dynamics a non-treated control group would have been preferable, to ensure that the changes in gait deviations were related to the pharmacological treatment and not to other factors. However, a control group including untreated individuals with RA and JIA with similar levels of disease activity would have been strongly unethical due to the proven effect of the drugs and the known negative effects of not receiving treatment when qualified to do so 84. The included sample in Study II is small and the inclusion period spans over six years. Thus, conclusions from this study should be drawn with care. Children with JIA participating in Study IV were included based on foot involvement. It has been suggested that foot involvement is predictive of more progressive disease 65, 68, 164, thus our sample of children with JIA most likely represents a group with a more severe disease than the average patient. Sixty-five percent of the children with JIA had polyarthritis, a high percentage as compared to the total JIA population (40% have polyarticular disease) 131. Only children injected under general anesthesia using fluoroscopy and contrast enhancement were included due to the proven superior result of injecting small joints in the foot using this method 88.

The results from Study III are based on data from a population based prospective longitudinal cohort, a design which supports the validity of the results. The cohort is multinational and includes 500 children from well-defined geographic regions in Sweden, Norway, Denmark and Finland. All ILAR categories were represented, even if the number of patients in some categories was small, restricting subgroup analysis. Effort was put into making the study as population based as possible, there are however always the risks of missing individuals, of individuals refusing to participate, of individuals being undiagnosed or wrongly diagnosed, and of cases referred to specialists other than the participating centers. Despite the study length of eight years only 12% were lost to follow-up, mostly older children transferred to adult rheumatology care 131.

3.3.2 Measuring gait dynamics

When analyzing gait with 3D gait analysis in individuals with RA and JIA there are several methodological issues to consider. Morning stiffness is a common problem and may affect gait pattern in individuals with RA. Systematic variations throughout the day have been
described with improved gait dynamics later in the day. Gait analyses included in this thesis are conducted in the afternoons, except for a few individuals reporting no morning stiffness and who preferred to come to the gait analysis laboratory in the morning.

All gait analysis was conducted with the participants walking barefoot. This approach could have elevated the degree of gait deviations. Some of the adults with RA mentioned that they, due to considerable foot impairment, never walked without shoes. Barefoot walking was not a problem that any of the children addressed in Study IV. Walking with footwear could be an alternative, but the potential impact of different shoe designs, time walked in the actual shoes, and insoles would have been confounding factors in such analysis.

In this thesis the choice was made to have participants walking at self-selected speed, as opposed to standardized cadence indicated by a metronome. From a clinical standpoint, self-selected speed is the most relevant as it is related to everyday activities, requires minimal energy expenditure, and has been associated with increased stability while walking. Before capturing gait dynamics the participants were instructed to repeatedly walk back and forth on the 10 meters walkway until they walked at their preferred pace. In Study IV, parents of the children were consulted to ensure that a typical gait pattern and speed was captured. However, almost all aspect of gait are sensitive to walking speed and conclusions about change in gait dynamics following interventions and between groups must be drawn with this in mind.

Gait analysis within this thesis was conducted by one of two experienced physiotherapists (EWB and ACE). Effort was made to ensure consistency between the assessors in marker placement and instructions to patients. In 3D gait analysis several aspects contribute to the achieved levels of reliability. First, aspects related to the assessor such as adequate training in marker placement and underlying biomechanical model, second aspects related to the patients, such as ability to cooperate and cognition. It is generally found that gait data from adults is less variable than from children and younger children were found to be more variable than older children. This coincides well with the impression the assessors gained at the gait analyses conducted for this thesis. However, despite many possible sources of error in 3D gait analysis it is clinically accepted that reliable measures are achievable and can be summarized as: Movements in the sagittal plane are most reliable followed by movement in the frontal and lastly in the transversal plane. In future studies, the reliability of the GDI, which incorporates movements from all three anatomical planes, should be addressed.

The aim and focus of the present study was on gait dynamics but in future studies inclusion of more demanding activities might be considered. Walking inside a gait laboratory is a simple physical activity with no obstacles, no inclinations and only short distances. It could be argued, especially for the children, that walking within these conditions is not a sufficiently challenging activity. However, impairments in gait dynamics were identified in both adults with RA and children with JIA indicating that more challenging activities such as outdoor walking, jumping and sport participation most likely amplify the deviations.

In this thesis the GDI was found to be a useful measure of overall gait quality in individuals with RA and JIA. The GDI scores can be used as a “stand alone” measure but there are several disadvantages related to the GDI to being considered. GDI scores are not informative about the cause or the nature of the deviation. The GDI is a distance measure that
Results and discussion

quantifies how far the kinematics of a specific stride is from the mean kinematics of the control group. There is no direction associated with this distance, meaning that the actual deviations (e.g. increased hip flexion, decreased dorsiflexion, etc.) cannot be deduced from the measure itself. Thus, to understand which gait deviations cause the lower GDI score, it is imperative that the gait parameters incorporated into the GDI scores are displayed (Figure 5) or that univariate measures (max, min, ROM, timing) are extracted from the gait data.

3.3.3 Measuring physical disability and pain

In Studies III and IV, physical disability was reported by children or their parents, depending on the child’s age. Using a proxy version of a questionnaire challenges interpretation since it could not be ensured that it is the child’s belief’s being documented. In children with JIA, the discordance between physicians and parents’ estimation of a child’s physical ability has been shown to vary with the severity of disease and pain. In Study IV, the questionnaires at the two separated evaluations were completed by the same parent to ensure consistency. There is no “gold standard” solution to the proxy problem and what strategy to use should be related to the study design and the intended use of the data.

In the JAFI some statements are positively formulated and others negatively formulated to make careful consideration of each statement necessary. This design was carefully explained in advance but might still have led to a higher proportion of reported foot-related disability, a concern also raised in earlier studies.

Measuring pain is challenging due to its subjective nature and may be complicated due to feelings of anxiety or by the age of the subjects. In Study IV, pain during walking was reported either by a VAS scale (children from eight years of age) or by the faces pain scale (children below eight years of age). The scales were thoroughly explained using a standard interactive procedure to help the children differentiate between, for example pain and stiffness. A few children still encountered scoring difficulties. For example, some of the children scored equally low levels of pain before and after IACI treatment, but after treatment they stated that “now I am in no pain!” This could be a potential reason why pain during walking did not improve with treatment as previously described. Whilst most participants experienced improvements, one participant reported increased pain after treatment. Due to the small sample size, we did not exclude the subject from the analysis.

3.4 STATISTICAL CONSIDERATIONS

When performing statistical analyses of walking it is important to remember that walking is a bilateral activity including two legs, not independent from each other. In this thesis different approaches have been used to handle this issue. In Studies I, II and in some of the analyses in Study IV, mean values of left and right GDI scores were used. This approach was taken for several reasons: there were no statistical differences between left and right sides (legs) and included individuals with RA and JIA had bilateral involvement. In Studies I, II and IV GDI scores were related to other measures considering general aspects of physical disability and disease activity. In this context the averaged GDI scores were thought to represent overall gait pattern. Other possible approaches to handle bilateral data include: to randomly select one of left and right observation or to use the lowest GDI scores, representing worst gait pattern. A personal reflection is that in individuals with arthritis, the
side with lowest GDI is not always the most involved side or even the treated side, posing challenges to this choice of analysis. In Study IV, evaluating the effect of foot IACI in children with JIA over a three months period, the interdependence (correlation) between the sides (legs) over the three evaluations was accounted for by using a linear mixed model \(^{172}\). Another advantage with this method is that those participants with missing data are kept in the analysis.

In Study IV, 37% of the included children increased their medication during the study period because of unacceptable levels of disease activity (e.g. changed or started new DMARD or biologic treatment). Due to the small sample size this factor could not be considered as a covariate in the statistical analysis, possibly affecting the results. With respect to gait dynamics the effect was probably small given that gait dynamics did not change following treatment, not for the total group, nor for the polyarticular or the oligoarticular group. Another possible way to handle this would be to dichotomize the children into one group with an increase in general medication treatment and another group with stable treatment. However, the result from such an approach would be challenging to interpret due to the heterogeneity in what new medical treatment was given (fast or slow acting drug) or when it was given (at what time point in relation to the follow-up times).

In Study I, the ICC-values between three strides were shown to be excellent and this could be influenced by what strides were included in the analysis. The ICC is dependent upon heterogeneity of the group and will be high if the variance of GDI scores between subjects is higher than within subjects \(^{147}\). In this study three strides were selected based on visual inspection with a potential risk of not being representative. However, both the adults with RA and adult controls were walking with a consistent gait pattern, thus the excluded strides showed a consistent pattern with the included strides. In future studies, however, a random selection of strides or inclusion of all available strides should be considered.

### 3.5 LIMITATIONS

As with most studies, the results from the studies included in this thesis have weaknesses that restrict generalization. Some of the limitations have already been discussed and others are outlined below.

An important limitation of Studies I-IV was that arthritis was clinically evaluated without verification with ultrasound or other imaging modalities, which might have led to an underestimation of the number of affected joints, as ultrasound has proven superior in detecting synovitis \(^{173}\). Moreover, evaluating foot arthritis using ultrasound may have added further information such as distinctions between talocrural, subtalar and tarsal involvement and detecting subclinical inflammation.

Gait dynamics may be altered for various reasons including the presence of deformities, an aspect not considered in the present thesis. In future studies evaluations of deformities in lower limbs could be of value when evaluating the impact of inflammatory and mechanical aspects on gait dynamics and walking disability \(^{16}\).

The aim of Study II and IV was to evaluate overall gait quality in relation to disease and to pharmacological treatment. However, it is well known that both adults with RA and children with JIA have inflammation from the small joints in foot. Deviations in these joints are not
covered in the present studies since the foot was modeled as rigid segment and only motions at the ankle joint were considered. This approach, to not include the different segments of the foot in the 3D gait analysis, may have led to an underestimation of gait deviations.

In Study I, both GDI and speed-matched GDI scores for adults with RA and healthy adults were calculated using a reference set based on children. The pediatric reference set was used because of the wide range of available speeds. A similar multispeed reference set was not available for adults. We acknowledge that an adult reference set would have been ideal but the mean values for our adult controls were, however, very close to 100 (10) indicating consistent gait pattern between the reference set and the adult controls participating in this studies.

3.6 CONCLUSIONS AND CLINICAL IMPLICATIONS

This thesis highlights the importance of considering gait quality when evaluating walking disability in individuals with RA and JIA; we recommend the use of measures of overall gait quality, such as the GDI, to quantify gait deviations. The GDI adds a quality aspect of walking function to more commonly evaluated aspects of function within arthritis care such as performance-based and self-reported function. Moreover, the GDI may facilitate comparisons of gait dynamics between groups, over time and following intervention.

In individuals with RA and JIA, gait quality is compromised despite potent pharmacological interventions. This indicates that gait quality should be considered to further evaluate the relationship between arthritis, gait dynamics and walking disability. Anti-TNF-α treatment improved gait dynamics in adults with RA. Significant gait deviations were, however, still present after treatment. As a result of IACI treatment in children with JIA, improvements were identified in foot-related disability and inflammatory joint symptoms, but gait dynamics were unchanged. Children with polyarticular disease and those reporting much difficulty with walking prior to treatment had the most impaired gait function and should be monitored carefully.

We suggest that ankle arthritis should be recognized in the assessment of prognosis and choice of treatment strategy in JIA, since it predicts a polyarticular disease course in young children and is associated with failure to achieve remission. Moreover, we recommend that foot involvement is routinely assessed in clinical practice, given the high occurrence of ankle and foot involvement in JIA and the persistent problems with foot-related disability and gait dynamics following pharmacological intervention. The CHAQ walking scale may be used to identify walking disability, but might not be sufficient to detect foot disability. To address this, CHAQ might be complemented by the JAFI.

3.7 FUTURE PERSPECTIVES

In individuals with RA research on gait dynamics has predominantly been focused on the foot with measures of foot kinematics obtained through the use of biomechanical foot models. It has, however, been suggested that the involvement of larger joints contribute to a higher extent to walking disability than the involvement of smaller joints. Therefore, the GDI, incorporating gait dynamics from pelvis, hip, knee and ankle, could reflect the
impact of specific foot impairments on overall gait quality and has the potential to serve as an additional measure of overall diseases severity, just as DAS28 and HAQ currently do for disease activity and physical disability respectively.

Future analysis of gait dynamics in prospective longitudinal studies with individuals starting new pharmacological treatments are needed to help in identify those at greater risk of gait deviations despite good response in disease activity. However, several factors contribute to walking disability in individuals with RA and JIA and, above pathology and gait dynamics, individuals experiences of walking should be considered. In future studies this could, for example, be enhanced by using a mixed methods approach integrating both quantitative and qualitative aspects. Thereby the understanding of factors contributing to walking disability can be revealed and walking ability improved.

We suggest that ankle arthritis should be recognized in the assessment of prognosis and choice of treatment strategy in JIA. Beyond the risk of extended disease and failure to achieve remission identified in Study III, the results from Study IV identified gait deviations as a persistent problem in children with JIA and ankle involvement. Easily administered instruments, such as questionnaires, have a great screening potential, and preliminary results from Study IV suggest that the CHAQ walking subscale might be useful identifying individuals with persistent gait deviations. This, however, needs to be further assessed in future studies.
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[Signature]

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