Patient-reported outcomes and medication satisfaction in adults with juvenile idiopathic arthritis

Doctoral thesis

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The work is part of a comprehensive study "Remission, disease progression and prognostic factors in young adults with juvenile idiopathic arthritis", started by Berit Flatø and Øystein Førre in 1995. This comprehensive study was later expanded with studies conducted by Anne Marit Selvaag and Hanne Aulie. Data previously collected by Berit Flatø, Anne Marit Selvaag and Hanne Aulie have provided a solid foundation for this study and enabled longitudinal follow-ups of patients. In addition, their extensive knowledge of the two cohorts used in the study, has been a great help for me.

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Summary

Background: Literature is scarce on long-term patient-reported outcomes (PROs) in juvenile idiopathic arthritis (JIA), and little is known about satisfaction with and adherence to disease-modifying antirheumatic drugs (DMARDs) among adult patients with JIA.

Aim: The purpose of this study was to describe PROs in adults with JIA, examine longitudinal changes of health status over time, and identify possible predictors and determinants of physical disability, pain and health-related quality of life (HRQOL). In addition, we aimed to provide information about treatment satisfaction with and adherence to DMARDs and the associations between treatment satisfaction, adherence and HRQOL.

Methods: The study participants comprised of JIA patients who previously participated in longitudinal follow-ups at Oslo University Hospital. Two cohorts of patients participated in the study. In cohort one, 176 patients were clinically examined and assessed with PRO measures (PROMs) 15 years after disease onset and reassessed with PROMs after 23 and 30 years. In cohort two, 96 patients were included in the study within 18 months of disease onset, clinically examined and assessed with PROMs each 6 months for 3 years, and reassessed with PROMs 19 years after disease onset. A total of 52 patients were using DMARDs after 19 years and participated in a cross-sectional study with self-reported questionnaires regarding medication satisfaction and adherence. In both cohorts, patients at their last follow-up were compared to controls from the general population.

Results: In both cohorts, patients reported lower physical HRQOL than controls and almost half the patients reported some physical disability. In cohort two, patients also reported higher levels of pain than controls. Physical disability and pain were the main correlates of lower physical HRQOL (paper 1 and 2). Pain, active joints and physical disability early in the disease course were identified as predictors of unfavorable outcomes after 19 years (paper 2). Physical disability, fatigue and low wellbeing after 15 years predicted reduced HRQOL after 30 years (paper 1). During the longitudinal follow-up, patients' wellbeing and physical HRQOL deteriorated over time (after 15, 23 and 30 years) in cohort one. Patients´ wellbeing was stable from 3 to 19-year follow-up in cohort two, although the level of fatigue and the number of patients reporting some physical disability increased. At 19-year follow-up, patients were more satisfied with

biological DMARDs than with methotrexate. Higher treatment satisfaction was associated with better HRQOL. Low adherence to medication was reported by almost half of the patients (paper 3).

Conclusion: The longitudinal follow-up of PROs in JIA patients up to 19 and 30 years after disease onset provides valuable information on changes and outcomes of physical disability, pain and HRQOL over time. In both cohorts, JIA had a detrimental effect on these outcomes. Such information provides an insight, which can increase patients´ and healthcare professionals´ understanding of the many aspects of JIA. This study demonstrated that patients were more satisfied with biological DMARDs than with methotrexate and higher medication satisfaction was associated with better HRQOL. Adherence to medication was low and associated with the inconvenience of taking the medication. Information regarding medication satisfaction and adherence should be included in the treatment decision-making process in order to facilitate best possible treatment and care.

Abbreviations

ACR	American College of Rheumatology
BPI	Brief Pain Inventory - short form
CI	Confidence interval
cJADAS	Clinical Juvenile Arthritis Disease Activity Score
CRP	C-reactive protein
DMARD	Disease-modifying antirheumatic drug
ERA	Enthesitis-related arthritis
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
GMM	Growth mixture modeling
HAQ	Health Assessment Questionnaire
HRQOL	Health-related quality of life
ILAR	International League of Associations for Rheumatology
JCA	Juvenile chronic arthritis
JIA	Juvenile idiopathic arthritis
JRA	Juvenile psoriatic arthritis
LROM	Limited range of motion
MCS	Mental Component Summary
MMAS-8	The 8-item Morisky Medication Adherence Scale
MTX	Methotrexate
NA	Not assessed
NRS	Numeric rating scale
NSAIDs	Non steroidal anti-inflammatory drugs
OMERACT	Outcome Measures in Rheumatology
OUH	Oslo University Hospital
PCS	Physical Component Summary
PsA	Psoriatic arthritis
PGA	Physician`s global assessment of disease activity
PRO	Patient-reported outcome
PROM	Patient-reported outcome measure
QOL	Quality of life
RA	Rheumatoid arthritis

RF	Rheumatoid factor
SCL-5	Hopkins Symptom Checklist-5 item
SF-12	Health Survey Short Form- 12 item
SF-36	Health Survey Short Form- 36 item
TSQM	Treatment Satisfaction Questionnaire for Medication
US	United States
VAS	Visual analogue scale
WHO	World Health Organization

List of papers

1. Tollisen A, Selvaag AM, Aulie HA, Lilleby V, Aasland A, Lerdal A, Flatø B. Physical functioning, pain, and health-related quality of life in adults with juvenile idiopathic arthritis: A longitudinal 30-year followup study. Arthritis Care Res (Hoboken). 2018;70:741-9.

2. Tollisen A, Selvaag AM, Aasland A, Lerdal A, Flatø B. Longitudinal health status from early disease to adulthood and associated prognostic factors in juvenile idiopathic arthritis. J Rheumatol. 2019; Published online first: March 15. 2019 doi: 10.3899/jrheum. 180948.

3. Tollisen A, Flatø B, Selvaag AM; Aasland A, Ingebrigtsen T, Sagen J, Lerdal A. Treatment satisfaction with and adherence to disease-modifying antirheumatic drugs in adult patients with juvenile idiopathic arthritis. Submitted (under review), Arthritis Care Res (Hoboken).

1. Background

1.1. Introduction

This study is part of a larger project at Oslo University Hospital (OUH): "Remission, disease progression and prognostic factors in adults with juvenile idiopathic arthritis". Since 1995, several studies have been conducted within this comprehensive project, and data collected during this time has offered an opportunity to explore changes in health and disease-related issues of patients with juvenile idiopathic arthritis (JIA) over time and identify possibly early predictors of long-term patient-reported outcomes (PROs). Two cohorts of patients participated in this study. In the first cohort, patients diagnosed with JIA from 1980–1985 were included, and results from previous data collections on this cohort have been published (1-3).

Treatment opportunities with respect to medication have improved since then and especially with the introduction of biological disease-modifying antirheumatic drugs (DMARDs) around 2000. The patients included in the second cohort were diagnosed 15 years later (1995 – 1999), and in an era when new and improved medications were introduced and DMARDs were initiated at an earlier stage. Studies from early follow-ups of these patients have previously been published (4-6). In Norway, an egalitarian and publicly funded health service has made specialist health care for patients with JIA easily accessible, and the vast majority of Norwegian patients with JIA have been referred to OUH early in their disease course.

Many children with JIA suffer pain symptoms, impaired physical functioning and reduced quality of life (7-10). During the last few decades, medication treatment for children with JIA has improved significantly and includes several options with proven efficacy (11, 12). The promotion of the patients' perspectives in order to reveal issues important to patients is important when assessing outcomes in patients with JIA. PROs can be defined as any report on a patient´s health condition that comes directly from the patient (13), and are recognized as important outcome indicators of the disease (14, 15). Prior to these present studies, longitudinal studies based on PRO measures (PROMs) following JIA patients into adulthood had been scarce and mainly restricted to measures of physical disability (16, 17). Despite an increased use of DMARDs during the last 2 decades, information regarding patients´ experiences with and adherence to these

medications was limited. In order to optimize medication treatment, information regarding patients' experiences with their medication was needed.

Both national and international health authorities have emphasised the importance of involvement of patients´ views in patient care through monitoring patients' experiences and symptoms (18, 19). This thesis aims to extend knowledge on the long-term consequences of JIA in adulthood based on PROs and on patients' experiences with DMARDs.

1.2. Juvenile idiopathic arthritis

1.2.1. Manifestation and incidence

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory rheumatic disease defined as inflammation in one or more joints for more than 6 weeks in children under the age of 16 and in whom other known causes have been excluded (20). Uveitis, defined as inflammation in the uvea of the eye, is reported to occur in 12 – 24 % of children with JIA (21-23). In Nordic countries, the annual incidence of JIA is reported to be approximately 15 per 100,000 children (24, 25), and the disease is more common in girls than boys (20, 24). The severity of JIA is highly variable and the disease course is hard to predict. JIA can be a continuous active disease, a fluctuating relapsing disease with flares of exacerbation or patients can recover fully soon after disease onset without permanent joint damage (4, 17, 26, 27).

1.2.2. Classification of chronic arthritis in childhood

The terminology used to describe and classify chronic childhood arthritis has not been unified and there has been inconsistency in its classification. In the 1970´s, the classification criteria for juvenile rheumatoid arthritis (JRA) were developed by the American College of Rheumatology (ACR) (28) while the classification criteria for juvenile chronic arthritis (JCA) were introduced by the European League Against Rheumatism (EULAR) (29). In 1995, the JIA classification criteria were proposed by the Pediatric Task Force of the International League of Associations for Rheumatology (ILAR) (30), and later revisions have been made (31, 32). Today, the ILAR classification remains the working classification (Table 1) (32), but further revisions may be required in order to define homogenous subgroups of patients.

Table 1. ILAR classification criteria for JIA

ILAR subgroups	Definition of each subgroup
Systemic arthritis	Arthritis in one or more joints with or preceded by fever of at least 2 weeks duration that is documented daily for at least 3 days, and is accompanied by: non-fixed erythematous rash and/or generalized lymph node enlargement and/or hepatomegaly and/or splenomegaly and/or serositis. Exclusions: a,b,c,d.
Polyarthritis (Rheumatoid factor negative)	Arthritis in 5 or more joints during the first 6 months and rheumatoid factor negative. Exclusions: a,b,c,d,e.
Polyarthritis (Rheumatoid factor positive)	Arthritis in 5 or more joints during the first 6 months with ≥2 positive tests for rheumatoid factor (assessed 3 months apart). Exclusions: a,b,c,e.
Oligoarthritis persistent	Arthritis in 1 – 4 joints throughout the disease course. Exclusion: a,b,c,d,e.
Oligoarthritis extended	Arthritis affecting 1 – 4 joints during the first 6 months of disease course, affecting a total of more than 4 joints after the first 6 months. Exclusion: a,b,c,d,e.
Enthesitis related arthritis	Arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following: sacroiliac joint tenderness and/or lumbosacral pain, HLA-B27 positive antigen, arthritis onset in male >6 years of age, anterior uveitis, history of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowl disease, Reiter´s syndrome, or acute anterior uveitis in a first-degree relative. Exclusion: a,d,e.
Psoriatic arthritis	Arthritis and psoriasis, or arthritis and at least 2 of the following: dactylitis, nail pitting or onycholysis, psoriasis in a first-degree relative. Exclusion: b,c,d,e.
Undifferentiated arthritis	Arthritis that does not fulfil criteria in any other category or in 2 or more of the other categories.

Exclusions: a) Presence of psoriasis or psoriasis in a first-degree relative; b) HLA-B27 positive male > 6 years of age; c) Presence of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowl disease, Reiter´s syndrome, or acute anterior uveitis in a first-degree relative; d) RF-positivity; e) Presence of systemic arthritis.

1.2.3. JIA into adulthood

Although JIA has its onset during childhood, the disease continues into adulthood in approximately half of patients (16, 17, 27, 33-36). In patients without clinical evidence of active disease, the burden of previous disease and received medication may have a detrimental effect on health-related outcomes (16).

1.2.4. Medications in JIA

The goals of medication treatment in JIA are to eliminate or reduce symptoms, prevent exacerbation, achieve clinical remission or halt damage. Disease-modifying antirheumatic drugs (DMARDs) are the main pharmacological treatment for JIA and often described as synthetic and biological DMARDs. The most commonly used synthetic DMARD is methotrexate (MTX), which has been used as a treatment option since the early 1980´s (11, 12, 37). Biological DMARDs have been a treatment option for children with JIA in the last 2 decades (38-41), and an increasing number of biological DMARDs are in use (12, 38-41). Synthetic DMARDs are administered as oral medication or subcutaneous injection, while biological DMARDs are usually administered as subcutaneous injection or intravenous infusion (42). In addition to DMARDs, non-

steroidal anti-inflammatory drugs (NSAIDs) are used to ease pain and inflammation while intra-articular glucocorticoid injections and systemic glucocorticoids are used to reduce inflammation (11). For uveitis, tropical corticosteroids are used, or other combinations of medications (systemic corticosteroids, NSAIDs, synthetic DMARDs or biological DMARDs) if indicated (43). Treatment selection in children with JIA is based on the different ILAR classifications and expected disease course, with recommendations of more aggressive treatment and early introduction of DMARDs in children with moderate to high disease activity and poor prognosis (11, 44). It is likely that the time for initiating new medications and treatment strategies could vary between countries due to regulations from health care authorities, and different health-care systems and treatment financing. Previous studies have indicated earlier initiations of synthetic DMARDs in JIA patients in Norway in the 80´s and 90´s, compared to patients in other countries (45-47).

1.2.5. Previous studies of patient-reported outcomes in adults with JIA

Studies assessing PROs such as physical disability, pain or health-related quality of life (HRQOL) in adults with JIA have previously been conducted as presented in Table 2. However, few of these studies have explored longitudinal changes in such outcomes (3, 16, 17, 48), or compared patients to matched controls (1-3, 35, 49, 50), and very few have been published during the last 10 years (17, 51). More specifically, longitudinal changes up to 30 years after disease onset have not previously been examined. Only one study had followed patients longitudinally from childhood into adulthood in order to explore the impact of early disease on long-term outcome (17), and the patients in that study were diagnosed several years prior to the introduction of biological DMARDs. Hence, these improved medication treatments have necessitated new studies describing the outcomes of such treatments. In our study, biologic agents became available during the first few years of the disease course for patients in cohort two. These patients were assessed every 6 months for 3 years, providing thorough information about the early disease course, which may also increase the predictive ability of the assessments. The impact of sequential assessment has to our knowledge not previously been explored.

Table 2. List of studies on patient-reported outcomes in adults with JIA from 01.01.1995 t0 01.01.2015

Authors, year	N	Patient age at follow-up	Main findings regarding patient-reported outcomes
Peterson et al, 1997 (49)	44	Median 33.5 years	Greater disability and worse physical functioning, bodily pain, fatigue and health perception compared with controls. [2]
Ruperto et al, 1997 (52)	118	Mean 21 years (including children cohort)	Favourable long-term outcome in most patients a mean of 15 years after disease onset. Only 118 (52%) of the 227 patients were adults. [3]
Zak and Pedersen, 2000 (16)	65	Median 32.2 years	More pain and physical disability were found in patients with active disease. One-third of the patients experienced no pain. [3, 4]
Minden et al, 2002 (53)	215	Median 23 years	Patients demonstrated good social integration with better educational and vocational achievements compared to the general population. One-third reported functional limitations. [2, 3]
Packham et al, 2002 (33)	246	Median 35.3 years	Differences in functional problems found in subgroups of JIA. Systemic JIA and sero-negative polyarticular JIA had relatively poor functional outcomes. [3]
Packham et al, 2002 (54)	246	Median 35.3 years	Over half the patients who were previously or currently sexually active had disease-related sexual problems. [3]
Packham et al, 2002 (55)	246	Median 35.3 years	Nearly one-third of patients had high anxiety levels, 5% reported high levels of depression, 7% were pain-free and one-third had severe pain. Psychological variables explain the majority of the variance in depression and anxiety. Both physical and psychological factors influenced pain. [3]
Foster et al, 2003 (34)	82	Median 30 years	Although physical outcome was relatively good, a profound effect on health status and HRQOL was found in all types of JIA. Despite excellent education, a high rate of unemployment was found in patients. [3]
Flatø et al, [1] 2003 (1)	268	Median 22.1 years	Compared with healthy controls, patients with JRA had impaired physical health and lower employment rates. Predictors of physical disability were: female sex, symmetric arthritis, hip joint involvement, long duration of elevated ESR and IgM RF. [3]

Authors, year	N	Patient age at follow-up	Main findings regarding patient-reported outcomes
Arkela-Keutianien et al, 2005 (35)	123	Mean 23 years	Social functioning and HRQOL were similar in JIA patients and controls. Patients with extended oligoarticular JIA had lower physical and mental HRQOL than oligo and polyarticular JIA patients. [3]
Flatø et al, [1] 2006 (2)	110	ERA mean 26.5 years, oligo/polyarticular JIA mean 21.8 years	Patients with ERA had poorer physical outcomes compared with patients with oligoarticular or polyarticular JIA and controls from the general population. [3]
Arkela-Keutianien et al, 2006 (50)	123	Mean 23 years	Patients with active disease had more pain and lower levels of mobility, self-care and social life compared to controls. [3]
Duarte-Salazar et al, 2007 (56)	32	PsA mean 25.8 years, polyarticular course JIA mean 26.8	Polyarticular course JIA and PsA have a significant impact on physical disability and QOL. Functional status has a significant impact on QOL. [3]
Flatø et al, [1] 2009 (3)	336	Mean 20.7 – 26.5 years (depending on disease subtype)	After 15 years, PsA patients had poorer physical health than healthy population controls. After 23 years, PsA patients had more pain and poorer physical health than patients with either oligoarthritis or polyarthritis. [3, 4]
Østlie et al, [1] 2009 (48)	55	Mean 27.4 years	Favorable physical and psychosocial outcomes reported at first follow-up (8.7 years after symptom onset) seem to persist. At 18.3-year follow-up, patients had lower physical health but similar mental health compared to controls from the general population. Pain was an important correlate of physical disability at first and second follow-up. At second follow-up, psychiatric distress was a significant correlate of pain and fatigue. [3, 4]
Malviya et al, 2012 (51)	103	Median 24 years	Functional disability was significantly lower in patients who were employed and in those with oligoarticular JIA. [3]
Bertilson et al, 2013 (17)	86	N/A	Lower HRQOL compared to controls from a normative database at 17-year follow-up. Long-term outcomes were best predicted by characteristics at 5-year follow-up rather than those at onset. [2, 4]

[1] Patients included from OUH; [2] Population based study; [3] Hospital/referral based study; [4] Longitudinal study.

1.2.6. Predictors of long-term patient-reported outcomes in adults with JIA

Although JIA can have a detrimental effect on physical disability, pain and HRQOL in adults with JIA (16, 17, 34, 49, 55), studies identifying possibly early predictors of these outcomes are scarce. Prior to our study, only two studies prospectively assessed possible early predictors of long-term PROs in adults with JIA (17, 57), hence studies to identify predictors of long-term PROs fill a knowledge gap.

1.2.7. Medication satisfaction and adherence in juvenile idiopathic arthritis

Medication is an important part of treatment for patients with JIA, and studies have shown their proven effect on disease-related outcomes (58-62). Several treatment options currently exist (63), however published information regarding JIA patients´ experiences with current medication is scarce. Adherence to medication can be defined as the extent to which a person´s medication use corresponds with the agreed recommendations from health care providers (64). Published studies regarding treatment satisfaction and adherence are limited, and to the best of our knowledge restricted to children and MTX (65-69). Hence, more studies regarding adult patient satisfaction with and adherence to medication used in JIA treatment are needed.

1.3. Outcome measures

1.3.1. Patient-reported outcome measures

Patient-reported outcome measures (PROMs) are defined as instruments used to measure outcomes directly reported by the patient without interpretation of the patient´s response by anyone else (70, 71). Different PROMs are used to assess different health constructs. PROMs are typically self-completed, but can be completed by others on behalf of an individual. For instance, in circumstances with children too young or unable to complete self-report for other reasons, patients' proxy-reports are needed (72, 73). PROMs can be categorized as generic or disease-specific (74). Generic instruments can refer to broader aspects of health and functioning in a variety of populations. The advantage of such measures is that they enable comparisons across different conditions and populations, including the general population. Specific instruments try to capture disease-specific symptoms related to specific conditions (74). PROMs can also be classified as individualized or standardized instruments. Individualized measures are

generated by the patient´s own definition of the outcome being measured without pre-defined outcomes, while the items of the instruments are pre-defined in standardized measures (75, 76). For children, a large number of self-reported and proxy-reported generic and disease- specific PROMs have been developed (15, 77, 78).

1.3.2. Other outcome measures in JIA

Outcomes can in this context be defined as something that follows as a result or consequence of JIA (79). JIA is a multifaceted disease with a wide range of potential consequences (17, 53, 80-93). Outcomes (both short-term and long-term) can provide important information on the influence of the disease on patients' lives.

In 1997, the following core set of outcome measures for JIA were proposed: physician´s global assessment of disease activity, parent´s/patient´s assessment of overall wellbeing, functional ability, number of joints with active arthritis, number of joints with limited range of motion (LROM) and erythrocyte sedimentation rate (ESR) (94, 95). Joints with active arthritis can be defined as joints with swelling or joints with LROM and pain, warmth and/or tenderness (96). The core set of outcome measures were based on clinician-reported, laboratory assessed and patient/parent-reported variables based on statistical and consensus formation techniques without patient/parent involvement (32). However, recently an international group, Outcome Measures in Rheumatology (OMERACT) suggested an update to the core domain set for studies in JIA with increased emphasis on patient/parent-reported domains and on aspects regarding living with JIA (97, 98). This work is still in progress.

1.3.3. Definitions of remission in juvenile idiopathic arthritis

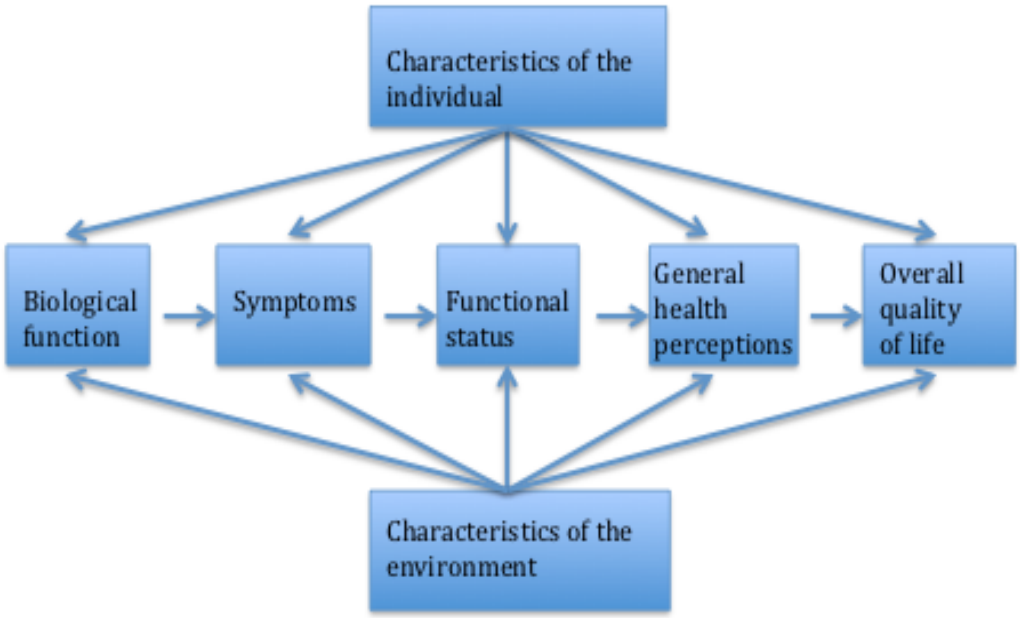
Clinical remission off medication is normally defined as a minimum of 12 months with inactive disease without anti-arthritis or anti-uveitis medication, while clinical remission with medication can be defined as a minimum of 6 continuous months with inactive disease while on medication (96). Inactive disease in JIA can be defined as no fever, rash, serositis, lymphadenopathy, uveitis and normal ESR or C-reactive protein (CRP) and physician´s global assessment of disease activity rated at the best possible score (96, 99). Two versions of criteria for defining clinical inactive disease/remission have been proposed (96, 99), in the latter version (the modified version) duration of morning stiffness was included.

1.3.4. Definitions of quality of life, health and health-related quality of life

It has been increasingly recognized that quality of life (QOL) and HRQOL are important issues in order to better understand the impact of a disease on a patient´s life. Both QOL and HRQOL are frequently used concepts, used in different contexts with no uniform definition and with several definitions in current use (100, 101).

QOL is a multidimensional concept, which may comprise different characteristics, meanings and perspectives in different contexts (102-104). Health is often included as an important aspect of QOL, describing aspects of QOL in relation to health. The World Health Organization has defined health as "a state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity" (105). This definition has been criticised for stating that health and disease cannot coexist, despite several studies having reported that people with severe chronic diseases have reported QOL equal or superior to people without a chronic disease (106, 107). HRQOL is difficult to define and to distinguish from health and QOL because some definitions of HRQOL resemble health and others resemble QOL (108). There is no consensus on the definition of the term HRQOL, and several definitions are in current use. HRQOL can be defined as a concept with multiple domains representing a patient´s general perception of the effect of illness and treatment on physical, psychological, and social aspects of life (13). Patients´ HRQOL is the main outcome of our study. Several variables have been identified as determinants or associates of HRQOL. Ferran´s revised version of Wilson and Cleary´s model includes a taxonomy of the variables that have often been used to measure HRQOL and this model will be used as a framework for this study (109, 110).

Figure 1. Conceptual framework of HRQOL (109)



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1.3.5. Definitions of validity and reliability in outcome measures

Validity and reliability are important criteria when evaluating the quality of a PROM (111). Validity refers to the degree an instrument measures what it is suppose to measure (111). Internal validity relates to the validity of results within the study (111). The instrument should include the research domains of interest (content validity) and have a good operationalization of the constructs they intend to measure (construct validity) (111). External validity relates to the degree to which the results from the study can be generalized to similar patients and settings (111).

Reliability refers to the degree the measures of an instrument are consistent and accurate (111). The instrument should yield reproducible results when repeated under stable conditions over time (test-retest reliability), and the items of the questionnaire should measure the same trait (internal consistency) and be able to detect changes over time (responsiveness) (104, 111).

2. Aims of the study

The overall aim of this study was to explore long-term patient-reported outcomes with respect to physical functioning, pain and HRQOL in adults with JIA, describe changes over time, identify risks factors for unfavourable outcomes, and examine treatment satisfaction and adherence among adults with JIA.

The specific aims were:

- To describe physical functioning, pain and HRQOL in two cohorts of adults (assessed 19 and 30 years after disease onset), compared to controls from the general population (papers 2 and 1, respectively).
- Examine the longitudinal changes in physical functioning, pain and HRQOL, assessed 15, 23 and 30 years (paper 1) and at baseline and 1, 3 and 19 years after disease onset (paper 2).
- Identify early (within 3 years after disease onset) and later (15 years after disease onset) predictors of physical disability, pain and physical HRQOL 19 and 30 years after disease onset (papers 2 and 1, respectively).
- Explore the influence of different pain trajectories during early disease course on long-term outcomes (paper 2).
- Provide information about JIA patients' treatment satisfaction and adherence with disease-modifying antirheumatic drugs 19 years after disease onset (paper 3).
- Explore the association between treatment satisfaction, adherence and HRQOL in adults with JIA (paper 3).

3. Materials and methods

3.1. Ethics

This project was carried out in accordance with the principles outlined in the Declaration of Helsinki (112), and approved by the Regional Committees for Medical and Health Research Ethics in Norway (approval number 2011/982 and 2015/532). Patients received written information about the study with an invitation to participate by mail, and informed consent was obtained.

3.2 Study design

This thesis comprises three papers presenting observational studies of adult patients diagnosed with chronic arthritis in childhood at the Department of Rheumatology at OUH. In papers 1 and 2, a prospective, longitudinal, cohort design was used. The patients were prospectively followed up with multiple assessments over a long period (111). In paper 3, a cross sectional design was used, assessing data at a single point of time (111).

3.3 Patients and controls

3.3.1. Patients and controls in cohort one

From a group of 400 patients with an initial clinical visit at OUH´s Department of Rheumatology between 1980 and 1985, 336 patients (84%) participated in a study 15 years later, of which 260 (65%) were reassessed with mailed questionnaires after 23 years and invited to participate in a third follow-up study after a mean of 29.7 years, of which 176 patients (44%) participated (Figure 2). Invitations to participate were sent by mail and one written reminder was sent if they did not respond to the first invitation. This third follow-up will be referred to as the 30-year follow-up. The patients in this cohort (cohort one) have been described in previous studies (1-3, 27, 113, 114). At disease onset, the patients were initially classified according to the ACR criteria of chronic arthritis in childhood (28), but reclassified according to the ILAR criteria based on physician´s clinical examination at 15-year follow-up and retrospective reviews of clinical records (32).

Of the 336 who participated in the 15-year follow-up, 160 (48%) did not participate in the 30-year follow-up. These patients were comparable to the 176

participants (52%) at 30-year follow-up with respect to duration of disease symptoms prior to the first visit at OUH, disease duration, JIA categories, and patient-reported outcomes regarding physical functioning, pain and HRQOL at 15-year follow-up. However, the non-participants were slightly younger at disease onset and had a higher percentage of men than the participants.

Patients were compared to 90 controls matched for age and gender and recruited randomly from the population register in Oslo and the surrounding county of Akershus by a company licensed to make random selections from the National Registry of Norway. Exclusion criteria for the controls at 30-year follow-up were rheumatic disease, previous cardiovascular events and diabetes. The controls were interviewed briefly by telephone before inclusion. The exclusion criteria for the controls were defined based on another study exploring cardiovascular risk in adults with JIA (113, 114). One potential control was excluded because of diabetes mellitus and 3 were excluded due to presence of inflammatory arthritis. Since the patient group consisted only of Caucasians, non-European controls were not invited. A total of 185 controls were invited, of which 94 (51%) accepted the invitation to participate.

3.3.2. Patients and controls in cohort two

A total of 197 patients with <18 months disease duration participated in a study at the Department of Rheumatology, OUH between 1995 – 2003. During the first 3 years of follow-up, patients were examined by a paediatric rheumatologist and assessed by self-reported questionnaires every 6 months. For younger children, parents answered questionnaires on behalf of their children. Results from the first 3 years of follow-up have been described in previous publications (4-6, 115).

A mean of 18.9 years after disease onset, one patient had been re-diagnosed and 4 patients were deceased, and thus, written invitations to participate and questionnaires were mailed to the remaining 192 patients. One written reminder was sent if the patients did not respond to the first invitation. A total of 96 patients (50%) agreed to participate (Figure 2). This follow-up will be referred to as the 19-year follow-up. Of the 192 eligible patients, 80 (42%) did not respond to the invitation and 16 (8%) could not be located. The non-participants (patients lost to follow-up, non-responders and deceased patients) were comparable to the participants regarding age at disease onset,

gender, polyarticular disease course and patient or proxy-reported outcomes regarding physical functioning and pain at 3-year follow-up.

Patients were matched to controls based on age and gender, selected randomly from the National Registry by a company licensed to do so. A list of 15 controls for each patient was selected and invitations were sent starting at the top of this list. If no response was received, an invitation was sent to the next control on the list. Controls were invited to participate by mail without any reminders. Since the patient group consisted only of patients with typically Scandinavian names, controls with typically Asian or eastern European names were not invited. A total of 435 controls were invited, of which 96 (22%) accepted the invitation to participate. The only exclusion criterion for controls in cohort two was the presence of inflammatory arthritis, and one control was excluded on this basis.

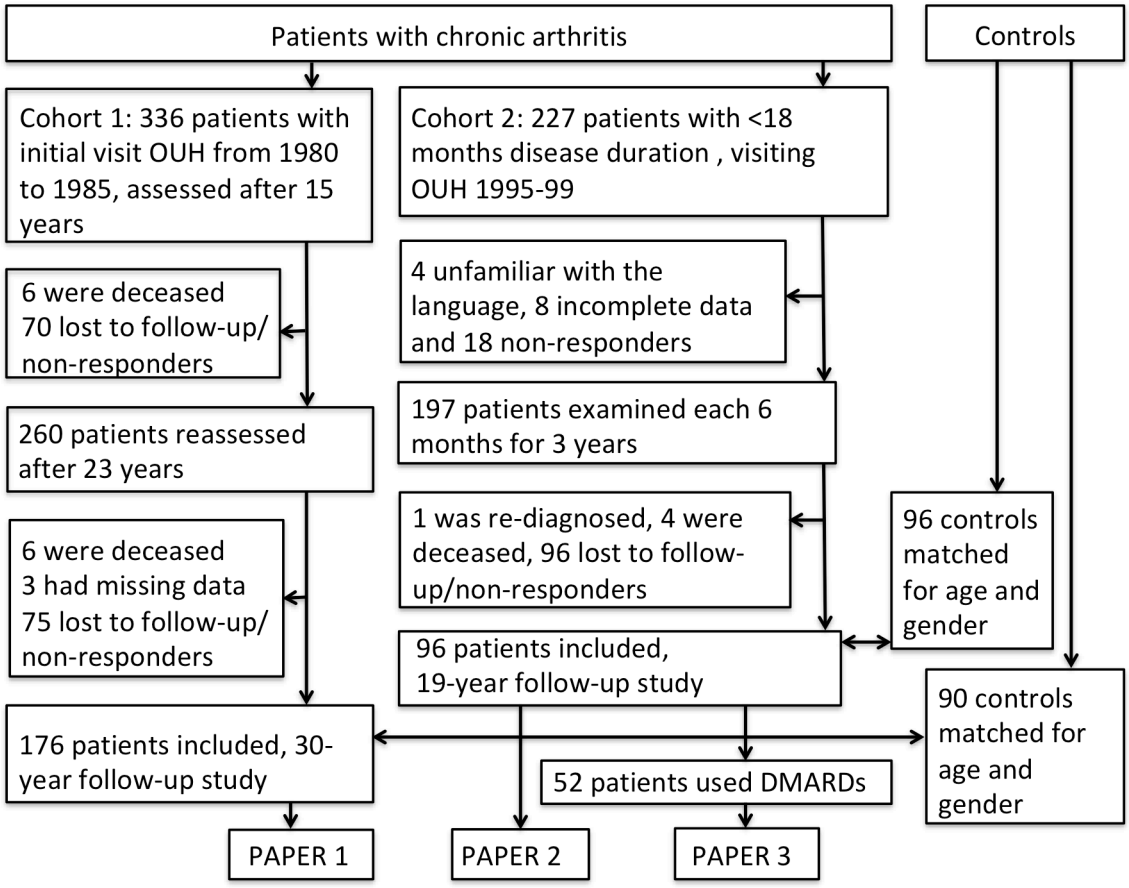

Figure 2. Illustration of patients and controls included in this study

3.4. Clinical examinations and measures

In cohort one, clinical examination was performed on all patients at 15-year follow-up. At 30-year follow-up, a physician's examination was performed on patients with signs of active disease and/or using anti-rheumatic medication a minimum of 15 years after disease onset. This information was based on the physician´s examination at 15-year follow-up and patient-reported questionnaires at 23 and 30-year follow-up. A total of 87 patients were assessed with clinical examination by one of three rheumatologists at OUH. Three patients with signs of active disease or using anti-rheumatic medication chose not to attend the physician's clinical examination, but still answered self-reported questionnaires.

Disease activity at 30-year follow-up was assessed using the validated instrument clinical Juvenile Arthritis Disease Activity Score (cJADAS) (116, 117) including number of active joints, physician's global assessment of disease activity (PGA), assessed with a VAS ranging from 0 (no disease activity) to 10 (severe disease activity), and the patients' global assessment of disease activity, ranging from 0 (doing very well) to 10 (doing very poorly). For unknown reasons the PGA was assessed on a 1–5 Likert scale at 15 and 23-year follow-up, even though a 10cm VAS scale is recommended (94). Thus, in order to analyse longitudinal changes in the PGA and use the recommended scale, both the Likert scale and the VAS scale were used in the PGA at the 30-year follow-up.
In cohort two, no clinical examination was performed at 19-year follow-up, however patients were clinically examined every 6 months for 3 years early in the disease course and clinical measures based on core set outcome variables recommended by ACR were assessed. Similar to cohort one, a Likert scale was used to assess PGA early in the disease course. All assessments used in this study are presented in Table 3.

3.5. Patient-reported outcome measures used in this study

In cohort one, patient-reported questionnaires regarding demographic characteristics, physical functioning, pain, wellbeing, fatigue, symptoms of psychological distress and HRQOL were collected from patients 15, 23 and 30 years after disease onset (Table 3).

In cohort two, patient-reported questionnaires regarding demographic characteristics, physical functioning, pain, wellbeing, fatigue, symptoms of psychological distress and HRQOL were collected from patients at 19-year follow-up (Table 3). Data collected during the first 3 years of follow-up were included in the analyses.

Table 3. Disease activity measures and patient-reported outcome measures used in this study

Measures	Reported by	Description	Paper	Cohort
HAQ	Patients >16 years	Physical functioning	1,2,3	1,2
CHAQ	Proxy-report in children <12 years, self-report ≥ 12 years	Physical functioning	2	2
Pain (VAS)	Proxy-report in children <8 years, self-report ≥ 8 year	Pain intensity	1,2,3	1,2
Patient´s global (VAS)	Proxy-report in children <8 years, self-report ≥ 8 years	Overall wellbeing	1,2	1,2
PGA [2]	Physician	Disease activity	1,2	1,2
Joints with active arthritis	Physician	Disease activity	1,2	1,2
LROM	Physician	Articular damage/ disease activity	1,2	1,2
Fatigue (VAS)	Proxy-report in children <12 years, self-report ≥12 years	Level of fatigue	1,2	1,2
SF-36	Patients >16 years	HRQOL	1	1
SF-12	Patients >18 years [1]	HRQOL	2,3	2
cJADAS-3	Patients/physician	Composite disease activity	2	2
Bone erosion	Radiography	Bone destruction	1	1
ESR	Laboratory	Measure of inflammation	1,2	1,2
BPI- Short form	Patients >18 years [1]	Pain severity and interference	2,3	2
SCL-5	Patients >16 years	Symptoms of psychological distress	1,2,3	1,2
Use of medication	Patients >18 years [1] and medical records	Medication use	1,2,3	1,2
MMAS-8	Patients >18 years [1]	Adherence to medication	3	2
TSQM	Patients >18 years [1]	Satisfaction with medication	3	2
Number of active joints (self-reported)	Patients >18 years [1]	Disease activity	2,3	2
Daily stiffness duration	Patients >18 years [1]	Disease activity	2	2

[1] One patient was 17.5 years old; HAQ = Health Assessment Questionnaire Disability Index; CHAQ = Childhood Health Assessment Questionnaire; Patient´s global = Patient global assessment of overall wellbeing; PGA = Physician´s global assessment of disease activity, [2] assessed by VAS and 1-5 Likert scale; LROM = Number of joints with limited range of motion; SF-36 = 36-item Health Survey Short Form; SF-12 = 12-item Health Survey Short Form version 2; cJADAS = Clinical Juvenile Arthritis Disease Activity Score 3; ESR = Erythrocyte sedimentation rate; BPI- short form = Brief Pain Inventory short form; SCL-5 = 5-item Hopkins Symptom Checklist; MMAS-8 = The 8-item Morisky Medication Adherence Scale; TSQM = Treatment Satisfaction Questionnaire for Medication.

3.5.1. Measures of physical functioning

Physical disability was assessed with the Health Assessment Questionnaire Disability Index (HAQ) at 15, 23 and 30-year follow-up in cohort one and at 19-year follow-up in cohort two (118, 119). The HAQ comprises 20 questions about the performance of physical activities across 8 categories (dressing, arising, eating, waking, hygiene, reach, grip and activities). The score for each question ranges from 0 to 3 and the highest score on any question within each category counts as the category score. If an aid, devices or help from another person is needed to perform the activity, the minimum score for that category is 2. The total score is the average score of the categories. During the first 3 years of follow-up for cohort two, physical disability was assessed with the Childhood Health Assessment Questionnaire (CHAQ) (120, 121). The CHAQ is a version of the HAQ that has been adapted to make the questions relevant for children. Similar to the HAQ, the CHAQ measures physical functioning in 8 areas and is scored in the same way. The CHAQ was used with children ≥12 years of age and with proxy-report by parents for children <12 years of age. Both the HAQ and the CHAQ are well-used measures of physical disability, with established validity and reliability (119, 121, 122).

3.5.2. Measures of pain

Pain intensity was measured on a 10 cm visual analogue scale (VAS), with a higher scores indicating more pain (123). VAS scales have been reported to be reliable and valid measurement tools (123) and all VAS scales used in this study were measured on a 10cm scale (0 = best possible score and 10 = worst possible score). In cohort two, self-report assessments of pain were obtained from children ≥8 years early in the disease course (first 3 years of follow-up) while proxy-reports from parents were obtained from younger children. At the 19-year follow-up pain was also assessed with the Brief Pain Inventory Short Form (BPI) (124), comprising the domains of pain intensity (4 items) and pain interference (7 items), measured on 11-point numeric rating scales (NRS) with a higher scores indicating more pain intensity or pain interference. Satisfactory psychometric properties of the BPI have been reported (125, 126).

3.5.3. Measures of fatigue, wellbeing and psychological distress

Levels of fatigue and patient´s global assessment of overall wellbeing were measured by 10cm visual analogue scales (VAS) with higher scores indicating more fatigue or less

overall wellbeing. Self-reported assessments of overall wellbeing were obtained from adults and children ≥8 years, while self-reported assessments of fatigue were obtained from children ≥12years of age. In younger children, proxy-reports from parents were obtained.

The 5-item Hopkins Symptom Checklist (SCL-5) was used to measure symptoms of psychological distress (127, 128). The SCL-5 is a short version of the 25-item version (SCL-25), which is based on the revised 90-item version (SCL-90-R) (129). The SCL-5 measures common symptoms of psychological distress, based on questions regarding anxiety and depression. The scores range from 1–4 (where 1 = not at all and 4 = extremely) based on symptoms during the previous month. The total score is the average score across all items. The questionnaire is not suitable as a diagnostic instrument but has shown good psychometric properties in measuring symptoms of anxiety and depression (128). Since no clinical examinations were performed in cohort two at 19-year follow-up, the patients were asked to report their numbers of active joints and joints with limited range of motion on a manikin figure. Although reasonable agreement on the joint counts has been reported between patients and physicians using the manikin figure, untrained patients had a tendency to overestimate the presence of joints with active arthritis (130).

3.5.4. Measures of health-related quality of life

HRQOL was assessed with the 36-item Health Survey Short Form (SF-36) in paper 1 and with the 12-item Health Survey Short-Form (SF-12) in papers 2 and 3 (131, 132). The SF-36 and SF-12 each include 8 subscales (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health), which are summarized into physical component summary (PCS) and mental component summary (MCS) scores. For the SF-36, the subscales scores range from 0–100, with higher scores indicating better health, while the summary scores (PCS and MCS) were standardized to a mean value of 50 based on the United States (US) general population(132). For the SF-12, both subscale scores and summary scores were norm-based standardized scores (mean of 50, standard deviation of 10) based on the US general population (131). For both questionnaires, higher scores indicated better health and both questionnaires are reported as reliable and valid measures (131, 133).

3.6. Patient-reported assessments regarding treatment satisfaction and adherence

3.6.1. Measures of medication satisfaction

Medication satisfaction was assessed with the Treatment Satisfaction Questionnaire for Medication (TSQM), a 14-item questionnaire measuring patient satisfaction with medication (134). The instrument covers 4 dimensions of medication satisfaction: effectiveness (3 items), side effects (5 items), convenience (3 items) and global satisfaction (3 items). The total score ranges from 0–100 with higher scores indicating higher satisfaction. The TSQM has been reported to have good psychometric properties (134).

3.6.2. Measures of adherence to medication

Adherence to medication was assessed with the 8-item Morisky Medication Adherence Scale (MMAS-8) (135, 136). The total score ranges from 0–8, with higher scores indicating higher levels of adherence. The MMAS-8 has been reported to be a valid and reliable instrument (135, 136).

3.7. Statistics

Statistical analyses in papers 1, 2 and 3 were performed using the Statistical Package for Social Sciences (SPSS), Version 22 (IBM Corp. Armonk, NY, USA). In paper 2, additional analyses were performed by growth mixture modelling (GMM) using the generalized linear latent and mixed models (GLLAMM) package in Stata, Version 14 (StataCorp, College Station, TX, USA).

In all papers, descriptive statistics were used to describe the samples and included absolute frequencies and percentages for categorical variables. Means and standard deviations were reported for normally distributed continuous data, and medians and ranges for non-normally distributed data. Comparisons between groups were performed using chi-square tests for categorical variables, independent sample t-tests for normally distributed continuous variables and Wilcoxon-Mann tests for non-normally distributed variables.

In order to compare changes over time as presented in papers 1 and 2, one-way repeated measures analysis of variance was used for normally distributed variables, Friedman´s test of variance was used for skewed variables, and Cochran´s Q test was

used to compare frequency differences in dichotomous variables over time. In paper 1, McNemar´s test was used to test for differences in physical disability at 15 and 30-year follow-up, since this variable was treated as a dichotomous variable.

Linear regression analyses were used in order to identify determinants and predictors of physical HRQOL (papers 1 and 2). In paper 2, linear regression analyses were also used to identify predictors of pain, while logistic regression analyses were used to identify predictors of physical disability.

To explore the impact of disease course (polyarticular course, persistent oligoarticular arthritis and enthesitis related or psoriasis arthritis) on physical disability, pain, HRQOL or disease activity assessed by cJADAS (paper 1), one-way between-groups analysis of variance was used for normally distributed variables, Kruskal-Wallis test was applied for non-normally distributed variables and chi-square test of independence was applied for dichotomous variables.

In paper 2, GMM was used to identify trajectories of pain early in the disease course, while linear and logistic regression analyses were used to identify the impact of distinct pain trajectories on patients´ experience of physical disability, pain and physical HRQOL at 19-year follow-up. GMM was used to identify subgroups of patients with distinct pain trajectories during the first 3 years of follow-up and 3 homogeneous subgroups were identified in cohort 2. GMM is a statistical method that aims to estimate between-person differences in within-person change over time (137).

In paper 3, paired sample t-tests were used to compare medication satisfaction in patients using two different DMARDs, while independent sample-t-tests were used in patients using either MTX or a biological DMARD. Linear regression analyses were used in order to identify determinants of treatment satisfaction and to explore the association between medication satisfaction and HRQOL. Associations between medication adherence and other variables were assessed using Spearman´s rank correlation (r_s) since the MMAS-8 was not normally distributed.

4. Summary of the papers

4.1 Paper 1

Physical functioning, pain and health-related quality of life in adults with juvenile idiopathic arthritis – a longitudinal 30-year follow-up study

The objectives of this study were to compare HRQOL in adults with JIA to controls from the general population, explore changes in physical functioning, pain and HRQOL over time (based on assessments 15, 23 and 30 years after disease onset) and identify predictors and determinants of lower HRQOL (based on assessments at 15 and 30-year follow-up).

A total of 176 patients (mean age 37.8 years) were assessed with questionnaires regarding physical functioning, pain, wellbeing, fatigue and HRQOL a mean of 30 years after disease onset. The patients were compared to 90 controls (mean age 37.5 years) selected from the general population. Data collected at 15-year follow-up were analysed in order to identify predictors of physical HRQOL, while data collected at 15, 23 and 30-year follow-ups were used in the longitudinal analyses.

Compared to age and gender matched controls, JIA patients had lower physical and comparable mental HRQOL assessed by the SF-36. Seventy-five patients (43%) had active disease or were still using medication. Lower physical HRQOL (assessed by the physical component summary of the SF-36) was found both in patients with active disease and patients in clinical remission without medication.

During the longitudinal follow-up 15, 23 and 30 years after disease onset, patients' experience of physical HRQOL and wellbeing deteriorated, but no changes were found in pain and mental HRQOL. Poorer physical HRQOL after 30 years was associated with physical disability, more fatigue and lower wellbeing after 15 years; and pain, physical disability, lower wellbeing and receiving disability or social living allowance after 30 years. This study confirms and extends our knowledge of the long-term consequences of JIA in adulthood.

4.2 Paper 2

Longitudinal health status from early disease to adulthood and associated prognostic factors in juvenile idiopathic arthritis

The objectives of this study were to explore longitudinal changes in health status over time from childhood to adulthood and identify early predictors of more pain, impaired physical functioning and lower HRQOL in JIA patients at 19-year follow-up. We also compared patient-reported outcomes at 19-year follow-up with that of controls from the general population.

A total of 96 JIA patients (mean age 25.1 years) were assessed with questionnaires regarding education/employment, use of medication and their health status a mean of 18.9 years after disease onset. The patients were compared to 96 controls (mean age 25.1 years) selected from the general population. Data assessed prospectively during the first 3 years of follow-up were included in the analyses in order to identify early predictors of impaired health status after 19 years.

At 3 and 19-year follow-up, similar levels of physical functioning, pain and wellbeing were reported, but level of fatigue did increase. Pain intensity, active joints and physical disability within the first 3 years of follow-up, were associated with physical disability, more pain and worse physical HRQOL after 19 years. Late pain recovery during early disease course was associated with more pain and physical disability and lower physical HRQOL after 19 years. At 19-year follow-up, JIA patients had less work participation, more pain and lower physical HRQOL than age and gender matched controls.

The JIA patients in this study were diagnosed in an era when biological DMARDs became available early in their disease course. Previous studies on long-term patient-reported outcomes among adults with JIA are limited and mainly restricted to patients diagnosed 1 – 2 decades prior to the introduction of new and better treatment regimens. Thus, our study provides information on the long-term consequences of JIA among patients where limited scientific information has been available about long-term patient-reported outcomes. Further, this study is the first to explore the long-term impact of sequential variables prospectively assessed early in the disease course. JIA is a fluctuating disease and multiple prospective assessments early in the disease course may increase the predictive ability of the variables assessed.

4.3 Paper 3

Treatment satisfaction with and adherence to disease-modifying antirheumatic drugs in adult patients with juvenile idiopathic arthritis

The objectives of this study were to explore medication satisfaction and perceived adherence to MTX and biological DMARDs in adults with JIA and the association between medication satisfaction, adherence and HRQOL.

A total of 96 patients (mean age 25.1 years) were assessed with questionnaires regarding education/employment and their health status a mean of 18.9 years after disease onset, of which patients using MTX and/or biological DMARDs were additionally assessed with questionnaires regarding medication satisfaction and adherence.

At 19-year follow-up, 52 patients (54%) were using synthetic and/or biological DMARDs. Of these 52 patients, 37 used biological DMARDs, 28 used MTX and 5 used sulfasalazine, with a total of 18 patients using two DMARDs in combination. Patients were more satisfied with biological DMARDs than with MTX. Patients using either MTX or biological DMARDs (but not in combination) were more satisfied with the effectiveness of biological DMARDs than MTX. Patients using MTX and biological DMARDs in combination were more satisfied with biological DMARDs than MTX with respect to side effects. Nearly half of patients reported low adherence to medication. Higher medication satisfaction was associated with better HRQOL and with better adherence. Our findings provide information on medication satisfaction and adherence among adults with JIA, which previously has received little attention. Such information can be used in the communication between patients and physicians regarding medical treatment in order to improve adherence. Since this is a rather small study, more studies are required to further address this issue.

5 Discussion

5.1. Discussion of the main findings

Based on the research questions outlined in chapter 2, the main results will be discussed and compared with other studies.

5.1.1. Physical disability, pain and HRQOL in adults with JIA

In both cohorts, 3% of the patients reported severe disability (HAQ>1.5), indicating that JIA still has a prominent detrimental effect on physical function in a small group of patients. This is in line with recent studies (138, 139), but is a considerably lower proportion than reported in earlier studies of adult JIA patients (33, 34). Almost half the patients in both cohorts reported some physical disability (HAQ>0), and a higher percentage of patients with polyarticular course JIA in cohort one (the 30 year follow-up) reported physical disability compared with patients with persistent oligoarticular arthritis. Similar results have been reported in previous studies (33, 36, 53, 139). In two recent studies however, no physical disability was reported by 72% and 58% of adults with JIA after mean disease duration of 18 and 14 years, respectively (140, 141), even though the latter study only comprised patients with more severe disease treated with biological DMARDs. The availability of improved treatment could be a plausible explanation for improved disability outcomes in recent studies of JIA patients. A cut-off value of HAQ >0 was used in our studies, as suggested by Krishnan et al (142). As previously noted in paper 1, there is a possibility that this cut-off level is too low, since the estimated prevalence rate of physical disability (HAQ>0) is 14% in people 30-45 years of age (based on the general population in Finland) (142). However, a floor limitation of the HAQ has been proposed, implying that people with mild functional limitations can have normal HAQ scores (143, 144).

We found that adults with JIA reported more pain than controls, which is similar to results from previous studies (17, 49, 50). The median pain scores in both our cohorts were generally more favourable than in other studies of adults with JIA (16, 34, 55, 145), however most of these previous studies were conducted 1-2 decades ago. In a recent population-based study by Glerup et al (140), pain assessments were performed on patients 18 years after disease onset. Their findings were similar to our results. When comparing our two cohorts, higher levels of pain and a higher proportion of moderate to

severe pain were found in patients assessed 19 years after disease onset compared to those assessed after 30 years, although pain has been found to increase with age in adults with JIA (145). A potential explanation for higher levels of pain in cohort two is that this is a period in life with increased demands in many different ways (doing well at school, getting a job and starting a family), which may have an impact on their experience of pain. Within JIA, more pain in older adolescents than in younger patients has previously been reported (83, 146). Differences in the number of patients with active disease between these two groups could also be an explanation. In cohort one, 43% of patients had active disease. Although, we did not have information regarding remission status in cohort two, 54% of patients were currently using DMARDs and therefore would be considered to have active disease. Levels of pain have been found to differ between different subgroups of JIA, with higher levels in patients with ERA (2, 83, 140). However, the percentage of patients with ERA in cohort two were lower than in cohort one and in the population-based study by Glerup et al (140), indicating that this would not explain the higher level of pain among patients in cohort two.

Patients had lower physical HRQOL but similar mental HRQOL compared to controls in both cohorts in our study. The scores on the role physical, bodily pain, general health and vitality subscales were significantly lower than the controls in both cohorts, which supports the reliability of these results. The physical functioning subscale was lower than controls in cohort one but not in cohort two. In a recently published study, better outcome was associated with early DMARD treatment (147), and a plausible explanation for this could be improved treatment options early in the disease course in cohort two. Another possible explanation could be the effect of age and longer disease duration, as the patients in cohort one were over 10 years older with longer disease duration. Data from a Norwegian SF-36 health survey has shown lower scores on physical health scales with increasing age (148).

In both cohorts, physical disability and pain were important correlates of physical HRQOL, and this relationship has been elucidated in several other studies (86, 140, 149). Pain has been found to have an impact on HRQOL, and in a study by Dhanani et al, a relatively small reduction in pain could result in a significant improvement in patients´ HRQOL (150). The comprehensive model of HRQOL (Figure 1) presents a comprehensive view linking relevant variables such as physical disability (functional status) and pain (symptoms) to the HRQOL construct, together with other relevant variables that might have an impact on HRQOL. It is however conceivable that great

variation exists between people regarding the amount of impact these relevant variables have on HRQOL, and factors other than those that are disease-related may contribute to patients' experience of physical disability, pain and HRQOL. Patients may have different references points when answering questions regarding physical disability, pain and HRQOL. Patients may also adapt to their situation differently. The term response shift has been introduced by Schwartz and Spangers to address people´s change in self-evaluation due to changes in internal standards, values or redefinition of the target construct (151).

5.1.2. Longitudinal changes in patient-reported outcomes over time

One of the strengths of our study is the sequential assessment of PROs in order to assess changes over time. In cohort one, mental HRQOL, level of pain and number of patients with physical disability did not change at the 15, 23 and 30-year follow-ups, but patients´ physical HRQOL and experience of wellbeing deteriorated. Side effects or sequelae from previous disease or medications could be a possible explanation for the deterioration of physical HRQOL and wellbeing over time. These changes could also be due to the normal range of variance in the studied population. Longitudinal data from controls participating in this study could have provided additional information on expected changes in HRQOL and wellbeing over time, however this was not collected. Results from a Norwegian survey of the general population have shown that physical HRQOL was strongly affected by age (148). However, it should be noted that the mean age of patients in this cohort was only 37.8 years and the possible impact of age might not be clearly apparent yet. To our knowledge, no other study has performed longitudinal assessment of HRQOL and wellbeing in adults with JIA.

In cohort two, the percentage of patients with no physical disability increased during the first three years of follow-up, but decreased from 3 to 19-year follow-up. Similarly, Zak et al found that the level of physical disability increased from 10 to 26 years of follow-up (16). However, the study by Zak et al was conducted over 20 years ago with longitudinal assessments regarding physical disability reported by physicians and not by patients. Additionally, changes in treatment since then may limit the present relevance, especially since recent studies have reported more favourable outcomes regarding physical disability in adults with JIA (140, 147).

In our study, patients reported more fatigue at the 19-year follow-up than at the 3-year follow-up. Studies of changes in fatigue over time have not been consistent. A stable level of fatigue over time has previously been reported among adolescents with JIA (48), but so has an increased level of fatigue over time (152). Fatigue is a common symptom in patients with JIA that warrants further studies (153). In our study, no assessment was performed between 3 and 19-year follow-up. This is an important period in life and several factors other than the disease may affect the changes reported in the study. Changes over time may also represent normal range of variance or individuals gradually changing their perception of their situation over time (151, 154). Within JIA, little information exists about long-term longitudinal changes based on patient-reported health status in JIA, and further studies are needed to increase the validity and reliability of these findings.

5.1.3. Predictors of physical disability, pain and HRQOL

In our regression model physical HRQOL after 30 years was predicted by physical disability, fatigue and patients wellbeing assessed at 15-year follow-up, while the most important predictors of physical HRQOL after 19 years were physical disability at 3-year follow-up, pain at baseline and presence of active joints at baseline and 3-year follow-up.

The most important predictors of pain at 19-year follow-up were physical disability at baseline and/or 3-year follow-up and number of active joints at baseline. In this cohort, we also used GMM in order to identify groups of patients with different pain trajectories early in the disease course. Patients with late pain recovery early in the disease course had more physical disability, pain and lower HRQOL in adulthood. Our findings indicate that pain early in the disease course is an important dimension of JIA, which has a detrimental effect on PROs in adulthood, and this warrants more research into the multidimensional aspects of pain and disability.

Physical disability after 19 years (cohort two) was predicted by pain at baseline and physical disability after 3 years in our model.

Previous longitudinal studies on early predictors of patient-reported outcomes in adults with JIA have been scarce. In line with our results, Bertilsson et al found physical disabilities 5 years after disease onset to be associated with physical disability and physical HRQOL at 17-year follow-up (17), and in a study of patients diagnosed >40 years ago, associations were found between physical disability 10 years after disease

onset and physical disability after 26 years (16). Identification of early predictors of long-term outcomes in JIA is difficult, as different studies may include different independent variables, which may lead to inconsistent results. Recently, suggestions for applicable prediction models for different outcome variables in patients with JIA have been published (155-157), although these models should be tested further in other cohorts before their applicability can be recommended. In Table 4, recent studies (during the last 20 years) on predictors of long-term (>8 years) outcomes, including patient-reported outcomes (as predictor or outcome), are presented.

Table 4. Longitudinal studies on predictors of long-term* PRO in patients with JIA

Author, year (follow-up time)	**Outcomes predicted**	**Identified early predictors**
Aasland et al, 1997 (9 years)(57)	Psychosocial outcome	Chronic family difficulties.
Flatø et al, 1998 (10 years) (45)	Physical disability	Persistent active disease 5 years after onset was identified as a predictor of physical disability.
Flatø et al, 2003 (15 years) (1)	Physical disability	Female sex, symmetric arthritis, early hip joint involvement and long duration of elevated ESR and positive IgM RF.
Bertilsson et al, 2013 (17 years) (17)	Physical disability and physical HRQOL	PF-positivity was identified as the most important variable associated with physical disability (defined as HAQ>0) after 17 years. Poorer physical HRQOL was associated with disease activity duration index first 5 years and with CHAQ, number of joints with arthritis and non-remission at 5-year follow-up in univariate analyses.
Rypdal et al, 2018 (8 years) (157)	Physical disability and lower physical HRQOL,	Cumulative joint count, ESR, CRP, morning stiffness, physician's global assessment of disease activity and pain predicted both outcomes. Finger joint arthritis predicted physical disability.
Arnstad et al, 2019 (8 years) (158)	More pain and functional disability	Pain at baseline (based on univariate analyses).

* > 8-year follow-up; HAQ = Health Assessment Questionnaire Disability Index; CHAQ = Childhood Health Assessment Questionnaire.

5.1.4. Treatment satisfaction with and adherence to DMARDs

Medication satisfaction in adults with JIA is a topic that has received little focus, despite the fact that many JIA patients continue to use medication into adulthood. In children, studies regarding medication adherence have been published (65, 66, 159-161), but only one of them explored patients´ experiences taking prescribed medication (66). We found that patients were more satisfied with biological DMARDs than synthetic

DMARDs. This is in contrast to Wolfe and Michaud who found that patients with adult-onset rheumatoid arthritis (RA) were more satisfied with non-biological versus biological DMARDs (162), although the patients in their study were older than the patients in our study and the cost of medication was found to impact their medication satisfaction (162). The health care system in Norway may differ from other countries, as medication costs are, to a large extent, covered by the public health system. Different systems may influence the results regarding medication satisfaction.

A key reason for taking prescribed medication is the effect it has to treat the disease and improve HRQOL (163, 164). Therefore, the association found between medication satisfaction and HRQOL was as expected.

In our study, we found adherence to medication to be low among our patients. Medication adherence rates have varied in different studies of patients with JIA or RA (65, 165-167). Among children with JIA, adherence to MTX has been found to decrease with age (65, 165). However, prior to our study, little was known about adherence to medication among adults with JIA. We used self-reported measures when assessing levels of adherence, and it is possible that more objective measures would have found even lower rates of adherence. However, a systemic literature review of adherence in adults with RA did not find differences in adherence for different measurement methods (168).

We also found an association between adherence to medication and patients' satisfaction with the convenience of taking medication. In an era with several treatment options for JIA, the inconvenience of taking prescribed medication should be included in the decision-making process. Patients' experience of side effects did not have an impact on adherence to medication in our study, although an association between adherence and medication side effects has previously been reported (163). Due to little knowledge about treatment satisfaction and adherence in JIA and the small number of participants in this cross-sectional study, larger studies are required to confirm our results and explore these issues further.

5.2. Methodological considerations

5.2.1. Study design

The major strength of the study presented in the first paper was the long-term longitudinal follow-up of a relatively large and well-characterized patient cohort, which

made it possible to explore changes and the direction of changes in adults with JIA over time. A challenge with a longitudinal prospective design is loss of participants over time, which can present notable threats to the representative nature of the sample and reduce survey estimate precision (111, 169, 170). All patients in cohort one were assessed with self-reported questionnaires at 15, 23 and 30-year follow-up (paper 1). Clinical examinations were performed on all patients at 15-year follow-up. However, at 30-year follow-up, only patients with signs of active disease and/or using anti-rheumatic medication at 15-year follow-up or later were invited for a clinical examination. Ideally, a comprehensive clinical examination of all participating patients at 30-year follow-up would have increased the accuracy and reliability of the information regarding disease activity and remission status of all patients. Unfortunately, this was not done for practical and economic reasons.

The major strength of the study design used in the second cohort (paper 2) was that patients were closely prospectively followed with clinical examinations and questionnaires at 6-month intervals over 3 years early in the disease course. Since JIA can be a relapsing disorder, sequential assessment may increase the predictive ability of the assessments. Unfortunately, there was a long period of time between the 3 and 19-year follow-ups. This is an important time of life, which is likely to have had a significant impact on patients' long-term outcome. Ideally, more information on patients between these two follow-ups would have increased the validity of the results. However, a major strength of this study is the repeated measurements of the patients early in their disease course. These patients were not clinically examined, but their current use of medication and self-reported number of active joints were assessed. However, the results regarding disease activity in joints should be interpreted with caution as patients´ tendency to overestimate the presence of active joints has been previously reported (130).

The longitudinal design in papers 1 and 2 made it possible to explore changes in patient-reported outcomes over time (104), which is a major strength. In both cohorts the patient-reported data were prospectively collected, which reduces the likelihood of recall bias (170).

We also aimed to study patients´ experience with medication as well as their adherence to medication. Therefore, questionnaires not previously assessed during the longitudinal follow-up were included in the study (paper 3). The number of patients participating in the cross-sectional study was small since only patients currently using DMARDs were included.

5.2.2. Study population

The patients participating in our cohorts were referral-based and recruited from the Department of Rheumatology at OUH. This could lead to sample bias due to the probability of including patients with more severe disease than in a population-based cohort (111). However, patient characteristics of the participants in our cohorts have been found to be comparable to those of population-based studies of the disease (17, 49). Traditionally, children with JIA are usually referred to specialist care early in their disease course through the Norwegian tax-funded health-care system, which reduces the probability of only including children with severe disease. Further, since the patients included in this present study were based on all referrals to OUH during specific time periods (1980–85 or 1995–2000), they were invited to participate in these follow-ups regardless of current disease activity.

Selection bias occurs when there is a systematic difference between the characteristics of those participating in the study and those who chose not to (171). During the longitudinal follow-up of both cohorts, patients were lost to follow-up as presented in Figure 2. Patients lost to follow-up during the longitudinal study can influence the representativeness of the results if they are different from the continuing participants. In cohort one, the percentage of participating men decreased during follow-ups and a small difference in age at disease onset was found between participants and non-participants. To what extent these issues impact on the results in our study is unknown. However, in this cohort, similar disease-related characteristics between the 30-year participants and non-participants were found at their 15-year follow-up. Similarly, when comparing the participating patients with the non-participants in cohort two, no differences were found regarding age at disease onset, gender or the distribution of diagnostic subgroups of JIA.

In both cohorts, patients were compared to age and gender-matched controls and differences were found in the response rate of the controls in cohort one and two. In cohort one, 51% of the invited controls agreed to participate, while the response rate in cohort two was only 22%. The higher response rate in cohort one could be because these controls were also part of a study regarding cardiovascular risk in adults with JIA, and the response rate may have been influenced by the invitation to have a cardiovascular examination (114). Selection bias is a problematic threat to internal validity if the results are attributed to factors other than the independent variables analysed in the study (111). The outcomes of the study could be distorted by the

characteristics of the participating controls if they are more likely to be concerned about their health than the group they represent. In cohort two, we experienced difficulties including controls between 20 and 30 years of age. Both self-selection bias (controls wanting clinical examinations) and non-response bias (controls not accepting the invitation) are possible limitations to the representativeness of the controls and a threat to both internal validity and external validity of our results.

5.2.3. Psychometric properties of the questionnaires

In order for the results of a study to be reliable and valid, the instruments used in the study need to be accurate, consistent, and measure what they are supposed to (111). A strength of this study is that the outcome measures used are in line with the core set outcome variables recommended by the ACR, although only 2 of the 6 core set outcome variables are PROMs (94). The patient-reported questionnaires used in our study are well known with documented satisfactory reliability and validity (119, 121-123, 125, 128, 131, 133-136, 172, 173). Using PROMs considered appropriate and relevant by the international rheumatology society increases the face validity and thereby the content validity (13). However, the validity and reliability of measures applied under one set of circumstances do not ensure generalizability of the instrument to other circumstances or populations. A limitation to this study is that the psychometric properties of the instruments used in our study to some extent are tested on patients with RA or other chronic diseases and not on adults with JIA. Additionally, outcome measures recommended by clinicians and researchers are not necessarily important to patients (13, 174). The participants in our study were assessed with multiple questionnaires, which to a large extent, yielded results in the same direction, thereby increasing the validity of the results.

The main outcome variable in our study was HRQOL as measured by SF-36 and SF-12. In previous studies, the scores from these questionnaires have corresponded well with other measures at group levels, been able to discriminate between study groups and been sensitive to differences in disease severity (17, 143, 144, 175, 176). However, they are generic measures and important HRQOL aspects related to JIA may not be measured. Ceiling and floor effects occur when the measures are unable to discriminate between patients reporting the highest possible or lowest possible scores on the questionnaire in use (177, 178). This can result in sub-optimal assessments of patients

at the upper and lower end of the score range and can reduce the reliability and validity of the study (178). Observed floor and ceiling effects have been reported with the HAQ and SF-36 in previous studies (144, 173, 179, 180), however the impact of this in our study is not known.

The TSQM and MMAS-8 are validated measurements of treatment satisfaction and adherence (134, 135), however little information exists about the psychometric properties of these instruments. In our study, we used Cronbach´s alpha to measure the internal consistency of the TSQM items. In patients using MTX, a Cronbach´s alpha ≥0.80 was found on all items. Among patients using biological DMARDs, a Cronbach´s alpha ≥0.83 was found on the effectiveness and global satisfaction items, although a weaker Cronbach´s alpha was found on the side effects (0.47) and convenience (0.64) items. In our study, patients used different biological DMARDs with different routes of administration, which could have an impact on these results. The TSQM has only been validated in patients with arthritis using oral medication (134).

5.2.4. External validity

One important aspect of external validity concerns the representativeness of the studied samples and to what extent our results can be applied to a broader group of adults with JIA. All patients participating in this study were enrolled from a single Norwegian centre. Referral-based cohorts may increase the probability of including patients with more severe disease. However, the patients in our two cohorts have been found to be comparable to patients in epidemiological studies of the disease regarding sex, age at onset and distribution of diagnostic subgroups (17, 24, 49, 181), which increases the generalizability of our results. Further, the health-care system in Norway may differ from health-care systems in other countries, with an impact on long-term outcomes. However, the results from our study regarding long-term physical disability, pain and HRQOL are in concordance with other studies of adults with JIA (16, 33, 34, 49, 145), which increases the external validity of this study.

In the cross-sectional study regarding patients´ experiences with DMARDs, the number of participants was low, and further studies are needed to confirm our results reported in paper 3.

5.2.5. Statistical considerations

In paper 2, patients were compared to controls matched for age and gender and paired sample t-tests could have been used instead of independent sample-t-tests. However, due to missing data on some of the questionnaires (both among patients and controls), independent sample t-tests were performed to be able to accommodate missing data without reducing sample size. However, paired sample tests performed on these data, yielded similar results.

The scores from the SF-36 and SF-12 in our study were treated as normally distributed, and parametric tests were conducted. However, the SF-36 and SF-12 contains 8 dimensions with a variety of distributions and not all were normally distributed. Therefore, we could have used non-parametric tests. However, like in many published studies, we used standards methods when analysing the data. In a previous study, Walter and Campbell yielded similar results when using both methods in analysing SF-36 in patients with early RA and osteoarthritis and concluded that both methods could be used (182). Similarly, non-parametric tests performed on our data yielded similar results.

6. Conclusions

- Adult patients with JIA reported poorer HRQOL (after 19 and 30 years) compared with matched controls from the general population.
- Almost half of patients reported some physical disability and 3% reported severe disability after 19 and 30 years.
- Poorer physical HRQOL was associated with more physical disability and pain in both cohorts.
- Compared with controls from the general population, adult JIA patients reported more pain after 19 years.
- A higher numeric level of pain intensity was found in JIA patients assessed 19 years after disease onset than in those assessed after 30 years.
- During the longitudinal follow-up of adults with JIA after 15, 23 and 30 years, patients' level of wellbeing and physical HRQOL deteriorated.
- From the 3 to 19-year follow-ups, the level of fatigue and percentage of patients with physical limitations increased, while the levels of physical disability, pain and wellbeing did not change.
- Lower wellbeing and more fatigue and physical limitations at 15-year follow-up were the most important predictors of lower physical HRQOL after 30 years.
- Physical disability, pain and/or active joints assessed during the first 3 years were identified as early predictors of physical disability, pain and physical HRQOL after 19 years.
- Late pain recovery during the first 3 years of the disease course had a detrimental effect on physical disability, pain and physical HRQOL 19 years after disease onset.
- Higher medication satisfaction was found with biological DMARDs than with MTX.
- Low medication adherence was reported by half of adult JIA patients.
- Better HRQOL was associated with higher medication satisfaction.

7. Implications and future perspectives

7.2. Implications

Information about patients' subjective experience of living with JIA may provide a better understanding of the impact of the disease on patients' lives and represents information emphasised as important by health authorities (18, 19). Results from our study will be of interest to physicians and other health-care professionals working with JIA patients. The results will also be of interest to patients with JIA and their families. This study extends the knowledge in the field of long-term outcomes in adult patients with JIA by identifying early predictors of unfavourable long-term outcomes and by exploring changes in patient-reported outcomes over time. Adult JIA patients' medication satisfaction and adherence have previously received little attention, although such information should be significant in patient-centred care and therapy.

7.2. Future perspectives

Our study provides valuable information about long-term outcomes in JIA. However, important changes in medication therapy have occurred during recent decades. New long-term, up-to-date studies of patients diagnosed after the introduction of biological DMARDs will be required in the future, as improved medical treatment will likely improve long-term outcomes. The patients in our study were followed for a long period of time (up to 30 years), however, further longitudinal follow-ups of these patients would be desirable, in order to explore the impact of JIA among adults over a longer period of time.

HRQOL is a broad multidimensional concept, which was in our study assessed using the SF-36 and SF-12 questionnaires. These are generic questionnaires, hence other domains that may be of significance to adults with JIA may not be covered. Additional data regarding HRQOL not yet analysed or published have been collected in our study, and these would be of relevance for further study in order to achieve a broader understanding of the impact of JIA on patients' lives.

Patients' experiences regarding medication treatment are important, however due to the small number of patients participating in our cross-sectional study, the results require confirmation in larger studies. Medication satisfaction in JIA is a topic that has received little attention so far, however this is an important issues in patients with chronic disease with expected long-term, expensive treatment. New studies with

reliable and validated measures are warranted, taking into account the current changes in treatment. In order to achieve more comprehensive knowledge of medication satisfaction and adherence in JIA, further research is required. Further research could also include qualitative research in order to gain more insight and reveal new dimensions important to patients regarding their treatment experience and adherence.

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Errata

1.
Abstract paper 1:
3rd line: "the visual analogue pain scale subscale" should be "the visual analogue scale pain".

2.
Reference number 39 paper 2:
Minden K, Kiessling U, Listing J, Niewerth M, Doring E, Meincke J, et al. Prognosis of patients with juvenile chronic arthritis and juvenile spondyloarthropathy. J Rheumatol. 2000;27:2256-63.
Should be:
Minden K, Niewerth M, Listing J, Biedermann T, Bollow M, Schontube M, et al. Long-term outcome in patients with juvenile idiopathic arthritis. Arthritis Rheum. 2002;46:2392-401.

3.
Table 3, paper 2:
"Anxiety and depression (SCL-5, range 0–4)" should read "Anxiety and depression (SCL-5, range 1–4)".

4.
Table 4c, paper 2:
The correct unstandardized regression coefficient on row 3 is "–0.6 (1.7, –0.2)" and not "–0.6 (1.7–0.2)".

5.
Page 6, paragraph 4, paper 3:
" …of 7 items rated on 1–10 numeric rating…." should read " …of 7 items rated on 0–10 numeric rating…."

6.
Page 10, paragraph 1, paper 3:
" Levels of education, physical disability and psychological distress were negatively……" should read " Levels of education were positively associated while physical disability and psychological distress were negatively……".

7.
Page 11, paragraph 2, paper 3:
"High levels of physical disability, pain intensity, psychological distress, education and numbers of active joints as well as current use of MTX correlated ….." should read " Higher levels of physical disability, pain intensity, psychological distress, number of active joints, current use of MTX and lower education level correlated ….. "

8.
Table 1, paper 3:
The pain severity score on all patients "1.25 (1–9)" should read 1.25 (0–9)".

Heading, table 3, paper 3:
"Physiological distress" should read "Psychological distress".

III

PAPER 3

Submitted to Arthritis Care & Research (Hoboken)

Treatment Satisfaction with and Adherence to Disease-Modifying Antirheumatic Drugs in Adult Patients with Juvenile Idiopathic Arthritis

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Abstract

Objectives: To examine medication satisfaction and adherence and their relationships to disease variables and health-related quality of life (HRQOL) in adults with juvenile idiopathic arthritis (JIA).

Methods: Patients (N=96, mean age 25 years, 67% female) completed questionnaires about their health-status 19 years after disease onset. Patients using biological disease-modifying antirheumatic drugs (bDMARDs) or methotrexate were assessed with the Morisky Medication Adherence Scale (MMAS-8) and the Treatment Satisfaction Questionnaire for Medication (TSQM), including dimensions of effectiveness, side effects, convenience and global satisfaction.

Results: DMARDs were used by 52 patients (54%)(mean age 25 years, 75% female), of which 28 used methotrexate and 37 used bDMARDs. Patients using combination therapy of methotrexate and bDMARDs (n=15) reported higher satisfaction with bDMARDs than methotrexate in the dimensions of side effects and global satisfaction (mean 92.9±15.5 vs 56.2±30.9 and 67.6±19.8 vs 47.1±21.7, $p<0.001$ and $p=0.016$, respectively). Patients using either bDMARDs (n=22) or methotrexate (n=13), reported higher satisfaction with bDMARDs than methotrexate in the dimensions of effectiveness and global satisfaction (mean 78.7±15.4 vs 60.2±19.9 and 73.6±17.7 vs 52.3±23.9, $p=0.004$ and $p=0.005$, respectively). Nearly half (46%) of patients reported low adherence (MMAS-8 score <6) and 25% reported high adherence (score =8). Higher levels of pain, psychological distress, more active joints and current methotrexate use were the strongest correlates of lower medication satisfaction. Perceived medication effectiveness and global satisfaction correlated positively with physical and mental HRQOL.

Conclusion: JIA patients were more satisfied with bDMARDs than methotrexate, and 46% reported low adherence. Higher medication satisfaction was associated with better HRQOL.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory rheumatic disease (1). The disease is not confined to childhood and approximately 40–60% of patients have continuous and recurrent disease activity after entering adulthood (2, 3). Significant advanced and effective treatments for JIA patients have been developed in recent decades and several alternative treatments currently exist (4). Disease-modifying antirheumatic drugs (DMARDs) are a group of medications used in JIA to inhibit the immune cells and mechanisms underlying the symptoms of the disease, and several studies have demonstrated the efficacy of both synthetic DMARDs (sDMARDs) and biological DMARDs (bDMARDs) (5-8). Methotrexate (MTX) is a sDMARD that has been essential in the treatment of JIA since 1980, while bDMARDs were introduced as a treatment option for JIA in 2000. Increased numbers of new DMARDs have made treatment decisions more complex as different DMARDs offer different choices for route of administration, possible side effects and efficacy, which may impact patients' satisfaction with the medication. In this study, satisfaction refers to the specific medication rather than the broader treatment experience and is defined as the patient's evaluation of the process of taking the medication and the outcomes associated with the medication (9). In order to foster success in treatment, patients preferences and experience of available medication need to be incorporated when evaluating the benefits and drawbacks of treatment alternatives. However, such information is scarce, and information regarding patients' satisfaction with different medications is needed.

Patients with JIA are encouraged to follow prescribed treatment regimens over a long period of time and adherence to medication represents a key requirement for successful treatment, as poor adherence can significantly compromise the efficacy of the medication (10). Adherence can be defined as the extent to which a person's behaviour

(in this respect, taking a medication) corresponds with agreed upon recommendations from a health care provider (11). A systematic literature review has estimated that only 66% of adult patients with rheumatic arthritis (RA) were adherent to their DMARD regimen (12). Published data on DMARD treatment adherence in JIA are limited and restricted to children (13). Thus there is a need to provide information regarding adherence to DMARDs among adults with JIA.

The goal of medical treatment for patients with JIA is to achieve remission, reduce symptoms and maximize patients' health-related quality of life (HRQOL). HRQOL is often measured through individuals' subjective appraisals of their physical and psychosocial health, as defined by the World Health Organization (14). Previous studies have found associations between perceived adherence and HRQOL and between subjective burden of medication use and HRQOL in children and adolescents with JIA (15, 16). However, little is known about the association between medication treatment satisfaction and adherence as well as their impact on HRQOL in adults with JIA. In Norway, excellent opportunities exist for studies regarding long-term treatment satisfaction and adherence, as the health-care system is largely tax-funded with equal access to specialist care and treatment for all JIA patients.

In order to address gaps in the research literature, the objective of our study was to examine treatment satisfaction and perceived adherence to MTX and bDMARDs and describe the associations between medication satisfaction, adherence and HRQOL in JIA patients a mean of 19 years after disease onset.

PATIENTS AND METHODS

Study population

The sample was recruited from a cohort of 197 JIA patients (with <18 months disease duration) who participated in a longitudinal study at Oslo University Hospital (OUH) from 1995 to 2003, in which patients were prospectively examined by a paediatric rheumatologist every 6 months for 3 years (17). Disease onset was defined as the day a physician documented symptoms or signs of JIA and all patients met the International League of Associations for Rheumatology criteria for classification of JIA based on physicians´ clinical examinations prospectively documented in the patients´ medical records (1). Invitations to participate in this follow-up study were sent by mail and informed consent was obtained in accordance with the Declaration of Helsinki. The Regional Committees for Medical and Health Research Ethics approved the study (approval number 2015/532).

Measures

Information regarding current and previous use of medication was obtained from patients' medical records and self-report questionnaires. All self-report questionnaires were processed by mail. Demographic information including age, gender and formal education was assessed with a multiple-choice questionnaire. Patients were asked to report number of active joints and joints with limited range of motion on a manikin figure (18). Additionally, the following structured self-report questionnaires were used: *Medication satisfaction* was measured with the 14-item Treatment Satisfaction Questionnaire for Medication (TSQM). The TSQM is a validated psychometric instrument assessing 4 key dimensions of treatment satisfaction with medication: effectiveness (3 items), side effects (5 items), convenience (3 items) and global satisfaction (3 items)

(19). The score on each dimension ranges from 0 to 100 with a higher score representing higher satisfaction. The patients completed the TSQM for each medication, except patients using sulfasalazine. Unfortunately medication satisfaction was not assessed regarding sulfasalazine.

Medication adherence was assessed using the 8-item Morisky Medication Adherence Scale (MMAS-8)(20-22). Scores range from 0 to 8, with higher scores representing higher levels of adherence (8 = high adherence, 6 to <8 = medium adherence, and <6 = low adherence). The validity and reliability of the MMAS-8 have been demonstrated in previous studies (20, 21).

Physical and mental HRQOL were assessed using the 12-item Short-Form Health Survey version 2 (SF-12) (23). The SF-12 covers a broad range of health dimensions in 8 subscales, with higher scores indicating better HRQOL. Physical and mental HRQOL are measured from two subscales: the physical component summary (PCS) and the mental component summary (MCS), respectively. SF-12 scores are standardized to a mean value of 50 and a standard deviation of 10 based on the average score of the US general population (23).

Physical disability was assessed by the Health Assessment Questionnaire Disability Index (HAQ). The HAQ has 8 sections assessing various areas of disability and a mean score ranging from 0 to 3, with a score of 0 indicating no physical disability (24).

Pain intensity was assessed with 10-cm visual analogue scales (VAS pain) (25). Pain severity and pain interference based on the last 24 hours were assessed by the Brief Pain Inventory Short Form (BPI)(26). The pain severity score is the mean of 4 items and pain interference score is the mean of 7 items rated on 1 – 10 numeric rating scales with higher scores indicating more pain (26).

Symptoms of psychological distress were assessed with the Hopkins Symptom Checklist (SCL-5). Scores range from 1 to 4, with higher scores indicating more psychological distress (27).

Statistical analysis

Descriptive statistics were reported in terms of absolute frequencies and percentage for categorical variables and mean, median, range and standard deviation (SD) for continuous variables. Chi-square tests, independent sample t-tests and Wilcoxon-Mann Whitney tests were performed in order to compare independent groups of patients and paired sample t-tests were performed to compare treatment satisfaction in patients using 2 DMARDs. Correlations were expressed by Spearman´s rank correlation (r_s) for non-normally distributed variables. Linear regression analyses were conducted in order to identify correlates of medication satisfaction and HRQOL. Variables from the univariate analyses with $p<0.05$ were included in the multivariate analyses (manual backwards regression method) with correction for age and gender. In the regression analyses (Tables 3, 4 and 5), patients using combination therapy of bDMARDs and MTX answered the TSQM twice and the mean of the two TSQM scores was used as the measure of their medication satisfaction in the analyses. Since DMARDs are not prescribed for daily use, one of the items of MMAS-8 ("Did you take your medication yesterday") was treated as a missing item in patients that did not have any prescribed medication "yesterday" (n=18). For these individuals, the median value of all non-missing values was substituted for the missing item. Statistical analyses were performed using SPSS software Version 22 (IBM Corp. Armonk, NY, USA). A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

Study participants

From a cohort of 197 patients who participated in a study at OUH between 1995 and 2003, 192 were eligible for this study, of which 96 (50%) agreed to participate a mean of 18.9 years after disease onset (Figure 1). No significant differences were found between the 96 participating patients and the 96 non-participants regarding age at disease onset, time with symptoms prior to diagnosis, gender and polyarticular course JIA after 3 years (data not shown).

At 19-year follow-up, 52 patients (54%) used sDMARDs and/or bDMARDs (Table 1). A total of 37 patients (39%) used bDMARDs (20 as monotherapy, 15 in combination with MTX, and 2 in combination with sulfasalazine), a total of 28 (29%) used MTX (12 as monotherapy, 15 in combination with bDMARDs, and 1 in combination with sulfasalazine), and a total of 5 patients (5%) used sulfasalazine (2 as monotherapy, 2 in combination with bDMARDs, and 1 in combination with MTX). Of the 37 patients taking bDMARDs, 29 (78%) used TNF-inhibitors and 6 (16%) used an IL-6 inhibitor. Of the 52 patients currently using DMARDs at the 19-year follow-up, 37 patients (71%) had used MTX and 6 (12%) had used bDMARDs during the first 3 years of follow up.

At 19-year follow-up, no significant differences were found regarding age at disease onset, scores on SF-12, SCL-5 or BPI pain severity between the participants currently using DMARDs and those not using DMARDs, but patients using DMARDs had worse scores on the HAQ and BPI pain interference and a higher percentage had polyarticular course JIA and currently active joints (Table 1).

Treatment satisfaction

Among patients using either MTX or bDMARDs (but not in combination), higher medication satisfaction on the dimensions of effectiveness (mean 78.7±15.4 vs 60.2±19.9, p=0.004) and global satisfaction (73.6±17.7 vs 52.3±23.9, p<0.005) were found in patients using bDMARDs compared to patients using MTX (Table 2). In patients using combination therapy of MTX and bDMARDs, higher medication satisfaction with bDMARDs than MTX was reported with respect to side effects (92.9±15.5 vs 56.2±30.9, p<0.001) and global satisfaction (67.6±19.8 vs 47.1±21.7, p=0.016). Among the 37 patients using bDMARDs, 7 patients (19%) reported side effects, including tiredness (n=3), weakened immune system (n=2), itching (n=2), fungal skin infections (n=1), headache (n=1) and discomfort at the injection site (n=1). A total of 15 (54%) of the 28 patients using MTX reported side effects, including nausea (n=13), headache (n=4), tiredness (n=2), hair loss (n=1), oral ulceration (n=1) and suppressed immune system (n=1). A total of 7 patients reported more than 1 side effect. Two patients using sulfasalazine in combination with bDMARDs reported nausea as a side effect to sulfasalazine. In patients using MTX, lower scores on effectiveness were reported by males (n=6) compared to females (n=22) (mean [SD] 44.4 [22.2] vs 64.0 [17.5], p=0.027).

Associations between demographic and health status variables and treatment satisfaction

In the multiple regression analyses (adjusted for age and gender) of the 50 patients taking bDMARDs and/or MTX (excluding the 2 patients on salazopurine monotherapy), a higher level of pain intensity was the strongest correlate of lower medication satisfaction with respect to effectiveness and side effects (p=0.001 and 0.028, respectively) (Table 3). More psychological distress was the strongest correlate of lower

global satisfaction with medication (p=0.003). Levels of education, physical disability and psychological distress were negatively associated with patients' satisfaction with medication effectiveness in the univariate analyses (p=0.003 – 0.022), but not in the multiple regression analysis. Physical disability and pain intensity were negatively associated with patients' global satisfaction with medication in the univariate, but not the multiple regression analyses (p=0.03 and p=0.009, respectively).

Associations between disease-related variables and treatment satisfaction

In the multiple regression analyses, current use of MTX and number of active joints correlated with less medication satisfaction with respect to effectiveness and global satisfaction (p<0.001 – 0.032) (Table 4). Current use of MTX was associated with less satisfaction with side effects (p=0.038). No associations were found between medication satisfaction assessed by TSQM and polyarticular disease course JIA or disease duration (data not shown).

Associations between medication satisfaction and HRQOL

In the multiple analyses, lower satisfaction with effectiveness of medication was strongly associated with lower physical HRQOL (p<0.001), and lower global satisfaction with medication was associated with lower mental HRQOL (p=0.02) (Table 5). An association was also found between lower global satisfaction with medication and lower physical HRQOL in the univariate analysis, (p=0.012), but not in the multiple analysis.

Medication adherence

The median MMAS-8 score was 6.0 (range 0.5 – 8.0) and 46% of the participants in this study population reported low adherence (score <6.0) to DMARDs, while 15 patients (29%) reported medium adherence (scores 6 – 7.9) and 13 (25%) reported high adherence (score =8). No associations were found between medication adherence and age, gender, disease duration, polyarticular disease course, self-reported number of active joints, or the medication satisfaction dimensions of effectiveness, side effects and global satisfaction (data not shown). However, a correlation was found between medication adherence and the convenience dimension (r_s=0.327, p=0.03). Among the 28 patients using MTX, 13 (46%) reported problems with nausea in connection with taking the medication, however this did not correlate significantly with the MMAS-8 adherence score (data not shown).

DISCUSSION

In our cohort of adults with JIA, 52 patients (54%) were using sDMARDs and/or bDMARDs a mean of 19 years after disease onset. Patients were more satisfied with bDMARDs than MTX as assessed by the TSQM dimensions of effectiveness, side effects and global satisfaction. High levels of physical disability, pain intensity, psychological distress, education and numbers of active joints as well as current use of MTX correlated with poorer medication satisfaction. Forty-six percent reported low adherence to medication, and a correlation was found between adherence to medication and the patient satisfaction convenience score. Among patients using DMARDs, associations were found between satisfaction with medication effectiveness and physical HRQOL, and between global medication satisfaction and both physical and mental HRQOL.

We found that patients in our study reported higher medication satisfaction with bDMARDs compared to MTX. To our knowledge, comparisons of JIA patients' experiences with bDMARDs and MTX have not previously been explored. Our results are in contrast to a study by Wolfe and Michaud on patients with RA, which found greater treatment satisfaction with medication among non-biologic users than biologics (28). However, these results were related to non-medical factors (cost and inconvenience) and the participants were older (median 62.7 years) than those in our study. Younger adults may have other treatment preferences than older adults. In our country, medication costs are covered by public health and therefore have no major impact on the results in this study.

Patients also reported higher scores on global satisfaction with bDMARDs compared with MTX. We found a strong correlation between the effectiveness score and global satisfaction score (r_s 0.8), indicating that effectiveness has a great impact on patient overall satisfaction with a medication.

Patients using DMARD monotherapy , but not those on combination therapy, were more satisfied with the effectiveness of bDMARDS than with MTX. Possible influencing factors for those on monotherapy could be that bDMARDs have a faster onset of action than MTX. Another factor could be that patients with inadequate response to methotrexate are likely to start with bDMARDs in order to achieve adequate treatment response. For patients using combination therapy, evaluating satisfaction with the effect of two medications used simultaneously may be difficult to interpret. Previous studies have emphasized the importance of early initiation of medication in order to achieve the best effect and clinical remission (8, 29). The patients in our study were diagnosed in the pre-biologic era. Although only 6 (12%) of the 52 patients currently using DMARDs received bDMARDs during the first 3 years of follow-up, 37 patients (71%) received

MTX. The approach to medication treatment in JIA is generally based on the severity of disease and symptoms with treatment guidelines (30, 31), indicating that our patients treated with combination therapy of MTX and bDMARDs could possibly have more severe disease than those on monotherapy. However no correlations were found between polyarticular versus oligoarticular course and patients' satisfaction with the effectiveness of bDMARDs and/or MTX.

In our study, patients using combination therapy of MTX and bDMARDs were less satisfied with MTX than with bDMARDs with respect to side effects ($p<0.001$). We found MTX-induced nausea in 46% of the patients. Side effects associated with MTX (including nausea) are well known and have significant implications for patients with JIA and RA (32-34). Patil et al reported higher prevalence of MTX-induced nauseas in adolescents and younger adults than in older patients with RA (34) and in a study among JIA patients treated with MTX, 64% experienced MTX-induced nausea and 27% experienced vomiting (33). With respect to side effects as measured by the TSQM, greater standard deviation was found with MTX compared to bDMARDS, indicating that greater differences in patients' experiences exist for MTX. However, the gastrointestinal effects of MTX including nausea should warrant consideration in clinical practice.

We found no differences between MTX and bDMARDs in the convenience dimension of patient satisfaction. Previous studies of adults with RA have found that patients prefer to receive treatment at home (35, 36). Among the 37 patients using bDMARDs in our cohort, 32 (86%) used self-administered medication at home. Information regarding prevalence of current use of DMARDs in adults with JIA has been scarce, however the number of patients using DMARDs in our study corresponds with other studies in adults with JIA (2, 3) and the spectrum of sDMARDs and bDMARDs used were similar to JIA patients in previous studies (7, 37, 38). The number of patients without medication in

our study is also comparable with the number of patients without medication in other studies (2, 3).

The strongest correlates of low treatment satisfaction in our study were high levels of pain, psychological distress, more active joints and current use of MTX. Since DMARDs are typically taken for their curative effects, it is likely that patients with more pain and more active joints are less satisfied with their medication treatment. Pain has been reported as a significant burden of JIA (39, 40), and in a study by Arkela-Kautiainen et al it was reported to be the most important preference for improvement in young adults with active JIA (41). In our study, an association was found between more psychological distress and lower global satisfaction with medication. Whether poor medication satisfaction leads to psychological distress or psychological distress negatively impacts patients' view of medication satisfaction warrants further study.

In the univariate analysis, an association was found between the level of formal education and patients' satisfaction with their medication's effectiveness, although no correlation was found between age and effectiveness. A possible reason for this could be that patients with higher education have better communication with doctors, which may lead to better management of the patient's disease and side effects. In adults with RA, Kjeken et al found that patients' satisfaction with care was associated with current involvement in medical decisions and that higher level of education was associated with patients' involvement in medical decisions (42).

We found an association between satisfaction with medication effectiveness and HRQOL. Previous studies have reported that DMARDs increase HRQOL in children with JIA. Cespedes-Crux et al found MTX to have a positive impact on HRQOL (43). Similarly, Lovell et al reported improved quality of life in children treated with abatacept (44). We found no association between side effects and HRQOL, which is in contrast to the study

of Mulligan et al who reported that patients who experience side effects with MTX had lower HRQOL (45). However, the lack of correlation between HRQOL and side effects in our study may be linked to low statistical power.

In our study, almost half of the patients reported low adherence. Rates of adherence to medication in patients with JIA and RA have been highly variable across studies (46-48). In a review article on adults with RA, Salt and Frazer reported rates of adherence to DMARDs from 30% to patients taking more than the prescribed amount of medication (47). In a study among children with JIA, Feldman et al found caregiver-reported adherence to medication to be between 86 and 90% (10). The administration frequency of DMARDs with simpler treatment regimens prescribed for weekly or monthly use may facilitate adherence (49). We found a positive association between the medication convenience dimension and adherence, but not with other dimensions of the TSQM. The convenience dimension of TSQM is derived from 3 questions; convenience of administration, ease/difficulty planning and follow schedules. In a systematic review assessing the link between treatment satisfaction and adherence in chronic diseases, greater treatment satisfaction, lower treatment regimen complexity and lower treatment burden were associated with better adherence (50).

This study has some limitations. Clinically relevant differences may be undetected due to a moderate sample size with insufficient statistical power. At 19-year follow-up, no clinical examination was performed and more information on current disease status assessed by physicians may have improved the interpretation of our results. On the other hand, patient and disease characteristics were well documented by repeated clinical examinations during the first 3 years of follow-up.

JIA is a heterogeneous disease and it is not clear under which circumstances one DMARD will yield better outcomes than another. Hence the relative effect of one DMARD

compared to another is difficult to measure, and thus our results must be interpreted with caution. However, patients satisfaction with medical treatment may represent more issues than disease control, highlighting the necessity to incorporate patients' experience with medication treatment in the decision making process. It should also be noted that one item of the MMAS-8 ("Did you take your medication yesterday") was treated as a missing item in patients that did not have any prescribed medication "yesterday" (n=18). However, the substitution of the median value made no changes to the total score of MMAS-8.

In conclusion, JIA patients' medication satisfaction was higher with bDMARDs than MTX 19 years after disease onset. Adherence scores were low in 46% of the patients. Higher medication satisfaction was associated with better HRQOL. Knowledge and incorporation of patients' experience with medication is important in order to promote patient centred care and achieve the best possible HRQOL. However, further studies with larger samples are required.

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Figure 1. Flowchart

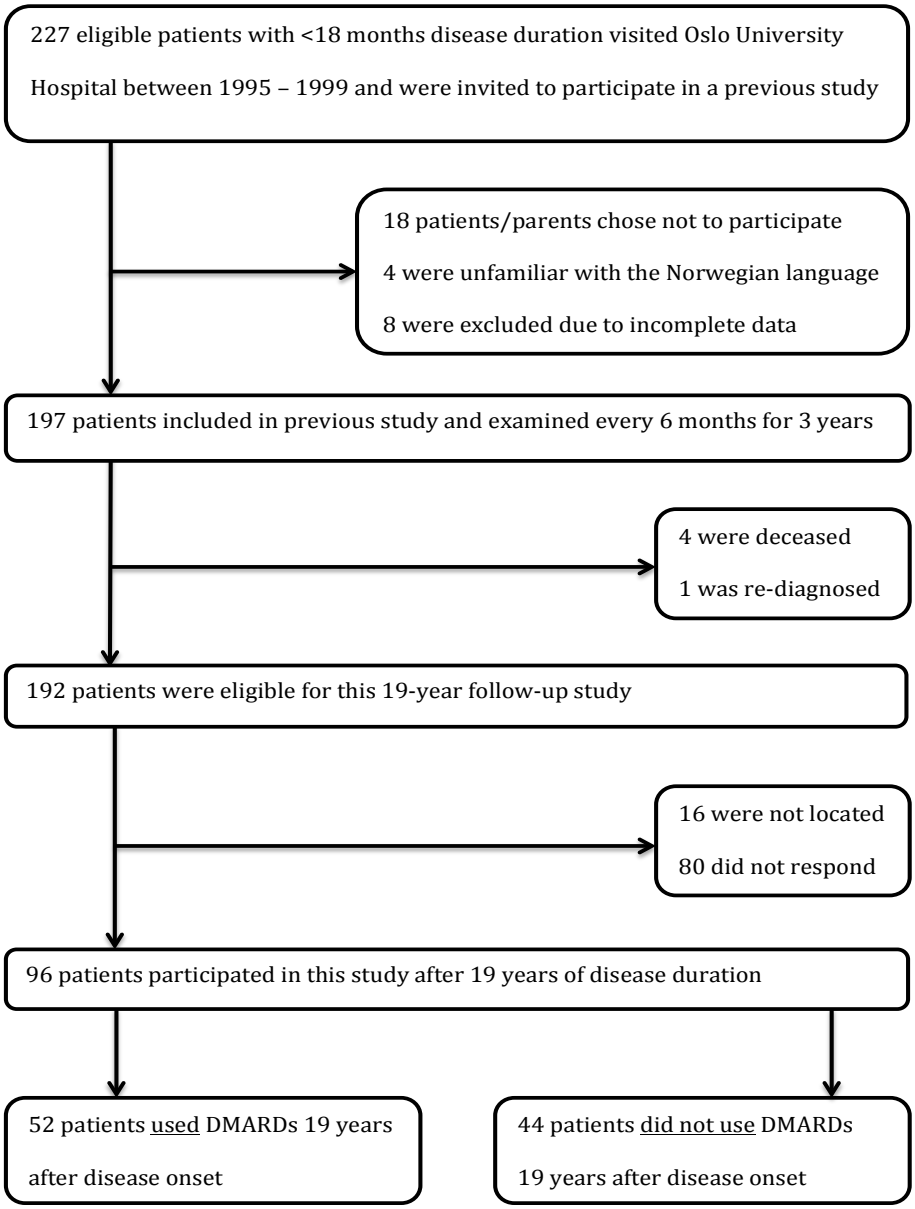

Table 1. Demographic, clinical and health characteristics at 19-year follow-up of 96 JIA patients using or not using DMARDs

Variables[Y]	All patients (N=96)	Patients not using DMARDs (n = 44)	Patients using DMARDs (n = 52)	P
Demographic variables				
Gender, female, n (%)	64 (67)	25 (57)	39 (75)	0.06
Age, years, mean (SD)	25.1 (4.2)	25.1(4.2)	25.1 (4.6)	0.97
College/university level education, n (%)	42 (44)	17 (39)	25 (48)	0.35
Full time study or pain job, n (%)	74 (77)	36 (82)	38 (73)	0.48
Receiving disability/social benefit, n (%)	12 (13)	3 (7)	9 (17)	0.12
Clinical and health-related variables				
Disease duration, years, mean (SD)	18.9 (1.5)	18.9 (1.5)	18.7 (1.6)	0.25
Age at disease onset, years, mean (SD)	6.1 (4.0)	6.1 (4.0)	6.3 (4.4)	0.63
Physical HRQOL (SF-12 PCS), mean (SD)*	49.6 (9.8)	51.2 (8.8)	48.3 (10.5)	0.15
Mental HRQOL (SF-12 MCS), mean (SD)*	48.5 (10.0)	48.3 (10.5)	48.6 (9.6)	0.90
Physical disability (HAQ range 0 – 3)	0 (0 – 2.13)	0 (0 – 1.75)	0.13 (0 – 2.13)	0.003
Pain severity (BPI range 0 – 10)	1.25 (1 – 9)	1.25 (0 – 7)	1.75 (0 – 9)	0.25
Pain interference (BPI range 0 – 10)	0.57 (0 – 8.4)	0.29 (0 – 8.4)	1.14 (0 – 7.43)	0.046
Psychological distress (SCL-5, Likert scale1 – 4)	1.4 (1 – 4)	1.4 (1 – 4)	1.3 (1 – 4)	0.80
Patients with active joints, n (%)	57 (59)	18 (41)	39 (75)	0.001
Polyarticular course JIA, n (%)	41 (43)	12 (27)	29 (56)	0.005
JIA subtypes (ILAR classification), n (%)				
Systemic arthritis	7 (7)	5 (11)	2 (4)	

Polyarticular rheumatoid factor negative	24 (25)	8 (18)	16 (31)
Polyarticular rheumatoid factor positive	1 (1)	0	1 (2)
Oligoarticular persistent	36 (38)	23 (52)	13(25)
Oligoarticular extended	10 (10)	3 (7)	7 (14)
Enthesitis-related arthritis	5 (5)	3 (7)	2 (4)
Psoriatic arthritis	4 (4)	0	4 (8)
Undifferentiated arthritis	9 (9)	2 (5)	7 (14)
Current use of synthetic DMARDs, n (%) [#]	30 (31)		30 (58)
Methotrexate [§]	28 (29)		28 (54)
Sulfazalazine	5 (5)		5 (10)
Current use of biological DMARDs, n (%) [¶]	37 (39)		37 (71)
Etanercept	13 (14)		13
Adalimumab	8 (8)		8
Tocilizumab	6 (6)		6
Other biological DMARDs [Ŧ]	10 (10)		10

JIA = Juvenile idiopathic arthritis; DMARDs = Disease-modifying antirheumatic drugs; [Y] Values are in median (range) if not indicated otherwise; SF-12 = 12 item Short-Form Health Survey version 2; * Norm-based score (SD) = 50(10); PCS = Physical Component Summary; MCS = Mental Component Summary; HAQ = Health Assessment Questionnaire; BPI = Brief Pain Inventory Short Form; SCL-5 = Hopkins Symptom Checklist-5; ILAR = International League of Associations for Rheumatology; [#] 19 patients used a combination of 2 DMARDs; [§] Oral medication (n=15) and injections (n=13); [¶] Intravenous infusion (n=5) and injections (n=32); [Ŧ] Other biological DMARDs = Infliximab (n=3), Certolizumab (n=3), Golimimab (n=2), Anakindra (n=1) and Rituximab (n=1).

Table 2. Medication satisfaction (measured by TSQM) in 50 patients using MTX and/or bDMARDs

Dimensions of medication satisfaction (range 0 – 100)	Medication satisfaction in patients using either MTX or bDMARDs (n = 35)			Medication satisfaction in patients using MTX and bDMARDs in combination (n = 15)		
	MTX (n=13)	bDMARDs (n=22)	P *	MTX (n=15)	bDMARDs n=15)	P #
Effectiveness	60.2 (19.9)	78.7 (15.4)	0.004	59.5 (20.1)	69.6 (15.3)	0.11
Side effects	73.5 (28.6)	88.7 (23.4)	0.10	56.2 (30.9)	92.9 (15.5)	<0.001
Convenience	65.0 (18.5)	67.4 (14.6)	0.66	69.2 (18.8)	71.5 (11.3)	0.67
Global satisfaction	52.3 (23.9)	73.6 (17.7)	0.005	47.1 (21.7)	67.6 (19.8)	0.016

Values are expressed as mean (SD); * Determined by Independent sample t-test; # Determined by Paired sample t-test; TSQM = Treatment Satisfaction Questionnaire for Medication; TSQM was not assessed regarding sulfasalazine (n=5); MTX = methotrexate; bDMARDs = biological Disease-modifying antirheumatic drugs.

Table 3. The relationship between health-status characteristics/education level and medication satisfaction (TSQM) 19 years after disease onset in JIA patients treated with methotrexate and/or biological DMARDs (n=50)*

	Health-status characteristics/education level			
Dimensions of TSQM (range 0–100)	College or university level education	Physical disability (HAQ, range 0–3)	Pain intensity (VAS 0–10)	Physiological distress (SCL-5, range 1–4)
Effectiveness				
Univariate analyses				
B (95% CI)	11.5 (1.8, 21.2)	-13.9 (-22.0, -4.8)	-3.0 (-4.6, -1.4)	-8.5 (-15.7, -1.3)
P	0.02	0.003	<0.001	0.022
Multiple analysis §				
B (95% CI)			-3.3 (-5.1, -1.5)	
P			0.001	
Side effects				
Univariate analyses				
B (95% CI)	4.4 (-9.5, 18.3)	-0.5 (-13.9, 12.9)	-2.5 (-4.8, -0.1)	-4.2 (-14.5, 6.1)
P	0.53	0.94	0.041	0.42
Multiple analysis ¶				
B (95% CI)			-3.0 (-5.6, 0.3)	
P			0.028	
Global satisfaction				
Univariate analyses				
B (95% CI)	3.8 (-8.1, 15.7)	-12.1 (-23.1 -1.2)	-2.7 (-4.6, -0.7)	-13.0 (-21.0, -5.0)
P	0.52	0.03	0.009	0.002
Multiple analysis ₸				
B (95% CI)				-13.2 (-21.5, -4.9)
P				0.003

* Results from the linear regression analyses with the Treatment Satisfaction Questionnaire for Medication (TSQM) dimensions effectiveness, side effects and global satisfaction as the dependent variables and adjusted for age and gender in the multiple analyses (backward regression model). The convenience dimension was not included since no significant correlations were found. TSQM was not assessed regarding sulfasalazine (n= 5); § R^2 = 24%; ¶ R^2 = 10%; ₸R^2 = 19%; B = unstandardized regression coefficients;; JIA = juvenile idiopathic arhtirits; DMARDs = disease-modifying antirheumatic drugs; HAQ = Health Assessment Questionnaire

Disability Index, VAS = Visual analogue scale; SCL-5 = Hopkins Symptom Checklist-5.

Table 4. The relationship between disease-related variables and medication satisfaction (TSQM) 19 years after disease onset in JIA patients treated with methotrexate and/or biological DMARDs (n=50)*

	Disease-related variables		
Dimensions of TSQM (range 0-100)	Number of active joints	Current use of 2 DMARDs	Current use of methotrexate
Effectiveness			
Univariate analyses			
B (95% CI)	-0.7 (-1.5, 0.1)	-5.4 (-16.6, 5.8)	-16.1(-25.3, -6.9)
P	0.08	0.34	0.001
Multiple analysis §			
B (95% CI)	-0.8 (-1.6, -1.1)		-17.0 (-26.0, -8.0)
P	0.032		<0.001
Side effects			
Univariate analyses			
B (95% CI)	-0.3 (-1.4, 0.8)	-8.5 (-23.8, 6.8)	-14.6 (-28.0, -1.2)
P	0.60	0.27	0.033
Multiple analysis ¶			
B (95% CI)			-14.7 (-28.5, -0.8)
P			0.038
Global satisfaction			
Univariate analyses			
B (95% CI)	-1.0 (-1.9, -0.1)	-4.4 (-17.5, 18.8)	-18.6 (-29.3, -7.7)
P	0.036	0.50	0.001
Multiple analysis ₸			
B (95% CI)	-1.1(-1.9, -0.2)		-19.2(-29.9, -8.7)
P	0.015		0.001

* Results from the linear regression analyses with the Treatment Satisfaction Questionnaire for Medication (TSQM) dimensions effectiveness, side effects and global satisfaction as the dependent variable and adjusted for age and gender in the multiple analyses (backward regression model); B = unstandardized regression coefficients; The convenience item was not included since no significant correlations were found; JIA = juvenile idiopathic arthritis; DMARDs = disease-modifying antirheumatic drugs. § R^2 = 31%; ¶ R^2 = 9%; ₸ R^2 = 31%.

Table 5. The relationship between medication satisfaction (TSQM) and HRQOL measured by SF-12 in 50 JIA patients treated with methotrexate and/or biological DMARDs *

	Dimensions of medication satisfaction			
	Effectiveness (range 0–100)	Side effects (range 0–100)	Convenience (range 0–100)	Global satisfaction (range 0–100)
Physical HRQOL (SF-12, PCS)				
Univariate analyses				
β (95% CI)	0.5 (0.2,0.5)	0.1 (-0.1, 0.2)	-0.1 (-0.2, 0.1)	0.4 (0, 0.3)
P	<0.001	0.32	0.53	0.012
Multiple analysis) §				
β (95% CI)	0.5 (0.1, 0.4)			
P	<0.001			
Mental HRQOL				
(SF-12, MCS)				
Univariate analyses				
β (95% CI)	0.3 (0, 0.3)	0.2 (0, 0.2)	0 (-0.2, 0.2)	0.3 (0, 0.3)
P	0.07	0.24	0.99	0.02
Multiple analysis ¶				
β (95% CI)				0.1 (0, 0.3)
P				0.02

* Results from the linear regression analyses with HRQOL as the dependent variable and the Treatment Satisfaction Questionnaire for Medication (TSQM) dimensions effectiveness, side effects, convenience and global satisfaction as independent variables, adjusted for age and gender in the multiple analyses (backward regression model); § R^2 = 37%; ¶ R^2 = 15%; β = standardized regression coefficients; JIA = juvenile idiopathic arthritis; DMARDs = Disease-modifying antirheumatic drugs; HRQOL = Health–related quality of life; SF-12 = 12-item Short Form Health Survey version 2 [norm-based score (SD) = 50 (10)]; PCS = Physical Component Summary; MCS = Mental Component Summary.