Physical activity and physical fitness in juvenile idiopathic arthritis

Kristine Risum

Doctoral thesis

Section for Orthopaedic Rehabilitation and Section of Rheumatology, Rikshospitalet, Oslo University Hospital

Department for Interdisciplinary Health Sciences, Institute of Health and Society, Faculty of Medicine, University of Oslo

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Table of contents

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Summary

Background: The management of juvenile idiopathic arthritis (JIA) has changed tremendously with the introduction of biologic therapy and use of modern treatment strategies, subsequently resulting in better outcomes regarding disease activity and physical function. Following these improvements, along with emerging evidence that exercise is safe in JIA, physiotherapy has moved from passive to active treatment modalities and patients have been encouraged to participate in physical activity (PA) like their healthy peers. Previous research has found poor PA levels and physical fitness in patients with JIA. Yet, knowledge is sparse on PA behavior and physical fitness in patients with JIA who have both been diagnosed after the introduction of biologic therapy and also received multidisciplinary management including the mentioned advancements.

Aim: The purpose of this study was to compare PA behavior and physical fitness in patients with JIA who were diagnosed in the era of biologics with controls from the general population, and to examine if disease variables were associated with PA behavior and physical fitness. Further, to investigate the measurement properties of a submaximal treadmill test for use in both clinical practice and research settings.

Methods: We used a comparative cross-sectional design, including a test-retest design to evaluate the reliability of the submaximal treadmill test. In 2015, we consecutively invited patients aged 10-16 years who had a routine follow-up at Oslo University Hospital to participate. Patients diagnosed with persistent oligoarticular JIA and polyarticular disease (extended oligoarticular JIA and polyarticular rheumatoid factor +/-) were included. Altogether, 60 patients (50 girls) were included (30 persistent oligoarticular JIA/30 polyarticular disease). Controls were randomly drawn from the National Registry matched for age and sex, and included in 2015-2016. PA behavior was examined by both objective and subjective measurements. Components of physical fitness, including cardiorespiratory fitness (CRF), muscle strength and endurance, body composition and bone mineral density (BMD), were assessed with state-of-the-art methods. Additionally, all participants performed a submaximal treadmill test for the evaluation of criterion validity. The reliability sample comprised 37 patients who performed the submaximal treadmill test on a second test day.

Results: The overall PA levels, levels of light and moderate PA, sedentary time and proportions achieving recommended PA levels were comparable between patients and controls. Patients had lower levels of vigorous PA. Patients participated in similar types and

amounts of both organized and unorganized PA as controls. Nearly all participants reported that they always participated in physical education, but 27 % of patients reported that they occasionally needed modifications of some activities to be able to participate. Both patients and controls reported enjoyment as the most important PA facilitator. Patients and controls had comparable CRF and body composition, while patients had lower muscle strength and endurance and total body BMD compared to controls. We found that the use of biologic medication was a correlate for higher overall PA levels and lower sedentary time. No other disease variables were identified as correlates for PA or any components of physical fitness. Other identified correlates for PA and physical fitness in patients were similar to those already established in healthy children and adolescents. Higher vigorous PA was a correlate for higher CRF and muscle strength in patients. PA levels and physical fitness were comparable between patients with persistent oligoarticular JIA and patients with polyarticular disease. The submaximal treadmill test was found to have acceptable criterion validity on group level, but not on individual level in patients. In controls, criterion validity was neither acceptable on group level nor on individual level. The reliability was acceptable in patients, but with large measurements errors.

Conclusions: The results from this study were encouraging regarding PA behavior and physical fitness in patients with JIA. The lower muscle strength, total body BMD and time spent in vigorous PA in patients compared to controls, along with the finding of higher vigorous PA as a correlate for higher CRF and muscle strength, suggest that patients should perform vigorous PA and bone- and muscle-strengthening activities at least three times per week according to national and international PA recommendations, preferably through enjoyable activities. The submaximal treadmill test was valid and reliable for research purposes on group level in patients, but not optimal for estimation of VO_{2peak} in individual patients.

Abbreviations

6MWT	Six-Minute Walk Test
ANA	Antinuclear Antibodies
BMC	Bone Mineral Content
BMD	Bone Mineral Density
BMI	Body Mass Index
CI	Confidence interval
CHAQ	Childhood Health Assessment Questionnaire
COSMIN	Consensus-based Standards for selection of Health Measurement INstruments
CPM	Counts per Minute
CRF	Cardiorespiratory Fitness
CRP	C-Reactive Protein
CVs	Coefficients of Variation
CVD	Cardiovascular Disease
DMARD	Disease Modifying Anti-Rheumatic Drug
DXA	Dual-energy X-ray Absorptiometry
ERA	Enthesitis-related Arthritis
ESR	Erythrocyte Sedimentation Rate
HLA	Human Leukocyte Antigen
HR	Heart Rate
HR_{peak}	Peak Heart Rate
ICC	Intraclass Correlation Coefficient
IL	Interleukin
ILAR	International League Against Rheumatism
JADAS	Juvenile Arthritis Disease Activity Scale
JIA	Juvenile Idiopathic Arthritis
LoA	Limits of Agreement
LPA	Light Physical Activity
MPA	Moderate Physical Activity
MVPA	Moderate to Vigorous Physical Activity
NRS	Numeric Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs

OUS	Oslo University Hospital
PA	Physical Activity
PE	Physical Education
PGA	Physician's Global Assessment of Disease Activity
RA	Rheumatoid Arthritis
RCT	Randomized Controlled Trial
RER	Respiratory Exchange Ratio
RF	Rheumatoid Factor
SD	Standard Deviation
SDC	Smallest Detectable Change
SEM	Standard Error of Measurement
SPSS	Statistical Package for the Social Sciences
TNF	Tumor Necrosis Factor
VAS	Visual Analogue Scale
VE	Minute Ventilation
VE/VCO_2	Ventilatory Efficiency for Carbon Dioxide Output
VO_{2peak}	Peak Oxygen Uptake
VPA	Vigorous Physical Activity
WHO	World Health Organization

List of papers

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1 Background

1.1 Introduction

Juvenile idiopathic arthritis (JIA) is the most common pediatric rheumatic disease. The disease is heterogeneous and the disease activity can vary from one episode with arthritis in one joint to arthritis in several joints acquiring treatment into adulthood (1). The introduction of biologic therapies in 1999, used in JIA in Norway from the year 2000, has been a major advancement in the management of JIA. During the first few years following the introduction of biologic therapies, we observed numerous improvements in patients during clinical examinations at Oslo University Hospital (OUS). This included better performance on functional field tests, less severe joint contractures and muscle deficits, fewer patients underwent orthopedic surgery and fewer patients presented with Cushing syndrome (altered body composition due to glucocorticoid treatment). Furthermore, the need for mobility and daily living aids was less frequent and more patients told us that they participated in varies modes of physical activities. Based on this clinical experience and research documenting that exercise was safe in patients with JIA (2), and also safe in patients with rheumatoid arthritis (RA) (3), our hospital changed our physical activity (PA) recommendations in JIA dramatically in 2003.

Until 2003, our recommendations included many restrictions on PA because of fear of disease exacerbation. Sports, particularly contact sports, and activities that were of vigorous intensity, should be avoided. In fact, our leaflet on PA for patients with JIA included a list of activities that we did not recommend; like soccer, handball, ice skating and alpine skiing, which are popular activities that most Norwegian children will try sometime during childhood. Activities that we did recommend were of low intensity; like playing with finger puppets and modeling clay, bicycling with easy resistance using low gears, swimming and cross-country skiing in flat terrain. Then, from mid 2003, patients with JIA were encouraged to participate in activities like their peers, emphasizing on enjoyment, with no general restrictions regarding PA. Simultaneously to our change in PA recommendations, we gradually stopped using exercise programs routinely, mainly because of poor adherence and our clinical observations of improved joint status and physical function.

In a master thesis (by the PhD candidate) from 2009 on climate therapy in Norwegian patients with JIA, patients had similar self-reported PA levels compared to reference values in healthy

Norwegian children; also, patients with JIA demonstrated good walking capacity compared to reference values from other countries and also Dutch patients with JIA (4). However, international studies reported poor physical fitness, particularly focusing on cardiorespiratory fitness (CRF) (5-8) and low PA levels in patients with JIA compared to controls (8, 9). Also, research in adult patients with rheumatic inflammatory joint diseases demonstrated a higher cardiovascular disease (CVD) risk (10-13), subsequently leading to research in JIA indicating increased subclinical CVD risk (14-17). This suggested a need for increased focus on CRF in our daily clinical practice. However, knowledge was sparse, both nationally and internationally, on physical fitness and PA behaviors in patients with JIA who were diagnosed after the introduction of biologic therapies, the so-called era of biologics. We therefore decided to carry out a comparative cross-sectional study to comprehensively examine physical fitness and PA behaviors with state-of-the-art methods in patients exclusively diagnosed in the era of biologics and compare results with controls from the general population. Hopefully, the results of the study will help provide a more tailored, detailed and ultimately, improved management of patients with JIA.

1.2 Juvenile idiopathic arthritis

1.2.1 Epidemiology

JIA is the most common rheumatic disease in children and adolescents with a prevalence of approximately 1 in 1000 internationally; in high-income countries of 16-150 per 100 000 in individuals <16 years (18, 19). In the Nordic countries, the incidence rate is about 15-22/100.000 children (20, 21). There is a female predominance which varies according to category (see section 1.2.3) (19, 22, 23). The average age at disease onset varies between 5-9 years, with a peak incidence in preschool-aged children and late childhood (24-27).

1.2.2 Clinical manifestations and diagnosis

JIA is characterized by arthritis of unknown cause in one or more joints that persists for more than 6 weeks and with onset before 16 years of age. Arthritis leads to swelling and often pain and stiffness of the affected joints. Uveitis is the most common extra-articular manifestation, and was reported in approximately 13 % of patients with JIA in a recent meta-analysis and a review (28, 29). Other extra-articular manifestations include enthesitis (inflammation at tendon-to-bone insertion sites) psoriasis, and systemic features like high spiking fever, transient episodic erythematous rash, serositis, lymphadenopathy and hepatosplenomegaly

(1). Subsequently, these impairments may contribute to limited physical functioning in daily life and limited participation in leisure activities and sports (30-32). If the arthritis is untreated, damage to the joint can develop, including structural cartilage and bone deformation. Uveitis can lead to permanent vision loss if untreated (1).

A JIA diagnosis is based on history, clinical examination and blood tests, and is often supplemented by imaging. Arthritis can be detected by clinical examination; nowadays imaging modalities, like ultrasound or less commonly magnetic resonance imaging, are also used (1, 33, 34). There is no specific diagnostic laboratory test, but many patients have elevated inflammation parameters (erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)). Also, the presence of antinuclear antibody (ANA), rheumatoid factor (RF) and human leukocyte antigen (HLA)-B27 can aid in diagnosis (1).

1.2.3 Classification

In order to include homogeneous groups in clinical studies, classification criteria are made. The current classification criteria of JIA were developed by the International League of Associations for Rheumatology (ILAR), comprising seven categories according to number of joints affected with arthritis, extra-articular manifestations and presence of ANA, RF and HLA-B27 (35) (Table 1). Each category differs with respect to clinical presentation and anticipated disease course (35). The JIA classification categories are primarily intended for research use and are not intended for use as diagnostic criteria (36). However, JIA category may have implications for treatment choices and access to treatment cost coverage (37).

There are some limitations of the current JIA criteria, i.e. heterogeneity within categories, possible change in category over time, the categories do not align with pathophysiologic processes and differences between pediatric and adult categorizations (25, 38, 39). Thus, there is an ongoing international work led by the Pediatric Rheumatology International Trials Organization to revise the classification criteria for JIA by using an evidence-based approach. A main aim is to identify homogeneous clinical groups using clinical and routine laboratory measures available worldwide and to harmonize categories with those seen in adult onset arthritis (40). These new criteria proposals have already been debated (37, 41). The revision of the classification criteria is still an ongoing work in progress with participation from OUS.

Table 1. The ILAR criteria for the classification of JIA

Systemic arthritis	Arthritis and quotidian fever for at least 2 week, accompanied by one or more of the following: (nonfixed) evanescent erythematous rash, generalized lymph node enlargement, serositis and hepatomegaly and/or splenomegaly. *Exclusions:* a, b, c, d.
Oligoarthritis	Arthritis affecting 1-4 joints during the first 6 months of disease. Two subcategories: Persistent oligoarthritis; affecting 1-4 joints throughout the disease course Extended oligoarthritis; Affecting 1-4 joints after the first 6 months of disease *Exclusions:* a-e.
RF-negative polyarthritis	Arthritis affecting 5 or more joints during the first 6 months of disease and negative test for RF. *Exclusions:* a-e.
RF-positive polyarthritis	Arthritis affecting 5 or more joints during the first 6 months of disease and 2 or more tests positive for RF at least 3 months apart during the first 6 months of disease. *Exclusions:* a, b, c, e.
Psoriasis arthritis	Arthritis and psoriasis, or arthritis and at least 2 of the following: dactylitis, psoriasis in a first-degree relative and nail pitting or onycholysis. *Exclusions:* b, c, d, e.
Enthesitis related arthritis	Arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following: the presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain, presence of HLA-B27 antigen, onset of arthritis in a male > 6 years of age, acute anterior uveitis, and history of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative. *Exclusions:* a, d, e.
Undifferentiated arthritis	Arthritis that fulfills criteria in no category or in 2 or more of the above categories.

Exclusions: a) Presence of psoriasis or psoriasis in a first degree-relative; b) HLA-B27 positive male >6 years old; c) Presence of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in patient or first-degree relative; d) RF-positivity on at least 2 occasions at least 3 months apart; e) Presence of systemic arthritis.
ILAR International League of Associations for Rheumatology; *JIA* juvenile idiopathic arthritis.

1.2.4 Etiology and pathogenesis

The etiology and pathogenesis of JIA is still poorly understood. It is hypothesized that a genetically susceptible individual could develop an uncontrolled and harmful immune response towards a self-antigen after exposure to an unknown environmental trigger (42).

The swelling of the joints is caused by hypertrophy of the synovial lining of the joint and increased amount of synovial fluid. The synovia that surrounds a tendon might also be inflamed (43). Synovial inflammation in JIA is characterized by infiltration of T-cells, B-cells, macrophages, plasma cells and dendritic cells (44). Inflammation in JIA is also associated with increased levels of inflammatory cytokines, including tumor necrosis factor (TNF) alpha, interleukin (IL)-1 and IL-6, which in turn may result in high level of CRP (45). RF antibody is present in the small JIA category of RF positive polyarthritis. ANA is associated with increased risk of uveitis (42).

1.2.5 Medical treatment

With modern treatment strategies, the aim of medical treatment is to reduce disease activity and optimally achieve remission and prevent damage (46, 47). In combination with

multidisciplinary management, this may subsequently enable children and adolescents with JIA to participate more in common activities in daily life. In the new millennium, biological medication was introduced (48). Biologics (also called biologic disease-modifying anti-rheumatic drugs (DMARDs) are used in moderately or more severely affected patients experiencing treatment failure on conventional DMARDs, also called synthetic DMARDs (22, 49). The terms “synthetic” or “biologic” refer mainly to how the drugs are produced; biologic DMARDs are created by biologic processes rather than chemical synthesis. Methotrexate is the most used synthetic DMARD in the management of JIA (46, 49). Biologic DMARDs are designed to selectively block the effects of cytokines implicated in JIA, including TNF alpha, IL-1 and IL-6 as well as signaling molecules involved in the regulation of B-cells and T-cells lymphocyte responses. Biologic DMARDs are recommended to use in combination with synthetic DMARDs (49, 50). In addition to DMARDs, non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular glucocorticoid injections and occasionally systemic glucocorticoids may also be used to manage pain and inflammation (46, 49). Recent studies have found that biologic DMARDs are increasingly prescribed, earlier in the disease course and in patients with lower disease activity (51, 52). We do not have data of the biologic DMARDs prescription rate at our hospital, but our publicly funded health care system allows for at least as early and aggressive introduction as suggested by international treatment guidelines (49, 50).

Recent guidelines for the management of uveitis in JIA have highlighted the importance of early introduction of systemic immunosuppressive therapies in order to reduce the use of topical and systemic glucocorticoids in cases of persisting uveitis activity. Methotrexate is the first choice of systemic immunosuppressive therapy. Adding or switching to biologic DMARDs is recommended in case of methotrexate inefficacy or intolerance (53).

1.2.6 Multidisciplinary management

Multidisciplinary management of JIA may include contributions from several health care professionals, like nurses, physiotherapists, occupational therapists and psychologists. For the purpose of the present thesis, only physiotherapy will be elaborated in section 1.7.

1.2.7 Prognosis and outcome

To study prognosis and outcome in JIA, different measures are used. To account for the heterogeneous nature of JIA when measuring disease activity, a composite disease activity

score integrating several different domains of disease activity has been developed; the Juvenile Arthritis Disease Activity Score (JADAS) (54), described more in detail in section 3.3.2.5. The JADAS, providing a single numeric value, has been increasingly used in prognostic and outcome studies. Definitions of inactive disease are published (55, 56), and are further described in section 3.3.2.5. Further, criteria for clinical remission off medication (12 months of clinically inactive disease off medication) and clinical remission on mediation (6 months with clinically inactive disease on medication) are also proposed (56, 57). The Juvenile Arthritis Damage Index measures permanent articular and extra-articular damage in JIA (58).To measure physical function, also referred to as physical disability, the Childhood Health Assessment Questionnaire (CHAQ) is the most widely used questionnaire (59) (described in section 3.3.2.6).

In the mid 1980s, with the introduction of methotrexate, and also evolving use of intra-articular corticosteroid injections, improvements regarding disease activity and physical function were reported. The outcomes have improved further in the era of biologics; recent studies have reported lower disease activity, better physical function, higher frequencies of inactive disease and lower frequencies of articular and extra-articular damage (24, 60-62).

A recent review on predictors for disease outcomes identified disease category, particularly persistent oligoarticular JIA, as the strongest predictor of remission (63). Others have reported that arthritis in the wrist, ankle and hip are associated with poorer outcomes (64-66). In addition to clinical predictors, biological markers are suggested to provide valuable data in predicting disease outcomes in future studies (63).

Two recent studies, a review and a systematic review, found that persistent oligoarticular JIA was most likely to achieve remission, while polyarticular RF positive JIA was least likely to achieve remission, followed by enthesitis-related arthritis (ERA) (67, 68). Both studies reported difficulties with comparing remission rates across studies due to the heterogeneity of the studies. Altogether, less than 50 % of patients with JIA achieved remission within the first 10 years following diagnosis, including JIA cohorts where biologic DMARDs were widely available. However, biologic DMARDs were initiated later in the disease course in most studies, indicating that the so-called window of opportunity to achieve favorable outcomes was passed (67). The importance of early aggressive treatment was underlined in a recent study (69).

Some studies using register data that only included patients diagnosed in the era of biologics have reported favorable results. Inactive disease was found in 50-75 % of all patients (n=43-1104) assessed 1-8 years after diagnosis (26, 27, 70, 71). Importantly, recent evidence indicates that long-term medical treatment may be expected also in the era of biologics, as 27 % of patients had active disease into adulthood and half of patients were on medication (72).

In several of these recent studies, physical function was measured by CHAQ. The mean or median scores of CHAQ were close to 0, indicating normal physical function (51, 70, 71, 73). The CHAQ was developed before the availability of biologic DMARDs and modern treatment strategies, and thus may lack domains that are appropriate and relevant for patients today. Ceiling effects of the CHAQ have been described for a long time (74). Taken together, this suggests that more complex measures of physical function, like PA and physical fitness, should be examined as outcome measures in patients with JIA who are diagnosed in the era of biologics.

1.3. Physical activity

PA has been defined in various ways. A commonly used definition is any bodily movement produced by skeletal muscles that requires energy expenditure above resting levels (75, 76). In children, PA may include playing indoors and outdoors, household activities, active transportation, physical education (PE), sports and exercise (77). Further, PA is often divided into different categories according to the intensity of the activity; light, moderate and vigorous (75, 77). Exercise is defined as a subset of PA that is planned, with a specific aim to improved one or more components of physical fitness through structured and repeated PA over a prolonged time period (78). Sedentary behavior is defined as "any waking behavior characterized by an energy expenditure ≤ 1.5 metabolic equivalents while in a sitting, reclining or lying posture" (79).

The Norwegian Directorate of Health and the World Health Organization (WHO) provide similar PA recommendations for children aiming to gain optimal health benefits (77, 80). These PA recommendations state that children and youth should accumulate at least 60 minutes of moderate-to-vigorous PA (MVPA) daily, and most of the daily PA should be aerobic. Also, vigorous PA (VPA), and muscle- and bone-strengthening activities should each be incorporated at least three days per week. They further state that amounts of MVPA greater

than 60 minutes provide additional health benefits (77, 80). The Norwegian PA recommendations for children also advise that sedentary behavior should be reduced (77).

For school-aged children, participation in PE classes constitutes a part of their overall PA levels, even if the amount of PE classes decreases from primary school to secondary school. In Norway, the main purpose of PE is to inspire a physically active lifestyle and a lifelong joy of movement. PE teachers should adapt the physical activities to enable all students to participate in classes (81). The importance of PE participation is underlined by the Norwegian Regulations for the Educational Act, stating that PE participation is compulsory to all students. Only when activity adaptations are not possible and the student has a physician's statement documenting that PE participation is harmful to the student, PE exemption may be approved by the headmaster (82).

PA is a complex behavior to measure. There is no gold standard method available for measuring PA in children. No single tool is perfect to measure all aspects of PA; all methods have advantages and disadvantages (83). To get an impression of the broad picture of PA behavior in children and adolescents, it may be appropriate to apply both objective (e.g. accelerometers or pedometers) and subjective methods (e.g. diaries and questionnaires) (76). Objective methods are often preferred in children because they reduce the risk of recall bias and social-desirability bias (84).

1.3 Physical fitness

Physical fitness has been defined in several ways, and the most overarching definition is "the ability to carry out daily tasks with vigor and alertness, without undue fatigue, and with ample energy to enjoy leisure-time pursuits and to meet unforeseen emergencies" (p. 128) (75). Further, physical fitness is defined as a set of attributes that people have or achieve and is composed of various elements that can be grouped into health-related physical fitness and skill-related physical fitness. Skill-related physical fitness includes balance, coordination, speed, power, agility and reaction time. Health-related physical fitness includes the following components; CRF, muscle strength and endurance, body composition and flexibility (75, 78, 85).

In the following, a brief description of the components of health-related physical fitness we assessed for the purpose of this thesis will be given.

1.3.1 Cardiorespiratory fitness

CRF is the ability of the circulatory and respiratory systems to supply oxygen during sustained PA, and to eliminate fatigue products after supplying fuel (75, 78). The most commonly used indicator of CRF is the highest oxygen consumption attained during a graded maximal exercise test on treadmill or bicycle to voluntary exhaustion (78, 85). Sometimes, the expression maximal oxygen consumption is used, referring to the plateauing of oxygen consumption despite an increase in work rate (86). However, many children do not achieve a plateau in oxygen uptake during maximal exercise testing, thus the term peak oxygen uptake (VO_{2peak}) is used in children (87-89). Measuring VO_{2peak} directly during a maximal exercise test is considered the gold standard method to assess CRF. VO_{2peak} may also be estimated using maximal or submaximal tests. CRF is often also assessed through the performance of a maximal or submaximal test by measuring the distance covered in a certain period of time or the time needed to cover a certain distance (78, 85). Different terms have been used to describe the performance of such submaximal tests, e.g., functional capacity and functional walking capacity (18, 90).

In children, sex, age, pubertal status and PA levels may influence CRF. Also, genetic factors are reported to determine more than 50 % of the CRF level in children (91).

CRF is one of the most important correlates for lifestyle diseases and general health, and high CRF has been shown to decrease CVD risk and mortality in the general adult population (92-94). Also, in healthy children, low CRF is an important cardiovascular risk factor (95).

1.3.2 Muscle strength and endurance

Muscle strength relates to the amount of external force that a muscle can exert. Muscle endurance relates to the ability of a muscle to exert external force for many repetitions or successive exertions (75, 78, 85). During an isometric muscle contraction the force increases, while the length of the muscle is constant. A dynamic muscle contraction increases the force, while the length of the muscle is either shortened or lengthened, often called concentric and eccentric muscle contractions, respectively. During daily life, PA involves all type of muscle contractions. Further, if a dynamic muscle contraction involves a fixed amount of resistance (requires specialized equipment), it is called an isokinetic muscle contraction (78, 96). In children, activities that improve muscle strength and endurance are often a part of their overall PA during play and sports. Structured strength training using body weight or weights may be appropriate if performed during professional supervision (97, 98). Both children and

adolescents gain strength following strength training programs, even if the strength gains in adolescents are greater. The benefits from strength training in children are due to neural adaptations rather than muscle hypertrophy, while increased muscle strength in adolescents is due the combined effects of neural adaptations and hypertrophy (99-101). Both boys and girls benefits from strength training, even if the evidence is stronger in boys, as substantial more studies are performed in boys compared to girls (102, 103). A variety of methods are used for the measurement of muscle strength and endurance in children, like observation of functional skills, manual muscle testing, handheld dynamometry and isokinetic dynamometry (96). A meta-analysis showed that genetic factors explained 61-63 % of the variance in vertical jumps (involving strength in lower extremities) and hand strength (104).

1.3.3 Body composition and bone mineral density

Body composition is the relative amounts of muscle, fat, bone and other vital parts of the body (75, 78). The terms bone mass, fat mass and lean mass are often used when measuring body composition. Excess fat mass is associated with increased risk for developing CVD in children and adolescence (78, 105). Childhood obesity is increasing worldwide (106), while the proportion of obese Norwegian children has stabilized in recent years (107). Appropriate development of lean mass during childhood is important for physical functioning and bone health, and PA is regarded essential for developing a healthy body composition (105). The measurement of body composition may include simple, cheap and easy to use methods. Body mass index (BMI) and waist circumference are often used to provide an indirect measure of body composition. More advanced and expensive methods, like air-displacement plethysmography and dual-energy x-ray absorptiometry (DXA) are needed to provide detailed and accurate information on body composition (78, 108).

Even if bone mineral density (BMD) is not specifically mentioned as a component of physical fitness, BMD is related to body composition. BMD and bone mineral content (BMC) are two different measurements of bone mass. BMC is a measurement of bone mineral in a specific area and is measured in gram (g). BMD is the amount of bone mineral in bone mass and is derived by dividing the BMC (g) by the area (cm^2), thus expressed as g/cm^2 (109). Such measurements of bone mass are of particular relevance in pediatric populations. To ensure bone strength (i.e., BMC and BMD) and bone growth, it is essential to perform bone-strengthening activities that produce a force on the bones. This force is commonly produced by impact with the ground and from muscle contractions (85, 110). Performing bone-

strengthening activities (e.g., running, jumping rope and different ball sports) is particularly important during childhood and adolescence because the greatest gains in bone mass occur during the years just before and during puberty. Additionally, the majority of peak bone mass is obtained by the end of adolescence. Furthermore, proper bone mass development in childhood is important for prevention of possible osteoporosis and fractures later in life (105, 111). Specific strength training also favorably influences bone growth and strength during childhood and adolescence (98, 112, 113). Thus, both muscle-strengthening and aerobic activities may be bone-strengthening activities as well. In children, BMC and BMD are usually measured by DXA (114).

1.4 Measurement properties

Measuring is essential in research and clinical practice. The quality of the measurements, both questionnaires and physical tests, is important (115). When assessing physical fitness, there are some tests that are considered gold standard tests or state-of the-art tests. Such a test is also referred to as criterion test. Such test may not necessarily be perfect, but is considered best to assess the outcome of interest. If other tests are used, often more feasible that than the gold standard tests, the precision of the tests is less accurate and it is important to have specific knowledge of the measurement properties to determine the quality of the tests (78). In this thesis, the measurement properties proposed by the Consensus-based Standards for selection of Health Measurement Instruments (COSMIN) panel are used. These include reliability, validity, responsiveness and interpretability (115). Only the measurement properties relevant for the purpose of this thesis will be briefly described. Reliability is defined as “the degree to which a measure is free from measurement error” (p. 743) (116). Further, test-retest reliability refers to the degree to which the measurements are consistent over time. Intra-rater reliability refers to the agreement of repeated measurements in the same rater while inter-rater reliability refers to the agreement of repeated measurements between different raters (115). Validity is defined as “the degree to which an instrument truly measures the construct(s) it purports to measure” (p. 743) (116). Criterion validity is defined as “the degree to which the scores of a measurement instrument are in adequate reflection of a gold standard” (p. 743) (116). If a gold standard test is not available, construct validity is used to assess if the scores of the test are as expected based on existing knowledge (115).

1.5 Physical activity in JIA

The PA recommendations by WHO state that whenever possible, children and youth with disabilities should meet the general PA recommendations for children. Importantly, they should work with their health care provider to perform the types and amounts of PA that are appropriate considering their disability (80). The latest specific PA recommendations for patients with JIA were published in 2003 (117). These recommendations were developed by an international expert panel, and include recommendation to perform at least 30 minutes of moderate intensity PA minimum three days per week with the intention to decrease pain, joint swelling/tenderness, improve CRF and gait efficiency. Further, to perform individualized resistance exercise three times per week to improve function, muscle strength and endurance. However, in recent years, it has become increasingly more common to apply the general WHO PA recommendations for children also for patients with JIA. Most JIA studies referring to the WHO PA recommendations include only the overall PA recommendation of 60 minutes daily MVPA (118-120).

1.5.1 Physical activity levels in JIA

Several studies have been published regarding PA levels in patients with JIA since this PhD project was started. Some of these studies are included in a recent review study, which concluded that patients with JIA are less physically active compared to controls (121). The most relevant studies published after 2000 that have compared PA levels in patients with JIA to controls or reference values are shown in Table 2. Different measurement methods (accelerometers, exercise diaries and questionnaires) are used in these studies, making it difficult to compare the results. But regardless of measurement methods, the main finding is that patients with JIA have lower overall PA levels, lower MVPA levels and spend more time sedentary compared to healthy controls (8, 9, 31, 118-120, 122). Interestingly, a recent Israeli study reported comparable self-reported overall PA levels between patients and healthy controls, and suggested that a treat-to-target approach could explain this finding (123). Also, even only published in Norwegian (the master thesis of the PhD candidate), patients with JIA self-reported similar PA levels compared to a reference group (4).

The evidence regarding associations between PA levels and JIA disease variables is conflicting. Most of the studies have examined associations with various disease variables, and reported associations with only one or two of all assessed disease variables and these associations were not consistent between studies. Also, some studies did not find any

Table 2. Studies of physical activity in patients with JIA compared to controls/reference group

Author	Participants	Assessment method/outcomes	Main results
Maggio et al. 2010, Switzerland (8)	35 JIA, 10.8 (0.5) years. 85 Ctr, 10.1 (0.3) years. Ctr: Peers of patients and children from local schools. Sex ratio not given other than it was similar among groups.	Accelerometer Sedentary behavior <500 cpm MVPA >2000 cpm	518 (28) vs 668 (35) cpm daily in patients vs controls, p<0.001. 54.1 (5.7) vs 71.3 (4.5) minutes with MVPA daily in patients vs controls, p=0.04. 73.8 % vs 69.7 % sedentary time daily in patients vs controls, p<0.01. 38.1 % vs 60.4 % of patients vs controls met WHO recommendations of 60 min MVPA daily.
Nørgaard et al. 2015, Denmark (118)	61 JIA (37 girls), 13.2 (1.7) years. 2055 Ctr (1015 girls), mean age not given. Ctr: Age- (±1.5 year) and sex-matched healthy controls from two population studies on PA in Danish school children (data collected in 1997-2008).	Accelerometer MVPA >1000 cpm VPA >2500 cpm	457.5 (172.2) vs 518.2 (83.9) cpm daily in patients vs controls, p<0.004. 97.1(40.4) vs 117.2 (23.5) minutes with MVPA daily in patients vs controls, p <0.001. 31.3 (19.4) vs 38.6 (7.7) minutes with VPA daily in patients vs controls, p<0.002.
Bohr et al. 2016, Denmark (119)	133 JIA (99 girls), 14.0 (3.4) years. 1692 Ctr (sex ratio not given in detail), mean age not given). Ctr: Age- (±1.5 year) and sex-matched healthy controls from two population studies on PA in Danish school children (data collected in 1997-2008).	Accelerometer MPA >2000 cpm VPA> 3000 cpm	475.6 (178.8) vs 522.7 (SD not given) cpm daily in patients vs controls, p<0.001. 48.4 (24.7) vs 52.8 (SD not given) minutes with MPA daily in patients vs controls, p >0.001. 24.7 (16.3) vs 26.5 (SD not given) minutes with VPA daily in patients vs controls, p>0.001. 19/45 % of JIA girls/boys vs 39/61 % of control girls/boys met WHO recommendations of 60 min MVPA daily.
Bos et al. 2016, The Netherlands (120)	76 JIA (50 girls), 10.0 (1.4) years. 131 Ctr (82 girls), 10.4 (1.2) years. Ctr: Reference data collected 2 years ahead of JIA patient data collection, from children aged 8-13 years without a mental or physical disability.	7-day activity diary Physical activity level (PAL) MVPA (hours/day) Sedentary time (hours/day)	1.6 (0.2) vs 1.8 (0.2) PAL daily in patients vs controls, p <0.01. 1.3 (0.8) vs 2.1 (1.2) hours daily with MVPA in patients vs controls, p <0.01. 19.3 (1.3) vs 18.2 (1.3) hours daily with sedentary time in patients vs controls, p <0.01. 4 % vs 16 % of patients vs controls met WHO recommendations of 60 min MVPA daily.

Author	Participants	Assessment method/outcomes	Main results
Lelieveld et al. 2008, The Netherlands (9)	30 JIA (18 girls), 17.0 (0.6) years. 106 Ctr (61 girls) 16.7 (0.9) years. Ctr: Data collected from healthy Dutch secondary school children 16-18 years from 5 secondary schools.	3-day activity diary Total energy expenditure (TEE), Activity-related energy expenditure (AEE) PA levels and PA pattern	TEE, AEE, and PA levels were significantly lower in patients vs controls. 87 vs 133 minutes with MVPA daily in patients vs controls. 23 % vs 66 % of patients vs controls met WHO recommendations of 60 min MVPA daily Patients spent more time sleeping and resting in bed than controls.
Condon et al. 2015, Ireland (122)	53 JIA (33 girls) 11.4 (3.0) years. Ctr: UK normative values for girls and boys were used for comparison.	Physical Activity Questionnaire for Children (PAQ-C)	Mean (95 % CI) PAQ-C score was lower in JIA girls (2.4 (2.2, 2.6)) and boys (2.7 (2.2, 3.0)) compared to normative values in girls (2.7) and boys (2.9). 32 % of patients met WHO recommendations of 60 min MVPA daily.
Hulsegge et al. 2015, Australia (31)	28 JIA (16 girls) 11.3 (2.4) years. 2750 Ctr (1349 girls) 11.3 (2.8) years. Ctr: National PA reference data from 2004.	The modified version of the Adolescent Physical Activity Recall Questionnaire	57.1 % vs 78.7 % (during summer) and 35.7 % vs 72.3 % (during winter) of patients vs controls met WHO recommendations of 60 min MVPA daily.
Sherman et al. 2018, Israel (123)	97 JIA (66 girls), 11.9 (5.0) years. 98 Ctr (61 girls), 11.7 (3.9) years. Ctr: Relatives of JIA patients or users of community pediatric health centers.	The Modified Godin Leisure-Time Exercise Questionnaire	7.7 (5.9) vs 11.0 (8.6) times/week with PA (total) in patients vs controls, p=0.51. 3.4 (3.2) vs 5.1 (2.9) times/week with mild PA in patients vs controls, p=0.672. 3.0 (2.6) vs 4.4 (3.0) times/week with moderate PA in patients vs controls, p=0.40. 2.1 (1.9) vs 3.4 (2.6) times/week with strenuous PA in patients vs controls, p=0.11.

Numbers are mean (SD) unless otherwise specified. *JIA* juvenile idiopathic arthritis; *Ctr* controls, *cpm* count per minute; *MVPA* moderate-to-vigorous physical activity; *VPA* vigorous physical activity; *MPA* moderate physical activity; *PA* physical activity; *PAL* physical activity level; *TEE* total energy expenditure; *AEE* activity-related energy expenditure; *UK* United Kingdom; *PAQ-C* Physical Activity Questionnaire for Children; *CI* confidence interval; *WHO* World Health Organization.

associations between disease variables and PA levels (8, 122). Regardless, lower PA levels have shown associations with higher disease activity (118, 124), arthritis in weight-bearing joints (118, 119), more pain (125) and lower wellbeing (120).

1.5.2 Participation in physical activities in JIA

Some studies have examined participation in PA in patients with JIA, often with different and not validated questionnaires. Based on parent reports, one study found that 53 % of patients participated in organized PA and 74 % participated in unorganized PA weekly. Further, patients with active disease participated less in PA than those without active disease (126). A recent study including patients and controls reported that the proportion of patients engaging in organized sports was significantly lower than in controls (66% vs. 75%). Also, patients participated more in individual, less intensive and weight-bearing sports (e.g., badminton, swimming and riding) than controls, who participated more in contact/team sports and strenuous sports (e.g., handball, martial arts and dancing). However, soccer was the most popular sport in both patients and controls (127). According to a German preliminary report, patients had lower participation in organized sport compared to controls (36% vs 60%) (128).

1.5.3 Participation in physical education in JIA

Several studies have reported low PE participation among patients with JIA (120, 129, 130). A recent German study including patients (n=23.016) enrolled in a national pediatric rheumatology database, reported that PE participation had increased significantly among patients from 2000 to 2015. However, only 64 % of patients participated fully in 2015, and 16 % was fully exempted from PE. The remaining 20 % of the patients was classified as sometimes/often not attending PE classes (131). Two other recent studies reported higher PE participation in patients with JIA than previous studies. In a Nordic JIA cohort (n=242), full participation in PE was reported by 80%, partly by 17%, and none by 3% eight years after diagnosis. Not participating in PE was associated with higher disease activity (132). In a Danish study, a similar proportion of patients and controls participated in PE, but the patients were significantly less consistent during participation and the main reason for not participating fully was joint pain (127).

1.5.4 Barriers and facilitators for physical activity in JIA

Knowledge is sparse on facilitators and barriers for PA participation in patients with JIA. In a recent Canadian qualitative study, pain was the most common barrier to PA participation.

Pain relief following PA and enjoyment were highlighted as facilitators for participation in PA (133). An older, small qualitative study reported symptoms of the disease, the treatment and the side-effects from treatment as barriers for PA participation (134). Nørgaard et al. (127) explored barriers and facilitators specifically for sport participation in patients and controls. The most reported barriers for sport participation in patients were joint pain, disliking exercise and shortness of breath/side stiches, while the most reported barrier in controls was disliking exercise. The most reported facilitators for PA in patients were enjoying motion, being with friends, liking competition and forgetting pain, while controls reported fun of doing PA and enjoying motion as main PA facilitators.

Summarizing, several studies on PA in patients with JIA have been published since we started our study. The evidence is still that patients with JIA do not have optimal PA levels and PA and PE participation. Further, the evidence regarding whether the disease still has an influence on PA levels is conflicting. However, a previous small Norwegian study indicated that patients had comparable PA levels to a reference group, which suggests that PA behavior in JIA should be addressed by applying more optimal measurement methods, and additionally should be examined in a control group for comparison. Furthermore, no study has yet included only patients diagnosed in the era of biologics to study a broad specter of PA behavior, including PA barriers and facilitators in the same study cohort.

1.6 Physical fitness in JIA

In this section, the most relevant studies of patients with JIA regarding the components of physical fitness that we included in our study will be presented.

1.6.1 Cardiorespiratory fitness in JIA

Poor CRF has consistently been found in patients with JIA compared to healthy peers in previous studies, both measured directly and estimated through performance on maximal (5-8, 118, 135-137) and submaximal tests (18, 138-140). Further, CRF is particularly poor in girls with JIA compared to healthy girls (5, 7). In contrast, but published in Norwegian only, patients with JIA performed excellent on a submaximal test compared to reference values from other countries and Dutch patients with JIA in a study on climate therapy in JIA (by the PhD candidate) (4). An overview of studies that have reported directly measured VO_{2peak} in patients with JIA compared to controls or a reference group is shown in Table 3.

Associations between CRF and disease variables have not been extensively examined, but CRF is reported to be lowest in patients with active disease (6-8). Low CRF is also present in patients in remission (5, 7). Conflicting evidence is reported regarding the influence of JIA category on CRF. One study found that patients with polyarticular JIA have poorest CRF among JIA categories (6), while the most recent study did not find any differences in CRF across JIA categories (7).

Thus, there is a need for examining CRF with direct measurement of VO_{2peak} in patients with JIA exclusively diagnosed in the era of biologics compared to controls and to explore if disease variables have an impact on CRF in those patients.

Table 3. Cardiorespiratory fitness (directly measured) in patients with JIA vs controls

Author	**Participants (n, years)**	**VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$)**	**p-value**	**Ergometer**
Maggio et al. (2010) Switzerland (8)	35 JIA, 10.8 (0.5) 85 Ctr, 10.1 (0.3)	39.3 (1.7) 45.3 (0.9)	0.001	Treadmill
Houghton et al. (2008) Canada (136)	13 JIA, 13.9 (10.5-17.7) 9 Ctr, 12.8 (11.3-16.5)	31.3 (20.2-49.9) 47.9 (32.7-54.1)	0.013	Bicycle
Van Brussel et al. (2007) The Netherlands (5)	62 JIA, 11.9 (2.2) 50 Ctr , 12.3 (2.5)	34.6 (8.0) 49.1 (8.0)	<0.0001	Bicycle
Lelieveld et al. (2007) The Netherlands (6)	22 JIA, 17.1 (0.7) Reference group matched for age and sex	35.36 (7.95) 43.98 (5.85)	<0.01	Bicycle
Metin et al. (2005) Turkey (135)	34 JIA, 11.5 (2.8) 21 Ctr, 12.6 (1.5)	29.1 (5.2) 33.9 (5.4)	<0.01	Bicycle
Dogru Apti et al. (2014) Turkey (137)	30 JIA, 11.4 (2.5) 20 Ctr, 11.0 (2.3)	32.5 (6.7) 37.0 (5.9)	<0.05	Treadmill

Numbers are mean (SD) and median (min-max). *JIA* juvenile idiopathic arthritis; *Ctr* controls.

Feasible assessment of CRF in JIA for clinical and research purposes

Measuring CRF with the gold standard test, maximal exercise testing with direct measurement of VO_{2peak}, has some disadvantages. Such testing requires advanced and expensive equipment and extensive experience is required for testing children to maximal aerobic levels. Furthermore, maximal testing is time consuming and may be unpleasant to perform. Therefore, submaximal tests to measure CRF in JIA are frequently used both in clinical practice and research. Submaximal tests provide less precise measurements, but are inexpensive, require less equipment and are easier to perform and administer.

The six-minute walk test (6MWT) is probably the most commonly used submaximal test in JIA, but is reported to be a poor predictor of VO_{2peak}, and rather a measure of walking

capacity (138, 139). The measurement properties of the 6MWT vary largely among other chronic pediatric conditions as well (90). The 6MWT is performed on flat floor, and the fact that Norwegian patients with JIA performed well on this test, indicates that more physically demanding submaximal tests may be advantageous for CRF measurement in JIA. Some field tests that may estimate VO_{2peak} are used for CRF measurement in children, but these require individuals to exercise to exhaustion (141, 142).

We were unable to identify a validated submaximal walking test which was more physically demanding than the 6MWT in pediatric populations. However, there is a valid and reliable submaximal treadmill test used in adults with rheumatic diseases for CRF evaluation (143). This test includes brisk uphill walking and may estimate VO_{2peak} from the submaximal performance. We therefore decided to examine the measurement properties of this submaximal treadmill test. Given that the measurement properties are acceptable, this would provide a feasible test for CRF measurement in JIA for both clinical and research purposes.

1.6.2 Muscle strength and endurance in JIA

Previous studies have reported lower muscle strength in patients with JIA compared to controls (144-148). However, the most recent studies also reported normal muscle strength in some of the muscles groups that were assessed (147, 148). Knowledge about associations between muscle strength and disease variables in patients is sparse. One study found that the majority of patients with JIA have normal strength in the hands, but some patients, especially those with polyarthritis and arthritis in the hands, had reduced hand muscle strength (144). The studies have used different measurement methods to assess muscle strength, even though most studies have measured muscle strength by some kind of isometric dynamometers. Also, different muscle groups have been tested, making it difficult to compare studies. Knowledge about isokinetic muscle strength compared to controls, which may be considered a more functional measure of muscle strength reflecting muscle activity that are more essential in daily life, is currently lacking in patients with JIA.

1.6.3 Body composition and bone mineral density in JIA

A recent review concluded that most studies showed lower BMD in patients with JIA compared to controls or reference values (149). The reductions in BMD were independent of corticosteroid effects. Systemic and polyarticular JIA had greater BMD reductions than

oligoarticular JIA (149). However, normal BMD in patients compared to reference values was demonstrated in a more recent study (150).

There is scarce knowledge of body composition in JIA; few studies have applied advanced measurement methods. A recent systematic review concluded that it was uncertain whether patients with JIA had an altered body composition compared to healthy children (151). The findings were conflicting; both lower muscle mass (152, 153), higher fat mass %, (154) comparable fat mass % (155) and lower fat mass % (152) in patients compared to controls were reported. The authors of the systematic review underlined that the results of their study were hampered by low quality of the included studies (151). Not included in the systematic review is a relatively recent study reporting normal body composition (similar fat and lean mass) in patients compared to controls. In general, the systemic glucocorticoid dose was low, and 60 % of patients were off systemic glucocorticoid therapy at the time of the study (156).

The side effects following long-term and high-dose systemic corticosteroids therapy include Cushing syndrome and possible osteoporosis (24). The conflicting evidence regarding body composition and BMD may partly be related to less use of systemic corticosteroid therapy after the introduction of biologic DMARDs. This suggests that body composition and BMD should be examined in patients exclusively diagnosed in the era of biologics.

Summarizing, knowledge is sparse on physical fitness in patients with JIA diagnosed in the era of biologics and also how the disease influences physical fitness in these patients. Further, no studies have examined several components of physical fitness in the same JIA cohort, which may enable providing a more specified and targeted management of the patients.

1.7 Physiotherapy in JIA

Evidence-based practice is warranted in pediatric physiotherapy, integrating the best research evidence with clinical expertise and patient values (157), and is also applied in physiotherapy in pediatric rheumatology. In addition, physiotherapy in pediatric rheumatology is inspired by theoretical framework and system theories of development. Essential in physiotherapy for patients with JIA is to measure and improve function and health. The most widely used framework in physiotherapy today, is probably the International Classification of Functioning, Disability and Health (ICF), based on the biopsychosocial model and developed by WHO (158). The ICF conceptualizes functioning and disability as a dynamic interaction between a

person's health condition, functioning and contextual factors (including environmental and personal factors (Figure 1). The ICF intended to provide a standard language and scientific basis for understanding and studying health and health-related states, outcomes and determinants. The ICF also contains a detailed coding classification of the different components of health which not will be discussed in this thesis.

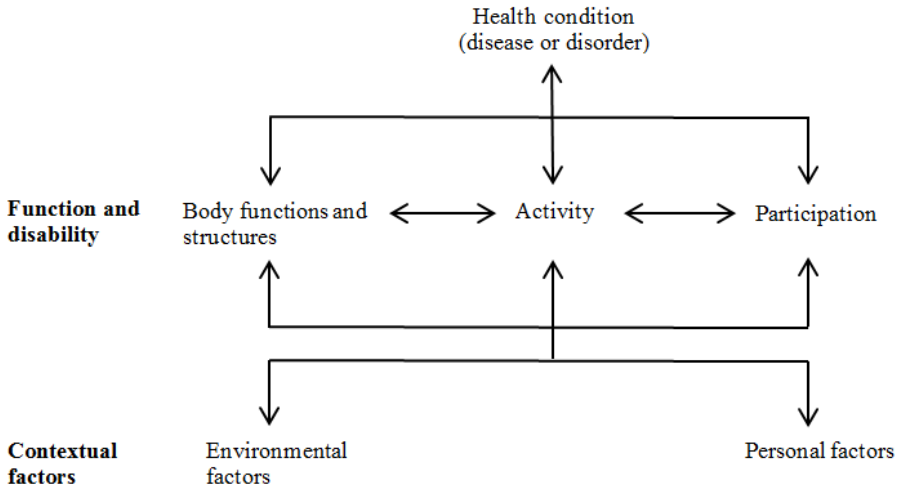

Figure 1. The International Classification of Functioning, Disability and Health framework.

Further, in pediatric physiotherapy, different models introduce the importance of the interaction between the child and the child's environment. The Dynamic System Theory is one such model, that proposes that movements and motor skills are produced and learned from the interaction of multiple subsystem within the person, the task and the environment (159). The Ecological System Theory developed by Bronfenbrenner is also influential in pediatric physiotherapy, underscoring that the children's development is affected by their social relationships and the world around them (160).

Subsequent to the implementation of the ICF framework and system theories of development in pediatric physiotherapy in general, the improved medical treatment with the introduction of biologic DMARDs and the evidence regarding safety of exercise in JIA, physiotherapy in pediatric rheumatology has changed tremendously. Rest, joint protection and passive treatment modalities have been replaced by active treatment modalities (161). Moreover, physiotherapy intervention used to focus mainly on the ICF dimension of body structure and function (e.g., joint contracture, muscle weakness and leg length discrepancy), while

physiotherapy in pediatric rheumatology today additionally includes the ICF dimensions of activity and participation (e.g., running and participation in PE and leisure time activities). Thus, physiotherapy may include intervention focusing on the task and environment to enable participation in PE. Both patient education about the safety and importance of PA in JIA and close collaboration between health professionals at the hospital, physiotherapists in primary health care, PE teachers and patients and parents may enable PE participation.

Also, including the child's personal factors (e.g., motivation) is considered essential when promoting a physically active lifestyle and also ensure adherence to therapeutic exercises during a period of physiotherapy. Self-determination theory emphasizes that being motivated by self-determined, intrinsic reasons leads to greater engagement than being motivated by controlled, extrinsic reasons (162).

Based on evidence on the safety of exercise in JIA without disease flare (2), supported by similar evidence in RA (3), our department has since mid 2003 encouraged patients with JIA to participate in PA and PE like, and together with, their healthy peers without any general restrictions, regardless of having active arthritis. Emerging evidence has subsequently supported the safety and possible benefits of exercise in JIA. A Cochrane review published in 2008 on exercise therapy in JIA included three randomized controlled trials (RCTs). No evidence was found of improved functional ability, quality of life, CRF or pain following exercise therapy. Importantly, exercise did not exacerbate arthritis (163). Recently, two systematic reviews (164, 165) on exercise therapy identified nine RCTs published since the Cochrane review, and concluded that exercise therapy appears to be well tolerated with no adverse effects of exercise reported. Exercise therapy was beneficial across clinically relevant outcomes in JIA patients (improved functional capacity, knee strength and quality of life and decreased pain). However, substantial heterogeneity in exercise interventions and study outcomes limited the ability to generalize the evidence. Notably, some of the RCTs included interventions that are not commonly used in Norwegian patients with JIA, probably because of sociocultural differences and differences in health care services regarding both accessibility and tradition of modalities provided to patients. The studies do, however, support the evidence of the safety of exercise and PA in patients with JIA.

At our hospital, we do not use general exercise programs anymore due to improved physical function in patients. Additionally, we experienced poor adherence to such programs, which is in line with research findings (166-168). Thus, our physiotherapy management of all patients

newly diagnosed with JIA includes individualized tailored patient education regarding the importance and safety of PA. In addition, the individual patient's perspectives and preferences of enjoyable activities are taken into account. Also, participation in PE is advocated and recommended.

Besides the evidence of exercise therapy in JIA, the evidence of other physiotherapy interventions is scarse. Therapeutic exercises are specific exercises addressing particular functional health problems, in JIA most often used at diagnosis and disease flares for a limited period of time. The effectiveness of such exercises has been less studied. The paucity of research evaluating physiotherapy for lower-limb problems in JIA were underscored in a recent systematic review (169). Despite low evidence for several physiotherapy modalities, physiotherapy is recommended in patients with JIA in recent treatment guidelines (170).

At the time of data collection for this thesis, the costs of physiotherapy in JIA were covered by the Norwegian social security system, both inpatients, outpatients and in primary health care. Per 01.01.2018, physiotherapy in primary care for all children < 16 years of age is covered by the Norwegian social security system regardless of diagnosis, while children > 16 years have to pay a deductible, and when this amount is reached, physiotherapy is covered by the Norwegian social security system for the rest of that calendar year. Costs of physiotherapy provided to patients with JIA in hospitals are covered by the Norwegian social security system.

1.8 Rationale for the thesis

Summarizing, Norwegian patients with JIA have long been recommended to participate in physical activities without general restrictions, and a Norwegian study indicated that patients had comparable PA levels and CRF to healthy peers (4). However, these results were hampered by small sample size and suboptimal measurement methods, suggesting a need for further examination in a larger study using state-of-the-art measurement methods. Physical fitness and PA levels have been scarcely studied in patients diagnosed in the era of biologics who have been provided with modern multidisciplinary health care services. Measuring a broad aspect of physical fitness and PA with state-of-the-art methods in patients and controls will extend knowledge on these outcome measures that are important for health. This also allows studying associations between PA levels and different components of physical fitness, and associations with relevant disease variables in patients with JIA. Such knowledge is

essential to improve the management of patients with JIA, including providing a more tailored patient education on PA to optimize the health benefits for patients.

2 Aims of the study

2.1 Overall aim

To examine PA and physical fitness in patients with JIA (persistent oligoarticular JIA and polyarticular disease) diagnosed in the era of biologics and controls from the general population; also, to evaluate the measurement properties of a submaximal treadmill test.

2.2 Specific aims

- To compare objectively measured PA in patients versus controls and between patient subgroups (persistent oligoarticular JIA versus polyarticular disease) (Paper I).
- To compare participation in leisure time PA (organized and unorganized PA), participation in PE and PA facilitators and barriers in patients versus controls (Paper I).
- To examine associations between disease variables and objectively assessed PA and physical fitness in patients (Papers I-III).
- To compare physical fitness in patients versus controls and between patient subgroups (Paper II and Paper III).
- To evaluate criterion validity of a submaximal treadmill test in patients and controls (Paper III).
- To evaluate test-retest and intra-rater reliability of a submaximal treadmill test in patients (Paper III).

3 Patients and methods

In this chapter, our rationale for chose of participants and methods will be discussed, focusing on main outcome measures.

3.1 Study design

We used a comparative cross-sectional design in all three studies in the thesis to address the aims of Papers I, II and III, with a test-retest design included for the assessment of reliability of the submaximal treadmill test in patients in Paper III.

3.2 Study population and organization of data collection

3.2.1 The patient group

We consecutively recruited eligible patients with JIA with a planned routine visit at OUS during 2015. To be able to compare homogeneous subgroups of patients with appropriate sample sizes we decided to include patients with persistent oligoarticular JIA and patients with polyarticular disease (extended oligoarticular JIA and polyarticular RF +/-) according to ILAR criteria. In this thesis, oligoarticular JIA refers to persistent oligoarticular JIA and polyarticular disease refers to extended oligoarticular JIA and polyarticular RF +/-, unless specified otherwise. We hypothesized that patients with persistent oligoarticular JIA would have higher PA levels and better physical fitness than patients with polyarticular disease given the difference in disease severity, i.e., the number of joints affected, in these categories. Thus, we decided not to include JIA categories that possibly would imply small sample sizes/JIA categories in which extra-articular manifestations (i.e., enthesitis or serositis) could influence the study outcomes (PA and physical fitness) in addition to the number of joints affected. Further, the extensive and complex measurements methods, particularly for physical fitness, required an ability to walk, absence of severe illness in respiratory and circulatory systems and an age ≥ 10 years.

The inclusion criteria for patients were:

- age 10-16 years
- disease duration > 6 months (to ensure that patients had started anti-inflammatory medication, if needed)

- JIA classified as persistent oligoarticular JIA or polyarticular disease (extended oligoarticular JIA and polyarticular RF +/-) according to the ILAR criteria (35)
- home address in the geographical area served by the South-Eastern Norway Regional Health Authority. This area has a denominator population of 2.8 million (57 % of the Norwegian population).

The exclusion criteria for patients were:

- comorbidities associated or potentially associated with impaired CRF (e.g., heart or lung disease)
- severe orthopedic conditions
- recent surgery
- inability to walk

We identified eligible patients through the waiting lists at the Pediatric Rheumatology Unit at OUS, and invited patients to participate in the study by mail 1-2 months prior to their preliminary visit date at OUS (one written reminder was sent). Patients who returned a pre-stamped reply letter to the hospital with their contact information and informed consent to participate, were called up by the PhD candidate and asked specifically about physical status, medical history and current medication to ensure that they did not have any of the criteria set for exclusion. A date for the routine visit at OUS together with study specific examinations/tests was then scheduled. All patients were clinically examined in conjunction with their routine visit by the treating physician at OUS between January and August 2015. If patients wanted a numbing cream (Emla cream) to reduce discomfort when drawing a blood sample, the numbing cream was sent to the patients by mail to be applied at least an hour before their visit time at OUS to optimize its effect.

A total of 96 patients received an invitation letter until the predefined number of 60 (30 in each subgroup) was reached, giving a response rate of 63 % (Figure 2) (see section 3.4 for sample size calculations).

To evaluate the reliability of the submaximal treadmill test, patients living in or nearby Oslo or with a new follow-up at OUS within 4 weeks, were asked to perform the submaximal treadmill test at OUS 1-4 weeks after the initial test. Thirty-seven patients agreed to participate in this sub-study. They performed the submaximal treadmill test twice on the

second test day, separated by approximately 15 minutes rest between each test. The majority of the reliability testing was conducted in the afternoon to avoid school absence.

3.2.2 The control group

We included individually age- and sex-matched controls randomly drawned from the general population (living in Oslo or in the neighboring county Akershus). For practical reasons we decided that the control population should live in these areas since the examinations had to be done during daytime, limiting the school absence for the controls to one day. Additionally, since most of the controls had to be followed by a parent, guardian, grandparent etc., we assumed it would be easier to participate for controls living relatively nearby OUS. Exclusion criteria for the controls were 1) inflammatory rheumatic or autoimmune disease, 2) severe heart or lung disease, and 3) other diseases involving mobility problems. The first exclusion criterion was set to avoid comparing our patients with controls having diseases that could influence the ability to perform PA and physical fitness in general, and having difficulties completing the specific study measurements. The second criterion was set because participation in the study included performing comprehensive exercise testing, some with high intensity extremely demanding for the respiratory and circulatory systems. Exercise testing involved walking and running, thus, the third criterion was set.

A company licensed to perform random selections from the National Registry identified matched controls (i.e., patients and matched controls in a 1:1 proportion for practical and economic reasons). We received a list of 900 eligible controls, i.e., 15 controls for each patient. Out of these 15, the first control per case was invited to participate by mail. If a positive response to participate was not received within three weeks (no written reminder was sent), the second control, and then the third control etc., was invited by mail until we had identified one control per patient. Controls, who returned a pre-stamped reply letter with their contact information and informed consent to participate to the hospital, were called up by the PhD candidate and asked specifically about physical status, medical history and current medication to ensure that they did not have any of the criteria set for exclusion. A day for examination and completing all the evaluations at OUS was then decided. If controls wanted numbing cream in conjunction with blood sampling, this was sent by mail to be applied at least an hour ahead of arriving to the hospital for maximal effect.

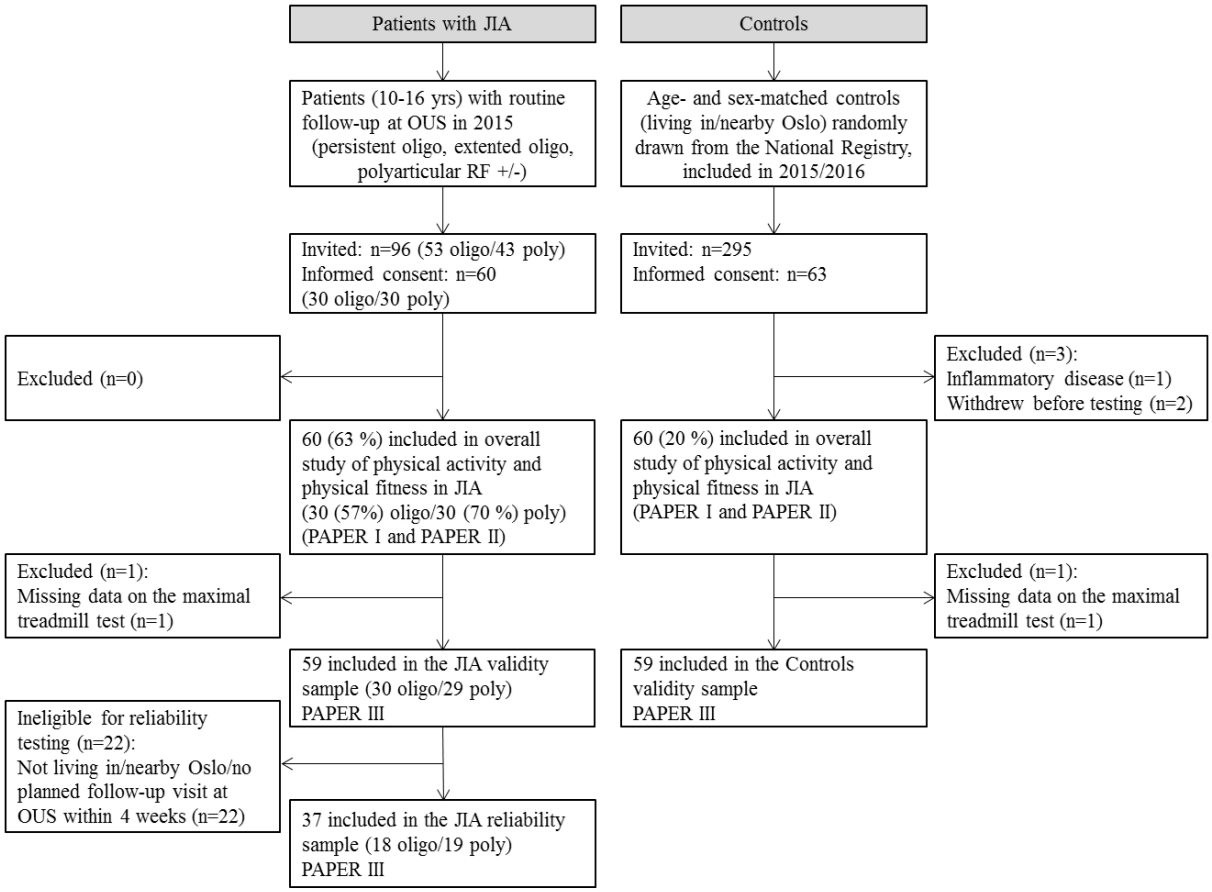

Figure 2. Flowchart of participants in papers included in this thesis.

To be able to recruit 60 controls, a total of 295 controls were sent an invitation letter by mail, giving a response rate of 20 % (Figure 2). All controls were examined during a one-day program between November 2015 and March 2016 at OUS.

3.3 Procedures for data collection and outcomes measures

3.3.1 Procedures for data collection

For this thesis (all Papers), the PhD candidate, with more than 15 years of clinical experience in pediatric rheumatology, performed all the tests to assess physical fitness, and also performed the structured interviews to explore PA behavior and to assess pubertal status, smoking and other tobacco-related habits in both patients and controls during the one-day program at OUS. The PhD candidate also carried out the measurements of height, weight and waist circumference. The treating physician completed the Physician's Global Assessment of

disease activity for each patient (PGA), which was used to calculate the JADAS 71 score and determine the patient's disease state (clinical active/inactive disease). The measurements of body composition and BMD by DXA were carried out by experienced personnel at the Section of Endocrinology, Rikshospitalet, OUS. Blood samples of the patients were drawn and analyzed at the Department of Medical Biochemistry, Division of Laboratory Medicine, Rikshospitalet, OUS, while blood samples of the controls were drawn and processed at the Clinical Research Unit, Department of Pharmacology, Rikshospitalet, OUS and analyzed at the Department of Medical Biochemistry, Division of Laboratory Medicine, Rikshospitalet, OUS.

In Paper III a single physiotherapist (the PhD candidate) assessed all submaximal treadmill tests used to evaluate the test-retest reliability. To evaluate the inter-rater reliability, the PhD candidate and a second physiotherapist, with more than 13 years of clinical experience in pediatric rheumatology, conducted the submaximal treadmill tests on the second test session.

3.3.2 Outcome measures

The different outcome measures used in this thesis are shown in Table 4. The outcome measures are described in the following sections.

3.3.2.1 Characteristics

Characteristics included variables such as age, sex, pubertal status, smoking and tobacco-related habits. Pubertal status and smoking and tobacco-related habits were registered during an interview without the parents present. Pubertal status was self-reported (showing drawings) using Tanner Stages 1-5 (171, 172). The puberty stages were then categorized into three categories: pre-puberty (Tanner 1), mid-puberty (Tanner 2-4) and post-puberty (Tanner 5). Girls were asked about age for menarche. Height and body weight were measured to an accuracy of 0.1 cm and 0.1 kg, respectively, with participants wearing light clothes and no shoes. BMI was calculated and age- and sex-specific BMI cut-off values were used to categorize the children as normal weight, overweight or obese (173). Waist circumference was measured at the midpoint between the bony markers of the ribs and the superior iliac crest in a standing position at the end of expiration with a measuring tape at the height of umbilicus to the nearest 0.1 cm.

Table 4. Overview of included measures in the papers in the thesis

	Paper I	Paper II	Paper III
All participants			
Characteristics	x	x	x
CRP and ESR	x	x	
Hemoglobin		x	
NRS current pain	x	x	x
NRS pain during previous week	x	x	x
NRS fatigue during previous week	x	x	x
Physical activity			
Objective measurement of PA (accelerometry)	x	x	
Subjective measurement of PA (structured interview; PA and PE participation, facilitators and barriers)	x		
Physical fitness			
Cardiorespiratory fitness (maximal treadmill test)		x	x
Cardiorespiratory fitness (submaximal treadmill test)			x
Isokinetic muscle strength and endurance (knee extensors and flexors)		x	
Isometric muscle strength (hand grip)		x	
Body composition and BMD (DXA)		x	
Patients			
JADAS 71	x	x	x
Active joints	x	x	x
Active joints in lower extremities	x	x	x
CHAQ	x	x	x
Wallace criteria for inactive disease	x	x	x
Use of medication	x	x	x

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate, *NRS* numeric rating scale, *PA* physical activity, *PE* physical education, *BMD* bone mineral density; *DXA* dual-energy X-ray absorptiometry, *JADAS* juvenile arthritis disease activity score, *CHAQ* childhood health assessment questionnaire

3.3.2.2 Physical activity and physical fitness

As presented above, there are no international guidelines regarding measurement methods to assess PA and physical fitness in patients with JIA. We therefore aimed to use methods that are considered state-of-the-art methods if available regarding the different components of physical fitness and PA in children in general. We decided to use both objective and subjective measurement methods to be able to explore a broad specter of PA behavior. In the following, the methods we used to measure PA behavior and physical fitness are described.

Objectively measurement of physical activity

We used Actigraph GT3X+ accelerometers (ActiGraph, Pesacola, FL, USA) to measure volume and intensity of PA objectively. Actigraph accelerometers are the most widely used PA devise in PA research (174, 175). The raw data from the accelerometers were converted to counts per minute (cpm) and steps daily, which both are measurers of overall PA. In this thesis, overall PA refers to cpm unless otherwise specified. Overall PA was the main PA outcome in Paper I. In JIA, different cut points have been used to study PA intensities, thus we decided to apply cut points previously established and validated in the general pediatric population; sedentary time (<101 cpm), light PA (LPA) (≤101 to ≥2295 cpm), moderate PA (MPA) (≥2296 to ≤4011 cpm) and VPA (>4011 cpm) (176, 177). We also reported the proportion of participants achieving the PA recommendations (60 minutes of daily MVPA). The procedures for the accelerometry assessments are given in Paper I.

The participants noted the time spent swimming, cycling and skiing during the days they wore the accelerometers, as the accelerometers do not capture these physical activities accurately. Sometimes such self-reported data of time spent on different activities are processed and summarized together with data from accelerometers, to account for data not precisely measured by accelerometry. However, such handling may preclude the concept of objectively measured PA because it includes both objective and subjective data.

Subjectively assessment of physical activity

To the best of our knowledge, there are no validated questionnaires available in Norwegian to measure neither children's participation in organized or unorganized PA or PE nor children's PA barriers and facilitators that were suitable for this thesis. Further, as mentioned above there are activities that are poorly measured by accelerometer, like swimming, cycling and skiing and also strength training. We therefore decided to explore participation in PA and PE, and facilitators and barriers for PA participation by conducting a structured interview. The interview guide was developed for this thesis by two physiotherapists (including the PhD candidate) and one nurse (all experienced in pediatric rheumatology), based on literature review and clinical experience. The questions included are shown in Table 5. The procedures for conducting the interviews are described in Paper I.

Table 5. Structured interview guide

Do you participate in organized physical activity? If yes, which activity/activities and how many hours/week?
Do you participate in unorganized physical activity? If yes, which activity/activities and how many hours/week?
Do you perceive barriers to being physical active? If yes, which?
Do you perceive facilitating factors to being physical active? If yes, which?
Do you participate in physical education classes in school? If yes, how often?

Cardiorespiratory physical fitness measured directly with a maximal treadmill test

In JIA, a bicycle test is most commonly used in studies reporting direct measurement of VO_{2peak}, possibly because bicycling may have been considered to minimize the stress on weight-bearing joints. However, cycling may be considered a less dynamic and functional exercise mode than walking and running, with use of less muscle mass, and therefore gives lower cardiopulmonary stress (178). In addition, leg discomfort during cycling may be an important contribution to exercise limitation, particularly due to development and growth of muscle mass during childhood and adolescence, indicating less stress to the cardiopulmonary system when using cycle-ergometer. Therefore, we considered treadmill testing as a more functional exercise mode, in combination to the fact that maximal treadmill testing traditionally has been used in pediatric populations in Norway. At OUS, we had never conducted maximal exercise tests in patients with JIA prior to our study. Other pediatric patient populations, like asthma and congenital heart diseases, have for years been tested with maximal treadmill tests. Based on clinical experience we considered that our patients with JIA would be able to perform a maximal treadmill test. Most treadmill exercise protocols are designed to test adults, including the Bruce protocol often used in children. The protocols often start at a high speed, have a steep incline and large increments between the stages (179), which are not optimal for exercise testing in children. Thus, various test protocols have been developed at OUS to enable specific pediatric patient populations to reach their VO_{2peak} (180, 181). However, these protocols have high speed or long exercise duration that we considered suboptimal in JIA. We therefore developed a test protocol specifically for our study for use in both patients and controls. The inclination was increased more than the speed during the maximal treadmill test to reduce stress on weight-bearing joints in case of arthritis or pain. Also, we considered our protocol suitable for participants inexperienced with treadmill exercising.

Outcomes from maximal CRF testing included VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$), VO_{2peak} ($L \cdot min^{-1}$), oxygen pulse ($mL \cdot min/HR_{peak}$), minute ventilation (VE)($L \cdot min^{-1}$), ventilatory efficiency slope (VE/VCO_2), running distance, running time, respiratory exchange ratio (RER), peak heart rate (HR_{peak}) and ratings of perceived exertion (obtained from Borg scale $_{6\text{-}20}$) (182). In this thesis, VO_{2peak} refers to VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$) unless specified otherwise, and was the main CRF outcome in Paper II. We defined poor CRF as VO_{2peak} values below 85% of the mean in controls, separately for girls and boys.

There are no internationally accepted end criteria for maximal exertion in children. To reduce the burden of possible painful procedures, we did not measure blood lactate after the maximal exercise test even if it may give an indication of maximal exertion. The test leader evaluated if the test was considered maximal based on high HR, RER and high rating of perceived exertion, and also signs of rapid breathing, facial flushing and unsteady walking. In addition, all participants reported the reason for terminating the test. The details of the maximal exercise test procedures are described in Paper II.

Cardiorespiratory fitness measured by a submaximal exercise test

We decided to evaluate the measurement properties of an eight-minute submaximal treadmill test originally developed and validated to estimate VO_{2peak} in healthy adults (183). The test requires a treadmill and a heart rate monitor watch and is described as easy to administer. Such equipment is usually available in hospitals and primary care settings. The eight-minute submaximal treadmill test consists of two stages, both lasting 4 minutes. First, the individual walks for 4 minutes with no inclination at a speed between 3.2 km/h and 7.2 km/h corresponding to a predicted heart rate (HR; 200- age (years)) between maximum HR x 50 % and maximum HR x 70 %. We aimed for a HR close to 70 % of the predicted maximum HR during this first stage of the test. Then, at the second stage, the individual continues to walk at the same speed while the inclination is gradually increased (within 15-20 seconds) to 5 % inclination, and walks at this treadmill setting during stage two.

Depending on the speed selected during the performance of the eight-minute submaximal treadmill test, the test is reported to over- or underestimate VO_{2peak} in adults. When repeating the test to evaluate changes in individuals, it is recommended to use to same speed on each test occasion (184). This submaximal treadmill test is valid and reliable in adult women with rheumatic disease (143). Because patients with pediatric rheumatic diseases may experience

similar symptoms as adults with rheumatic diseases, we wanted to examine the measurement properties of this test in patients with JIA and also in healthy controls. A more detailed description of the eight-minute submaximal treadmill test and the details of the test procedures we applied for our study are given in Paper III.

In addition to estimated VO_{2peak}, outcomes from the performance of the submaximal treadmill test were HR, speed and rating of perceived exertion at 3 and 8 minutes, and walking distance.

Muscular strength and endurance

In JIA, muscle strength has often been tested isometrically in studies, with a fixed angel with sustained contraction against resistance, often with hand-held dynamometers, and different muscle groups have been tested in different studies. Isokinetic muscle strength involves assessment with the joint moving through full range at a constant angular velocity. Isokinetic muscle strength may reflect muscle activity more related to functional activities than isometric muscle strength. Test equipment to measure isokinetic muscle strength is usually developed for adults, but previous studies at OUS indicated that children within the same age range as our study population were able to perform isokinetic muscle testing (185). The validity and reliability of isokinetic muscle strength and endurance assessments are established in children (96). We therefore decided to test bilateral knee extension and flexion isokinetically using a Cybex 6000 (Cybex-Lumex Inc, Ronkonkoma, NY, USA).

We also wanted a measure of grip strength in both hands, and since grip strength most often is of isometric quality in daily life we decided to use the Baseline dynamometer (Fabrication Enterprises, White Plains, NY). We use this dynamometer regularly in our physiotherapy practice at OUS, particularly in patients with JIA with wrist and finger involvement, and our experience is that it an easy and suitable test to use in children in this age range. Isometric muscle strength testing is reliable and valid in children (96).

The test procedures we used for measurements of muscle strength and endurance are given in details in Paper II.

Body composition and bone mineral density

There is no gold standard method for measurement of all tissues included in body composition, but DXA is the preferred measure of bone mass in children (114, 186).

Additionally, DXA provides detailed and accurate information of lean mass and fat mass (108). Thus, we measured the pediatric total body composition and BMD by DXA with anterior–posterior projection at the lumbar spine (L2–L4) and total body. A Lunar Prodigy narrow fan beam from GE Healthcare (Lunar Corp. Madison WI, USA) densitometer was used and all the scans were analyzed using enCORE software version 14.10 (from the same manufacturer). Standard imaging and positioning protocols were used to scan the subjects. Absolute BMD values (g/cm^2) and BMD z scores of total body BMD and lumbar spine BMD were estimated by comparison to the Lunar-reference database incorporated in the software suitable for clinical use in the Norwegian population (187). Z score values ≤ 2 were defined as below the expected range for age and sex. Additionally, outcomes for body composition included total body lean mass, total body BMC mass, total body fat mass and total body fat %. Calibration of the DXA machine was performed daily using a calibration block consisting of tissue equivalent material with three bones, simulating chambers, as supplied by the manufacturer (188). The short- and long-term coefficients of variation (CVs) for our densitometer were 0.8% and 1.4%, respectively. The precision error at lumbar spine was about 1% (189) and CVs for total body tissue and fat mass were 0.1% and 2.5%, respectively (190).

3.3.2.3 Measures of pain and fatigue

Pain and fatigue are common symptoms in JIA. As described above, the association between PA levels and pain is conflicting (8, 118-120, 125), while the association between pain and physical fitness is barely examined. Further, knowledge is limited regarding possible associations between fatigue and PA and physical fitness. One study suggested that fatigue may influence the PA levels negatively in JIA (130). Hence, when investigating PA and physical fitness in JIA, measures of pain and fatigue are relevant variables to include. Importantly, pain and fatigue are not disease specific symptoms and are relatively common complaints in the general pediatric population as well (191-193). Thus, we also wanted to measure pain and fatigue in the controls, and used a generic numeric rating scale (NRS) 0-10 (where 0 = no pain/fatigue, and 10 = worst pain/fatigue) to assess current pain and pain and fatigue during the previous week in all participants. NRS is recommended for measurement of pain in pediatric populations from the age of eight years (194, 195). Although not disease specific, we included pain and fatigue as disease variables in association analyses in all papers (Papers I-III) because these symptoms are common and important in JIA.

3.3.2.4 Blood sample

Standard laboratory values were obtained from a blood sample in all study participants including ESR, CRP, thrombocytes, hemoglobin and creatine kinase and analyzed according to hospital routine.

3.3.2.5 Disease characteristics of the patient group

JIA classification, disease duration and current use of medications were obtained from the patients' medical records.

We used the JADAS to evaluate disease activity (54). This is a validated composite score comprising four components of disease activity measures; number of joints with active disease, PGA measured on a 10-cm visual analogue scale (VAS) where 0 indicates no disease activity and 10 indicates severe disease activity, the patient/parent assessment of global well-being measured on a 10-cm VAS, where 0 indicates doing very well and 10 indicates doing very poorly, and the ESR (54). Originally three versions of the JADAS were developed based on 71- joint (range 0-101; JADAS 71), 27- joint (range 0-56; JADAS 27) and 10-joint (range 0-40; JADAS 10) counts. The JADAS sum score is calculated as the sum of these four components, where higher score indicates higher disease activity (54). We used the JADAS 71 as a measure of disease activity since we wanted a comprehensive joint assessment. Further, we also used the joint counts to examine if overall active arthritis and active arthritis in lower extremities were associated with PA and physical fitness.

We used the most recent criteria to define clinical inactive disease; the Wallace criteria published in 2011 (55). These criteria include; having no active arthritis; no fever, rash, serositis, splenomegaly or generalized lymphadenopathy attributable to JIA; no active uveitis; normal ESR or CRP; PGA rated at the best score possible for the instrument used, and duration of morning stiffness of $\leq$ 15 minutes.

3.3.2.6 Patient-reported outcome measures

The CHAQ is widely used to measure functional disability in JIA (59). Some disadvantages have been reported and the ceiling-effects may be of particular interest to our study (74, 196). A newer version of the CHAQ with different scoring systems has been developed by adding eight questions on more physically demanding items, which suffers less from ceiling-effects (197-200). This CHAQ version has not been translated to Norwegian. Despite the reported

ceiling-effects, we decided to measure functional disability by the Norwegian version of the original CHAQ (201) to be able to compare our patient population with previous studies. It comprises 30 questions, covering eight functional ability domains related to daily living during the past week (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities). The score ranges from 0-3 in each domain, of which a CHAQ disability index is calculated; a score of 0 indicates no disability and a score of 3 indicates severe disability.

The CHAQ also incorporates a double-anchored, horizontal 100 mm visual analog scale for assessment of the child's overall well-being and of the intensity of the child's pain during the previous week. The patients completed the CHAQ themselves, with assistant from their parents if needed. The score on the global assessment of well-being was used to calculate the JADAS 71 sum score.

As already described, we also used other patient-reported outcome measures, which additionally were reported by controls. These measures include the NRS measurements of pain and fatigue. Also, the questions regarding participation in PA and PE, and PA barriers and facilitators were patient-reported outcome measures, although these questions were asked through structured interviews.

3.4 Statistics analyses

All statistical analyses were conducted using the IBM SPSS Statistics for Windows, Versions 22-23 (IBM Corp. Armonk, NY, USA). The level of significance was set at $P < 0.05$ (two-sided).

Controls were matched individually to patients for age and sex, and one could argue that analyses comparing results between patients and controls should be conducted by using paired analyses. However, we used matching as a convenient method of drawing the control sample, and in such situations unpaired analyses are recommended (202). Moreover, we did not match patients and controls on important independent variables for physical fitness, i.e., physiological variables, hormone status, puberty status, height and weight. Thus, we chose to apply unpaired analyses when comparing results between patients and controls in all papers comprised in this thesis.

Descriptive analyses were used in all papers. Continuous measures that were found to be close to normally distributed are presented as means with standard deviations (SDs). Skewed

measures are presented as medians with the 25th percentile -75th percentile. Dichotomous variables are presented in frequencies and percentages.

Group comparisons were performed in all papers between patients and controls, between patients with persistent oligoarticular JIA and patients with polyarticular disease, and between patients with clinical active disease and patients with clinical inactive disease. Group comparisons of continuous variables that were close to normally distributed were performed by independent t-tests. Skewed measures were compared using Mann-Whitney U-tests. Dichotomous variables were compared by chi-square tests. Additionally, in Paper I we used analyses of covariance to examine differences between groups regarding PA intensities using accelerometer wear time as covariate. To be able to perform frequency analyses in Paper I, variables for PA and PE participation and PA facilitators and barriers were categorized and coded as reported (1) and not reported (0) according to the participant's responses.

We examined associations between disease variables and PA in Paper I and between disease variables and physical fitness in Paper II and Paper III. In Paper I and Paper II, multiple regression analyses were used to identify correlates for PA and physical fitness in patients. In paper I, the dependent variables included overall PA, VPA and sedentary time. In paper II, the dependent variables were VO_{2peak}, maximal knee extension strength and total body BMD (considered main outcomes for each component of physical fitness). Disease variables that were associated ($p<0.15$) with the dependent variables in univariate analyses were evaluated in multiple regression analyses (method enter). However, in Paper I we chose to include age, sex, and accelerometer wear time in the models regardless of significance since these variables could be confounders for the dependent variables. Highly correlated independent variables ($r > 0.7$) were avoided. Because the sample size did not allow us to simultaneously include all potential variables into the multiple linear regression models, we preselected a maximum of seven variables. In paper II, age and puberty status correlated highly, and we chose to include age over puberty status since the variable provided most power to the models. In Paper I, effect size for difference in PA intensities was determined by using the partial Eta Squared value, and was defined as small = 0.2, medium = 0.5 or large = 0.8 (203). In Paper I and Paper II, the results are presented as unstandardized betas with 95% confidence intervals (CIs). We used adjusted R^2, the proportion of variance in the dependent variable explained by the final model, as measure of goodness-of-fit. The amount of missing data was low; primarily accelerometry data was missing (less than 8 %). We chose to assess missing

data as missing completely at random, and no further adjustments were made. In Papers I and II the distribution of the residuals in the multiple regression analyses was explored graphically with P-P plots and histograms.

In Paper III, possible correlations between disease variables and VO_{2peak} and walking distance were tested with Spearman rank correlation. We defined a correlation coefficient <0.30 as small, 0.30-0.49 as medium and >0.49 as large (202).

In Paper III, the COSMIN panel recommendations for analyzing measurement properties were followed for the evaluation of criterion validity and reliability (115). The observed VO_{2peak} from the maximal treadmill test was considered the criterion measurement for the evaluation of criterion validity in both patients and controls. Criterion validity and reliability were analysed with intraclass correlation coefficient (ICC) and measurement errors were evaluated by calculating limits of agreement (LoA), standard error of measurement (SEM) and smallest detectable change (SDC). ICC > 0.70 was considered acceptable (115). The statistical analyses used to evaluate the measurement properties of the submaximal treadmill test are described in detail in Paper III.

A power analysis was conducted based on previous research on differences in VO_{2peak} between patients with JIA and controls (5, 6). With an alpha of 5% and power of 80% we would need at least 13 participants in each group. To be able to compare patient subgroups and to examine other study outcomes, we aimed at recruiting 60 patients (30 patients with persistent oligoarticular JIA and 30 patients with polyarticular disease) and 60 controls.

In general, a sample size of 50 participants is considered to be adequate when assessing reliability and validity (115). However, due to a rare disease and limited number of patients living at an acceptable distance to come for an additional day for re-testing, a statistician performed a power analysis to estimate the required sample size. To achieve an ICC of 0.85 with a 95% CI and an interval width of 0.2 (0.75 and 0.95), a sample size of 31 participants was needed to evaluate the reliability in patients.

3.5 Ethical considerations

All procedures complied with the Declaration of Helsinki (204), and the study was approved by the Norwegian South East Regional Ethics Committee for Medical Research (2014/188).

An additional change notification was approved by the same committee regarding the reliability study of the submaximal treadmill test in patients. All participants gave written informed consent to participate (the children themselves if aged ≥16 years and the parents/guardians of children aged <16 years together with the children's assent).

Research on children requires greater responsibility to ensure that children's needs and concerns are looked after. Even if parents have given permission for their children to participate and children have given their assent, special care should be taken to listen when children express a desire not to participate. In this study, all participants seemed highly motivated to participate during the examination day, including patients who returned to OUS for a second day of testing for the reliability study.

Patients performed all the physical fitness tests in conjunction with their routine follow-up at the hospital. The treating physician was responsible for follow-up in cases where medical problems were discovered during the examinations. In the case of abnormal values from the blood samples in controls, a letter, accompanied by the test results, was sent to the participant/parents/guardians as appropriate by age, advising them to contact their/their child's general practitioner for further follow-up.

The tests were considered to be of no harm or danger to the participants. The amount of radiation from DXA measurements is small (less than a day's exposure to natural exposure) and was considered acceptable. Participants that were inexperienced with treadmill performance were familiarized with this exercise mode until they felt safe to start the submaximal treadmill test. All participants performed the submaximal treadmill test prior to the maximal test to optimize the experience of treadmill performance before starting the maximal treadmill test involving exercising at maximal intensity. Both the submaximal and maximal treadmill tests were performed with close evaluation of HR and a panic button and an automatic electronic defibrillator were available in the test room. The physiotherapists (the PhD candidate and a pediatric physiotherapist) involved in treadmill testing were standing close to the treadmill during the tests. The test protocol was developed specifically for our study. Since patients with JIA may experience joint pain in the lower extremities during weight-bearing activities, this was accounted for in the protocol by increasing the incline more than the speed during the maximal test. There were no adverse events during the physical tests.

All participants were informed that the tests performed could result in transitory delayed onset muscle soreness, which is considered normal after completing many physical tests, particularly those of maximal intensity. Also, in our experience, many children dread taking blood tests; thus, we offered numbing cream to reduce pain during the procedure. The patients' blood samples were taken as part of their routine control and implicated no additional puncture of the vein. An extra blood sample of the study participants after completion of the maximal treadmill test was voluntary, and numbing cream was offered if wanted (data not included in this thesis).

3.6 User involvement in research

At the time we conducted our study, user involvement in research was neither commonly nor formally established. User involvement could have provided valuable information to our study. User involvement is now mandatory in research in specialized health care services and we would have included patient partners early in the research process if we were to start our study today.

4.0 Summary of results

4.1 Paper I

Physical activity in patients with oligo- and polyarticular juvenile idiopathic arthritis diagnosed in the era of biologics: a controlled cross-sectional study

The main objective of this study was to comprehensively examine PA in patients with JIA and controls. We aimed to compare objectively measured PA in patients with persistent oligoarticular JIA and polyarticular disease (extended oligoarticular JIA and polyarticular RF +/-) diagnosed in the era of biologics with controls and to examine associations between PA and disease variables; furthermore, to explore participation in PA and PE and facilitators and barriers for PA participation in patients and controls.

A cohort of 60 patients with JIA aged 10-16 years (30 persistent oligoarticular JIA/30 polyarticular disease) and 60 age- and sex-matched controls from the general population were included. There was a female predominance, with 83 % girls. There were no significant differences in age, height, weight, BMI, waist circumference and pubertal status between patients and controls or between patients with persistent oligoarticular JIA or polyarticular disease. Furthermore, patients and controls reported similar levels of pain and fatigue, as did patients with persistent oligoarticular JIA and polyarticular disease. Median (25^{th} -75^{th} percentile) JADAS 71 score and CHAQ score were 3.3 (1.1-4.8) and 0.0 (0-1.4), respectively. In total, 25 (42 %) patients used biologic DMARDs. More patients with persistent oligoarticular JIA were off medication and more patients with polyarticular disease used biologic DMARDs, but the current disease activity and functional disability were comparable between the two patient subgroups.

Patients spent less time in VPA than controls, while overall PA, steps daily, MPA, LPA and sedentary time did not differ. No differences were found between patients with persistent oligoarticular JIA and patients with polyarticular disease in any of the accelerometer variables. Furthermore, overall PA was similar between patients with clinical active and patients with clinical inactive disease. The use of biologic medication was the only disease variable associated with PA and was a correlate for higher overall PA and lower sedentary time. Additionally, lower age and participation in organized PA were identified as correlates

for higher overall PA, and lower age and accelerometer wear time were identified as correlates for lower sedentary time. Participation in organized PA was the only correlate for VPA.

Most patients and controls participated in organized or unorganized PA, and they participated in the same modes of activities. Enjoyment was the most reported facilitator for PA participation by both patients and controls. More patients than controls reported pain as a PA barrier. Nearly all patients (97 %) and controls (98 %) participated regularly in PE, but 27 % of patients reported that they occasionally needed modifications of some activities.

4.2 Paper II

Physical fitness in patients with oligoarticular and polyarticular juvenile idiopathic arthritis diagnosed in the era of biologics: a controlled cross-sectional study

The aims of the study were to perform a comprehensive evaluation of physical fitness in consecutive patients with JIA diagnosed in the era of biologics and to compare the results with those obtained in healthy controls; also to identify correlates for physical fitness in patients and to compare physical fitness between patients with persistent oligoarticular JIA and patients with polyarticular disease.

We included 60 patients with JIA aged 10-16 years (50 girls) (30 persistent oligoarticular JIA/30 polyarticular disease) and 60 age- and sex-matched controls from the general population. The mean age at examination was 13.6 years (SD 2.2) and 13.5 years (2.6) in patients and controls, respectively. Mean disease duration in patients was 7.5 (3.8) years.

We found that patients with JIA had lower muscle strength and total body BMD (absolute values and z scores) than matched controls, but observed no differences in CRF, body composition and lumbar spine BMD (absolute values and z scores). The maximal physiologic responses (RER and HR_{peak}) and ratings of perceived exertion at the end of the maximal exercise treadmill test for CRF assessment were comparable between patients and controls. All participants reported exhaustions as the reason for terminating the maximal treadmill test. Similar proportions of patients and controls stratified by sex had poor CRF. None of the participants had total body BMD z scores ≤ 2, while two patients had lumbar spine BMD z scores ≤ 2.

All components of physical fitness were comparable between the patients with persistent oligoarticular JIA and patients with polyarticular disease and also between patients with clinical active disease and patients with clinical inactive disease.

In patients, we identified higher VPA as a correlate for both higher CRF and muscle strength. Additionally, male sex and lower BMI were identified as correlates for higher CRF, while male sex, higher BMI and higher age were identified as correlates for higher muscle strength. For higher total body BMD, we identified female sex, higher age and higher total lean mass as

correlates. No disease related variables were identified as correlates for any components of physical fitness.

4.3 Paper III

Measurement properties and performance of an eight-minute submaximal treadmill test in patients with juvenile idiopathic arthritis; a controlled study

The main objectives of this study were to evaluate the measurement properties and submaximal performance of an eight-minute submaximal treadmill test in patients with JIA and controls.

Out of our cohort comprising 60 patients with JIA and 60 controls, one male patient and one male control were excluded due to missing data on the maximal treadmill test. Thus, 59 patients with JIA (50 girls; 30 persistent oligoarticular JIA/29 polyarticular disease) and 59 age- and sex-matched controls from the general population were included. Additionally, 37 (30 girls) of these patients also took part in the reliability study of the submaximal treadmill test. There were no significant differences between these two patient samples regarding demographic and disease specific variables.

We found no significant difference between the observed and estimated VO_{2peak} neither in patients (44.8 (8.8) vs 43.2 (10.3), respectively, P=0.18) nor in controls (46.5 (8.5) vs 44.6 (7.9), respectively, $P = 0.12$). The ICC (95 % CI) at group level was acceptable for criterion validity in patients, 0.71 (0.51-0.82), but not in controls, 0.52 (0.21-0.71). The ICC at individual level was neither acceptable in patients nor in controls. In patients, the test-retest reliability and inter-rater reliability measured by ICC were acceptable at individual (0.84 (0.71-0.91) and 0.92 (0.83-0.96), respectively) and group levels (0.91 (0.83-0.96) and 0.96 (0.91-0.98), respectively).

At individual level, the measurement errors were large for test-retest reliability and inter-rater reliability in patients, with SDC_{95} values indicating that a change in VO_{2peak} greater than 11.4 $mL \cdot kg^{-1} \cdot min^{-1}$ and 8.6 $mL \cdot kg^{-1} \cdot min^{-1}$, respectively, would be required to be 95% certain that a change would not be the result of measurement error, but of a real change. The measurement errors at group level were small, with $SDC_{95group}$ values indicating that a change in VO_{2peak} greater than 1.5 $mL \cdot kg^{-1} \cdot min^{-1}$ for the test-retest and 1.1 $mL \cdot kg^{-1} \cdot min^{-1}$ for the inter-rater reliability, respectively, would be required to be 95 % certain that a change would not be the result of measurement error, but of a real change.

The Bland-Altman plots showed no systematic differences, but confirmed the large variability for the criterion validity in both patients and controls, and also for the test-retest and inter-test reliability in patients.

The estimated VO_{2peak} and all other outcomes from the submaximal treadmill performance were comparable between patients and controls. These outcomes were also comparable between patients with persistent oligoarticular JIA and polyarticular disease, and between patients with clinical active and patients with clinical inactive disease. In patients, we found weak correlations between disease variables and estimated VO_{2peak} and walking distance (all r's<0.03, p=NS).

5 Discussion

5.1 Discussion on methodological aspects

5.1.1 Study design

Cross-sectional studies are descriptive and can be used to examine different outcomes in populations of interest and associations between variables of interest at a fixed point in time (205). We chose to conduct a comparative cross-sectional study because we had sparse knowledge of PA behavior and physical fitness in Norwegian patients with JIA who were diagnosed in the era of biologics. Moreover, there was limited knowledge internationally about these study outcomes and possible associations with measures of disease activity in patients diagnosed in the era of biologics. Even if patients are examined regularly with physical performance tests and asked about their PA habits during routine visits at our hospital, these methods were not standardized or appropriate for research purposes. Also, since reference material for the study outcomes were lacking, suboptimal regarding age range or considered old, we included the matched control group for comparison.

We chose to compare each patient with one control. More controls per case could have strengthened the study, but this was not possible due to restricted economy and time. The controls were tested within a year after the patients avoiding changes in PA behavior in society over time, which also could influence the physical fitness levels.

A limitation of the study is the cross-sectional design, which does not allow for conclusions of causality. Also, we studied cross-sectional associations between disease variables and measures of PA and physical fitness. There might be longitudinal associations between these variables even if we did not find associations in our cross-sectional analyses.

When investigating measurement properties of the submaximal treadmill test, we also used a cross-sectional design for the assessment of the criterion validity in patients and controls. Additionally, we used a test-retest design to assess reliability of the submaximal treadmill test in patients. Assessment of reliability should be measured in a stable population (115). This may be a challenge in JIA, as disease symptoms may vary from day to day. Unfortunately, we did neither perform any objective measurements of disease variables nor structurally collect

self-reported data (i.e., pain and fatigue) that could have impacted the test performance on the second test occasion. However, patients participating in the reliability study reported no major changes in an overall question regarding their disease status and pain between the two time points. We chose to test the patients on two occasions separated by one to four weeks, anticipating that a change in physical fitness was not to be expected in this time span.

5.1.2 Representativeness of study populations

A strength of the study was the consecutive recruitment of all eligible patients at our hospital, representing a real-world setting. Recruiting patients from a hospital setting could lead to inclusion of patients with more severe disease, but in Norway most patients with JIA have checkups in hospitals. Including patients from only one hospital might have introduced a weakness of the study, possibly reducing the generalizability of the findings to the Norwegian JIA population. However, OUS has the biggest pediatric rheumatology unit in Norway, and the included patients had a home address in a geographical area comprising 58% of the Norwegian population. Also, the publicly funded Norwegian health care system may increase the external validity. Additionally, the Norwegian National Advisory Unit on Rheumatic Diseases in Children and Adolescents (NAKBUR) is located at our hospital. NAKBUR aims to secure equal health care services across regional health authorities in Norway, for example by making treatment recommendations, which are made in collaboration with representatives from all regional health authorities. Nevertheless, slight differences may occur across regional health authorities.

The good access to biologic DMARDs and the possibility of relatively close follow-up by physiotherapists in Norway may reduce the generalizability of our findings to other countries with stricter criteria for initiating biologic DMARDs or less physiotherapy services available.

To be able to compare homogeneous JIA subgroups, we included patients with persistent oligoarticular JIA and polyarticular disease (extended oligoarticular JIA and polyarticular RF +/-). These JIA categories constitute approximately 75 % of the JIA population included in a JIA patient registry run at our hospital since 1999, which is similar to European JIA cohort studies (25, 27, 206). This indicates that our JIA cohort is representative regarding the distribution of persistent oligoarticular JIA and polyarticular disease populations in Europe. However, lower proportions of the included categories in our study are reported in other JIA cohorts (60-63%) (26, 207), possibly reflecting the different category distributions in different

countries and among ethnicities. Regardless of differences in category distribution geographically, the results of our work cannot be generalized to the JIA categories not included in our study. Thus, physical fitness and PA should be investigated in patients diagnosed in the era of biologic belonging to excluded JIA categories in future studies. Patients with ERA may be of particular interest to examine due to poor disease related outcomes reported recently (67, 68). Interestingly though, ERA patients had highest VO_{2peak} among JIA categories in a previous study, although the results are hampered by small sample size and not reporting sex distribution for JIA categories specifically (135). The most recent study reporting VO_{2peak} found no differences across JIA categories (7), but these results are also limited by small sample sizes in the categories we chose to exclude in our study.

In Norway, the health care system has allowed for early introduction of biologic DMARDs in JIA ever since 2000, securing that the patients are aggressively treated following international guidelines (49). All the patients in our JIA cohort were diagnosed after 2000, and the multidisciplinary management of these patients has since 2003 included individualized patient education. Our JIA cohort seems well treated, indicated by modest disease activity and low functional disability, comparable to recent studies of PA and physical fitness in JIA (7, 8, 31, 118-120). Also, patients' pain and fatigue scores were low and comparable to those reported by controls, supporting that patients were well treated. Even if patients were recruited consecutively, 37 % declined to participate. There is a possibility that patients enrolled in our study might be biased towards more physically active and fit patients with a milder disease than those who declined participation. We do not have data on patients declining participation due to ethical regulations. However, 42 % of our patients were treated with biologic DMARDs. In large JIA cohort studies, 12-24 % of patients were treated with biologic DMARDs (25-27), indicating that our study was not biased towards patients with mild disease.

We had more girls in our JIA cohort compared to other cohort studies (25, 27, 206). This could possibly be explained by the included categories and a higher study participation rate among eligible JIA girls than among boys (68 % vs 43 %). Thus, multiple regression analyses including sex as an independent variable should be interpreted with caution due to a low proportion of boys.

We consider it a strength of the study that patients were matched with controls randomly drawn from the National Registry. Yet, the response rate among controls was low, and lower than among patients, 20 % versus 62 %. The reason for this different response rate is not known, but a study focusing on PA and physical fitness may have led to a selection bias towards participants that were physically active and fit, particularly among controls. Patients with JIA and their parents might have a personal interest in contributing to research on their own disease regardless of their physical fitness and PA levels. Also, controls were recruited from Oslo and Akershus (mostly city, but some rural areas), while patients were recruited from both city and rural areas. This may be a limitation to the study because differences in PA and physical fitness levels with regards to home address have been described (208). Importantly, the results on CRF, muscle strength, PA levels and types of PA participation in the controls are in accordance with data from Norwegian population studies in children and adolescents, indicating that the controls are representative for the general population (185, 209).

Norwegian population studies indicate that children and adolescents with non-western immigrant background have lower PA levels compared to children and adolescents with a western background (193, 208). Our study does not reflect the proportion of children and adolescents with non-western immigrant background in the Norwegian population.

5.1.3 Assessors

The PhD candidate conducted the physical tests of the participants in Paper II and Paper III and was also responsible for the inclusion of participants. The PhD candidate might have had different expectations to the patient and control groups which could have influenced the results. However, test procedures were standardized and followed strictly. Moreover, physiologic responses and self-reported ratings of perceived exertion from the maximal and submaximal treadmill tests were similar between patients and controls, indicating equal intensity during testing.

Both assessors of the physical tests, the PhD candidate (all papers) and the physiotherapist conducting submaximal treadmill testing for inter-rater reliability evaluation (Paper III), had more than 13 years of experience in pediatric rheumatology, increasing the internal validity of our results.

5.1.4 Outcome measures

The same equipment was used for all measurements in patients and controls, strengthening the internal validity of the results. Additionally, all components of physical fitness were assessed by state-of-the-art methods. We did not experience any adverse events during any assessments. We had not used physical tests of maximal intensity in patients with JIA at OUS prior to this study, but patients completed these tests without any adverse events. The physiologic responses during treadmill testing suggested that patients and controls were tested at equal intensities, indicating that treadmill testing of both submaximal and maximal intensities is suitable in patients with JIA. All participants were able to complete the isokinetic muscle testing without difficulties other than experiencing tiredness in the tested leg immediately after completing the test.

The study participants self-reported data on some specific physical activities (swimming, bicycling and cross-country skiing) that are not accurately captured by accelerometry. Because our data from these self-reported activities did not differ between patients and controls, and in general accounted for a small amount of PA, we decided to not include data from the time spent on these self-reported activities in Paper I and Paper II, to keep the accelerometry data strictly objective. However, in other studies using accelerometry for PA assessment in JIA, such adjustments were applied, making direct comparison difficult (118, 119). Furthermore, hip-worn accelerometers mainly capture ambulatory PA, thus upper body movements and load carrying activities are underestimated. In our study, this is relevant as some participants reported performing strength training at home or in fitness centers, possibly resulting in PA behavior not captured by the accelerometers. However, this concerns both patients and controls, and the proportion reporting practicing strength training was comparable between patients and controls. Thus, the combination of objective and subjective measurement is a strength in our study. Yet, since no validated questionnaires were available to assess PA and PE participation and PA facilitators and barriers, we used a structured interview to assess these outcomes, which may be considered a weakness of the study.

We measured pain and fatigue with a generic unidimensional measure (NRS). Pain and fatigue are complex symptoms and it has been recommended to use both unidimensional and multidimensional measurements to capture the complexity of these symptoms (195, 210). Yet, due to the focus in our study, we chose to measure these symptoms in both patients and controls only by NRS to reduce total number of measurements for the participants.

5.1.5 Statistical considerations

To evaluate differences in PA behavior and physical fitness in patients and controls, we performed our sample size calculation based on reported differences in $VO2_{peak}$ between patients with JIA and controls, resulting in a need for at least 13 participants in each group. We decided to include more participants to be able to compare patient subgroups and to study other outcomes. Thus, 60 patients (30 patients with persistent oligoarticular JIA and 30 patients with polyarticular disease) and 60 controls, were considered appropriate sample size. Importantly, we did not perform any sample size calculation specifically for the evaluation of PA behavior in Paper I, and cannot rule out that this could have introduced a potential for type II errors.

Furthermore, all studies are explorative with analyses of many variables without adjustments for multiple testing increasing the risk of type I errors (211). Therefore, results must be interpreted with this in mind. However, we have defined main outcome variables in all studies.

In paper III, a strength of the study is that the COSMIN panel recommendations were applied to evaluate the criterion validity and reliability of the submaximal treadmill test. These recommendations are based on an international Delphi process and are the most recently published recommendations to evaluate measurement properties (115). Also, we used the gold standard test as criterion measurement. Further, the sample size was appropriate according to the general recommendations by COSMIN and a specific sample size calculation for the evaluation of reliability in patients. However, previous studies evaluating the measurement properties of the submaximal treadmill test have applied other statistical analyses, introducing some difficulties to compare the results.

5.2 Discussion of main results

5.2.1 Physical activity in patients with JIA (Paper I)

We found that patients with JIA had comparable overall PA with controls measured with accelerometers. This is in contrast to other studies using accelerometry, all reporting lower overall PA in patients with JIA compared to controls (8, 118, 119). The disease activity and functional disability were low in all studies, and all have a female predominance. Our results of comparable overall PA levels are also in contrast to studies measuring overall PA with self-

reported methods, showing lower overall PA levels in patients with JIA compared to controls (9, 31, 120, 122, 212). However, one recent study found similar results to ours (123), and the authors suggested that a treat-to-target strategy contributed to their results. At the time our study was conducted, we did not have a treat-to-target strategy in our hospital, but patients were treated according to international guidelines (49).

Most of the other objectively measured PA variables derived from cpm were also comparable between patients and controls, including MPA, LPA and sedentary time. Our results are in contrast to other accelerometer studies in JIA, reporting less MPA and LPA (118, 119) and more sedentary time (8) in patients compared to controls. However, our findings of lower VPA in patients compared to controls are in line with previous studies (8, 118, 119). In our study, the mean difference in VPA was 5 minutes. We argued in Paper I that even if the effect size was small, patients with JIA have been reported to have increased risk of subclinical atherosclerosis (213), and should therefore be encouraged to increase the time spent in VPA since VPA is needed to reduce the CVD risk. Further, we suggested that patients with JIA should reduce their sedentary time, although equally high in patients and controls (almost 10 hours daily). Our suggestions are supported by a recent study on children from the general population; replacing 10 minutes of sedentary time with MVPA showed beneficial associations with CVD risk factors, even though theoretically by using isotemporal substitution modelling. Similar replacement with LPA found no such benefits, indicating that higher PA intensities are important for cardiovascular health (214). Moreover, prolonged sedentary time has been suggested as an independent CVD risk factor in healthy children and adolescents, but a recent systemic review and meta-analysis concluded that there was no evidence for an association between sedentary time and cardiometabolic outcomes. As long as children and adolescents are sufficiently active (achieve WHO PA recommendations), sedentary time is not an independent risk factor for CVD (215). In contrast to other studies, we found comparable proportions of patients and controls that achieved the WHO PA recommendations (8, 119, 120). Yet, the high sedentary time spent by our participants and suboptimal proportion fulfilling the PA recommendations, underline the importance of increasing MVPA, and VPA in particular due to its importance for cardiovascular health.

We also reported number of steps daily and found no differences between patients and controls. We have not identified other studies comparing this variable between patients with JIA and controls. However, both the number of steps daily and cpm are measures of overall

PA; thus comparable levels of steps daily supports our findings of comparable overall PA levels measured by cpm.

As shown in Table 2, there are large variations in cut points for PA intensities between studies in JIA using accelerometry for PA measurement. By applying internationally accepted and recommended cut points (176, 177), our cut point values are substantially higher for both MPA and VPA compared to previous studies, making direct comparison of the time spent in different PA intensities and the proportion of patients achieving the WHO PA recommendations difficult.

Our results from the subjectively measured PA participation support our results from objectively measured PA. We found no differences between patients and controls regarding participation, type and amount of organized and unorganized physical activities. In contrast, other studies have reported lower participation in organized sports in patients with JIA compared to controls (127, 128), and also that patients participated in activities with lower intensities (127). Comparison of participation in unorganized PA between patients with JIA and controls has, to our knowledge, not been reported in previous studies. Patients have previously reported to participate more in unorganized than organized PA (126), which is in contrast to our results with a higher proportion of patients participating in organized than unorganized PA.

We found that 97 % of patients and 98 % of controls reported to always participate in PE, which is in accordance to a recent study (127). However, some aspects need mentioning; to be able to always participate, 27 % of our patients reported that they occasionally needed slight modification of activities, while Nørgaard et al. (127) reported that patients were less consistent in their participation compared to controls. Other studies reporting PE participation in patients with JIA are not controlled, but we found higher PE participation in our patients compared to these studies (120, 130-132). Importantly, different categories are used for PE participation, making comparison challenging. In our study, the category “always participating, but occasionally with modifications” emerged from the structured interviews. In contrast, some studies have categorized patients needing PE modifications to “sometimes participating”, which could partly explain the differences between studies. The category “always participating, but occasionally with modifications” in our study may reflect the Norwegian school regulations strongly advocating PE participation and use of activity modifications if necessary (81, 82).

In Paper I, enjoyment was by far the most reported PA facilitator in both patients and controls. This is in line with another controlled study (127), previous studies in JIA (133) and healthy children (216). PA barriers in our study were different between patients and controls, as more patients reported pain as a barrier compared to controls, while more controls reported time as a barrier. Pain is also reported as a PA barrier in previous studies in JIA (127, 133, 134). Even though pain was low in our patients, pain is a PA barrier that health professional should address in patient education. In a systematic review, lack of time has previously also been reported as the most reported PA barrier in healthy children (216).

5.2.2 Physical fitness in patients with JIA (Paper II and Paper III)

We found that CRF was similar between patients and controls, both measured directly with a maximal treadmill test and estimated through the performance on a submaximal treadmill test. In contrast, all previous studies have reported poorer CRF in patients with JIA compared to controls or reference values measured directly and estimated through performance on maximal tests (5-8, 118, 135-137) and submaximal tests (18, 138-140).

Because cycling involves less muscle mass, VO_{2peak} is underestimated by more than 8-10 % compared to treadmill testing (87).Thus, direct comparison of our VO_{2peak} values with those obtained in studies using cycle ergometer is difficult. Since the publication of Paper II, we have identified another study measuring VO_{2peak} directly using a treadmill test. However, in this study from Turkey (137), the VO_{2peak} values in both patients and controls are low (32.5 (6.7) vs 37.0 (5.9), respectively, $p<0.05$) compared to our results in patients and controls (45.1 (8.5) vs 46.5 (8.5), respectively, $p=0.38$). This might indicate that comparing CRF between populations from different countries may not be appropriate, particularly between countries with sociocultural differences. The Swiss study by Maggio et al. (8) obtained VO_{2peak} values of 39.3 (1.7) vs 45.3 (0.9), in patients and controls, respectively, $p=0.001$, thus comparable VO_{2peak} values with our controls, yet lower VO_{2peak} values in patients compared to our results. Importantly, the direct comparison of results must be made with caution because participants in our study were mean 3 years older since VO_{2peak} often may increase with age.

We found that the physiologic responses and levels of exhaustion were comparable between patients and controls. Further, exhaustion as reason for terminating the test was reported by all participants. Taken together, the results suggest that both patients and controls were tested at maximal intensity levels. In contrast, Maggio et al. (8) reported that patients had lower

physiologic responses compared to controls (patients were tested at lower intensities), which could partly explain the higher VO_{2peak} values in our patients. A possibly explanation of the higher physiologic responses in our patients could be that our patients had a lower number of joints with active arthritis.

The performance on the submaximal treadmill test was similar between patients and controls. Also, the mean HR and rating of perceived exertion were similar between patient and controls. The submaximal treadmill test has not been used in other studies with patients with JIA. However, our results from the submaximal treadmill test performance confirmed the results of comparable CRF measured directly in patient and controls in Paper II, and also previous results from a small Norwegian study that suggested good walking capacity in patients with JIA measured with the 6MWT (4).

Again, we believe that these encouraging results on CRF might be explained by the advances made regarding multidisciplinary management of JIA in the era of biologics. Interestingly, a study on renal-transplanted children found significantly higher VO_{2peak} in patients who received early physiotherapy, including a higher focus on PA, compared to a group of patients from a period where such interventions were not implemented (44.3 vs 33.5 VO_{2peak}) (217). This supports that focusing on PA in patient education is important for higher CRF in the management of pediatric populations with chronic diseases.

We found that patients had lower muscle strength and endurance in most of the assessed variables. This is in agreement with previous studies (144-148, 218). Some muscle variables were comparable between patients and controls, which is also in line with two studies, reporting comparable strength in a few of the muscle groups tested (147, 148). Differences in measurement methods and assessed muscle groups complicate further comparison. We have not identified isokinetic dynamometry for knee-muscle evaluation in controlled studies. However, isokinetic knee-muscle strength was assessed in a study that evaluated the magnitude of changes after intra-articular injections in unilateral knee arthritis in patients with JIA, but unfortunately we cannot compare our results with this study due to differences regarding machine hardware and test procedures (219).

We found comparable body composition in patients and controls. Similar results were recently reported (156). One study found lower lean mass and higher fat mass % in patients

compared to controls (218). Another study reported comparable lean mass, but higher fat mass % in patients compared to controls (154), while similar fat mass % also has been reported (155). Older studies have reported lower lean mass in patients compared to controls (152, 220). The advances in medical therapy and multidisciplinary management may possibly explain the more favorable body composition in recent studies.

In agreement with previous findings (149), our patients had lower total body BMD (absolute values and z scores) compared to controls. However, normal total body BMD compared to reference data has previously been reported (150). We used the same equipment (machine and software) as this study. Comparing the patients' total body BMD absolute values in the two studies, we see that our patients had slightly higher total body BMD. This may indicate that even though we found lower total body BMD when compared to our controls, the total body BMD in our patients may be close to normal. Further, the mean total body BMD z score in our patients was above 0, also indicating normal score compared to the software reference data. Additionally, none of our patients had z score values $\leq$ - 2, defined as below the expected range for age and sex.

We found no significant differences between patients and controls regarding lumbar spine BMD (absolute values and z scores) compared to controls, which line with some studies (150, 221, 222), yet in contrast to most of the studies included in a comprehensive review (149). The inconsistency in findings may be explained by differences in study populations, measurement methods, medication and time of inclusion.

5.2.3 Physical activity and physical fitness; associations with disease variables (Papers I-III)

In our regression models using overall PA, VPA and sedentary time as dependent variables, the use of biologic DMARDs was found to be a correlate for higher overall PA and lower sedentary time. To our knowledge, no other studies have identified use of biologic DMARDs as a correlate for PA in patients with JIA. This surprising association may possibly reflect the effectiveness of these medications. Additionally, patients using biologic DMARDs may have been provided with more patient education about the importance of PA due to more contact with health professionals than patients with less severe disease not using biologic DMARDs. No other disease variables were identified as correlates for PA in our patients. In contrast, other studies have reported other disease variables as correlates for PA levels. A study by Bos et al. found that worse wellbeing and less pain were correlates for lower overall PA (measured

by activity diaries), lower MVPA and higher sedentary time. In addition, a higher CHAQ score was a correlate for lower MVPA (120). Nørgaard et al. found that ESR was the only variable that remained significantly associated with overall PA in the regression model. The other variables in the regression model included disease activity (JADAS 27), swollen joints, joints with limited motion and 6MWT, however not with unique significant contributions to the model (118). In another study by Nørgaard et al., disease activity (JADAS 27) was identified as correlate for lower MVPA, while no disease variables were found as correlates for VPA and overall PA (124). Other studies have reported associations between PA and disease variables using univariate linear regression analyses or correlation analyses. These disease variables included disease activity (118, 124), arthritis in lower extremities (118, 119), fatigue (130) and pain (125), which are in contrast to our findings. However, in agreement with our findings, other studies found no association with pain (8, 118, 119).

The other correlates for PA that we found were similar to those found in healthy children (208, 216, 223). Lower age was identified as correlate for higher overall PA and lower sedentary time, while participation in organized PA was a correlate for higher overall PA and VPA. In our study sex was not identified as correlate for PA, in contrast to results in healthy children. However, due to low proportion of boys in our study, this finding should be interpreted with caution.

Improvements in the multidisciplinary management of JIA given to patients that are diagnosed in the era of biologics might be a plausible explanation for the lack of disease variables as correlates for PA in our study (apart from use of biologic DMARDs).

In Paper II, we found that none of the disease variables were correlates for any component of physical fitness in our regression models in patients. Correlates identified for physical fitness in our patients were similar to those found in healthy children and will be discussed in the following.

Male sex, lower BMI and higher VPA were correlates for higher CRF in our patients. To the best of our knowledge, regression models have not been applied in previous studies for identification of correlates for CRF in patients with JIA, thus there are no existing models available for comparison. However, some studies have reported associations between CRF and disease variables by applying correlation or univariate linear regression analyses. Thus, we can compare results from our univariate linear regression analyses used for identification

of possible independent variables for inclusion in our models. In univariate analyses, we found that CRF showed an inverse association with pain and fatigue during the previous week. Yet, these disease variables did not reach significance in our regression model. This may suggest that the association were week or mediated through other variables. Pain and fatigue have not been reported to be associated with CRF in previous studies. However, CRF have been found to inversely associate with disease activity (6-8), articular limitations (8), swollen, limited and active joints, CRP, ESR, thrombocytes and hemoglobin (7). In contrast, we found no associations with these disease variables. Furthermore, in Paper III we found weak correlations between disease variables and estimated VO_{2peak} and walking distance, supporting our findings in the regression model. The stronger correlations between CRF and disease variables in previous studies may be explained by more joints with active arthritis, higher disease activity and higher inflammation markers in patients included in those studies compared to our JIA cohort.

In our patients, correlates for higher muscle strength were male sex, higher age, higher BMI and higher VPA. We are not aware of previous studies that have examined associations between muscle strength and disease variables. However, our correlates for muscle strength are in line with findings in healthy children (224).

We found that female sex, higher lean mass and higher age were correlates for total body BMD. In line with a previous study, we did not identify any disease variables as correlates for total body BMD (150). In contrast, other studies have found that higher disease activity, medication use, longer disease duration and higher functional disability were associated with lower total body BMD (149, 225, 226). In our univariate linear regression analyses, CHAQ was negatively associated with total body BMD, but the significance did not remain in multiple regression analyses. In healthy children, higher lean mass and higher age are also important for higher BMD (227, 228).

Contrary to our hypothesis, we found comparable levels of objectively measured PA and physical fitness (all components, including submaximal performance) between patients with persistent oligoarticular JIA and patients with polyarticular disease. In contrast, previous studies have reported better CRF and higher PA levels in patients with persistent oligoarticular JIA compared to other JIA categories (6, 118). As mentioned in section 5.1.2, comparing our results with other studies can be challenging due to the JIA categories we included in our study. The proportions of categories vary between studies, but in general,

persistent oligoarticular JIA and patients with polyarticular disease comprise the biggest proportions of patients. Furthermore, we did not find any differences in overall PA levels and physical fitness (all components, including submaximal performance) between with patients with clinical inactive disease and patients with clinical active disease. These findings, together with our results from the regression analyses, indicate that disease variables are less important for PA levels and physical fitness in patients diagnosed in the era of biologics provided with modern multidisciplinary management. Our findings implicate that the PA recommendations for children and adolescents to perform VPA and muscle- and bone-strengthening activities at least three days per week also should be applied in JIA.

5.2.5 Measurement properties of the submaximal treadmill test (Paper III)

We found acceptable criterion validity at group level for the submaximal treadmill test in patients with JIA. Previous studies have reported that the submaximal treadmill test is valid in healthy adults (183, 184) and women with rheumatic diseases (143). In contrast, we found that the criterion validity neither was acceptable at individual level in patients nor controls, nor at group level in controls. Our findings indicate that the submaximal treadmill test is valid for research purposes at group level in patients with JIA.

There were large limits of agreement and no systemic bias in patients and controls regarding the criterion validity at individual level. Agreement analyses were not performed in previous studies, but systematic overestimation when testing at moderate intensity (70 % of predicted HR_{peak}) and systematic underestimation when testing at low intensity (50 % of predicted HR_{peak}) have been reported (184). Direct comparison must be made with caution due to different statistical analyses approaches, yet the limits of agreement for VO_{2peak} in our study were considerably larger that the previously reported systematic over- and underestimation of VO_{2peak}.

In patients, test-retest reliability and inter-rater reliability were acceptable at individual and group levels. This is in line with findings in women with rheumatic disease, reporting reliability on group level (143). Due to the reported systematic over- and underestimation of VO_{2peak} depending on test intensity, it has been recommended to test the individual at the same HR intensity when the purpose is to evaluate individual change (184). Thus, we tested the participants at same individual HR intensity (close to 70 % of predicted HR_{peak}) in all assessments of the submaximal treadmill test. We found large measurement errors for test-

retest reliability and inter-rater reliability at individual level, which must be taken into account if the submaximal treadmill test is used to evaluate change in individual patients. The measurement errors were small at group level, suggesting that the submaximal test is reliable for research purposes. Measurement errors have not been reported in previous studies evaluating the reliability of the test.

The less favorable measurement properties found in our study might possibly be explained by differences in statistical analyses applied and that the equation for VO_{2peak} estimation originally was developed in an adult population, and it may be questionable if the equation is appropriate for VO_{2peak} estimation in the age range of our study participants.

6 Conclusions

The following conclusions can be drawn concerning the specific aims of the study:

- Patients and controls had comparable objectively measured overall PA levels. Also, there were no differences in LPA, MPA and sedentary behavior between patients and controls, but patients spent less time in VPA.
- Most of both patients and controls participated in organized and/or unorganized PA, and patients participated in similar physical activities as controls. Almost all patients and controls participated regularly in PE, but 27 % of patients reported that they occasionally needed minor adaptations to some activities to be able to participate. The most reported facilitator for PA was enjoyment in both patients and controls, while more patients reported pain as a PA barrier.
- Use of biologic DMARDs was the only disease variable identified as correlate for PA, and was associated with higher overall PA and lower sedentary behavior. The other identified correlates for PA behavior were similar to those established in healthy children.
- Patients had comparable CRF, body composition and lumbar spine BMD compared to controls, but lower muscle strength and endurance and total body BMD.
- No disease variable was identified as correlate for any of the components of physical fitness. Higher VPA was identified as correlate for higher CRF and muscle strength.
- Objectively measured PA levels and physical fitness did not differ between patients with persistent oligoarticular JIA and patients with polyarticular disease.
- In patients, the submaximal treadmill test showed acceptable criterion validity at group level, but not at individual level. Neither at group nor at individual level was the criterion validity acceptable in controls.
- In patients, the reliability of the submaximal treadmill test was acceptable, but with large measurement errors for both test-retest- and inter-rater reliability.

7 Clinical implications and future perspectives

This thesis shows encouraging results regarding PA behavior and physical fitness in JIA patients diagnosed in the era of biologics who have been provided with modern multidisciplinary management. Our results suggest that disease variables no longer are associated with PA and physical fitness, important outcome measures in JIA. Yet, lower muscle strength and endurance, total body BMD and VPA were found in patients compared to controls. These results indicate that there is still room for improvements in the multidisciplinary management of JIA. VPA was identified as a correlate for both higher CRF and higher muscle strength. Thus, patients should perform 60 minutes of MVPA daily, and specifically also perform VPA and muscle- and bone-strengthening activities at least three times per week according to recommendations from health authorities to optimize the health benefits of PA. Importantly, patients and their parents can be reassured that CRF, body composition, PA participation and most PA levels in JIA today are comparable to peers. Our findings reinforced the importance of enjoyment for PA behavior in both patients with JIA and children and adolescents from the general population. Health professionals involved in patient education should emphasize encouraging patients to participate in PA that they find enjoyable. Also, the importance of VPA and muscle- and bone-strengthening activities at least three times per week should be highlighted in patient education, in addition to the recommendation of 60 minutes of MVPA daily. Further, it is still important to address possible PA barriers, like pain, in patient education, even in patients with mild disease and low self-reported pain.

The submaximal treadmill test was valid and reliable on group level in patients with JIA, thus appropriate for research purposes. The validity was not acceptable at individual level. Therefore, if the test is to be used in clinical practice in individual patients, it is important to take the large limits of agreements into consideration. Even if the test is not optimal to estimate VO_{2peak} in individual patients, the test might still give valuable information about submaximal performance in clinical settings on other measures than VO_{2peak}, e.g., HR, rating of perceived exertion and walking distance. There are still patients who have low PA levels and poor CRF, and using the submaximal treadmill test in these patients may be helpful to tailor the treatment.

Due to the cross-sectional design of our study and novelty of some results, PA behavior and physical fitness should be explored further in future studies in patients with JIA who are diagnosed in the era of biologics, preferably also with more boys included. Importantly, future studies should examine PA and physical fitness in JIA categories not included in this thesis. Prospective studies are also warranted.

We have collected data in our study that are not analysed yet, which may contribute to extend knowledge about PA and physical fitness in JIA. In pediatric rheumatology, theoretical models have been proposed on possible anti-inflammatory effects from exercise, but clinical studies are scarce. Analyses of blood samples from our patients and controls may contribute to this aspect, at least the acute responses to exercise. Also, investigating possible differences in visceral adipose tissue between patients and controls may be of relevance.

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RESEARCH ARTICLE Open Access

Physical activity in patients with oligo- and polyarticular juvenile idiopathic arthritis diagnosed in the era of biologics: a controlled cross-sectional study

Kristine Risum[1,2*], Bjørge Herman Hansen[3], Anne Marit Selvaag[4], Øyvind Molberg[4,5], Hanne Dagfinrud[2,6] and Helga Sanner[4,7,8]

Abstract

Background: Knowledge about objectively measured levels of physical activity (PA) and PA participation (included facilitators and barriers for PA) in patients with juvenile idiopathic arthritis (JIA) diagnosed in the era of biologics is limited. We aimed to compare objectively measured PA in patients with oligo- and polyarticular JIA diagnosed in the biologic era with controls and to examine associations between PA and disease variables; furthermore, to explore participation in PA, physical education (PE) and facilitators and barriers for PA participation in patients and controls.

Methods: The study cohort included 60 patients (30 persistent oligo JIA/30 poly-articular disease) and 60 age- and sex-matched controls. Age range was 10–16 years and 83% were female. PA was measured with accelerometry for seven consecutive days. Disease activity, current treatment, disease duration, functional ability, pain and fatigue were assessed. Structured interviews were applied to explore participation in PA and PE, and PA facilitators and barriers.

Results: Patients spent less time in daily vigorous PA than controls, (mean(SE) 21(2) min vs. 26(2) min, $p = 0.02$), while counts per minute (cpm), steps daily, sedentary time and light and moderate PA did not differ. No differences were found between JIA subgroups. The use of biologic medication was associated with higher cpm and lower sedentary time. Most patients and controls participated in organized or unorganized PA and PE, and enjoyment was the most reported facilitator for PA participation. More patients than controls reported pain as a PA barrier.

Conclusion: The PA levels and participation in patients with oligo- and polyarticular JIA are mostly comparable to controls, but patients still need to be encouraged to increase vigorous PA. Enjoyment is the most important facilitator for PA participation in patients with JIA.

Keywords: Juvenile idiopathic arthritis, Physical activity, Sports, Exercise, Facilitators, Barriers, Biologics, Pediatric rheumatology

* Correspondence: krisum@ous-hf.no
[1]Section for Orthopaedic Rehabilitation, Oslo University Hospital, Rikshospitalet, Postboks 4950 Nydalen, 0424 Oslo, Norway
[2]Department of Health Sciences, Institute of Health and Society, Faculty of Medicine, University of Oslo, Oslo, Norway
Full list of author information is available at the end of the article

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Background

Juvenile idiopathic arthritis (JIA) is the most common pediatric rheumatic disease [1]. The progress in medical therapy has caused a paradigm shift in the management of these patients, reflected by a strong focus on early aggressive treatment, including methotrexate and selective immune-modulators (so-called biological drugs) in recent international guidelines [2]. Accordingly, physiotherapists working with patients with JIA today can focus more on promoting physical activity (PA).

There have been concerns about disease triggering adverse effects of intense PA in JIA, but studies support that exercise is safe [3, 4]. Associations between PA and JIA disease variables are not conclusive. Some studies reported that lower levels of PA were associated with higher disease activity [5, 6], arthritis in weight-bearing joints [6, 7], more pain [8, 9] and lower wellbeing [8], while others did not find any such associations [10, 11].

There is no gold standard method available for measuring PA in children; both *objective* methods including accelerometry, and *subjective* methods like diaries and questionnaires have been applied. Accelerometry is often considered the best option since the method reduces recall bias and social-desirability bias [12]. However, regardless of method used, available studies indicate that patients with JIA have lower levels of PA, spend less minutes in moderate to vigorous PA (MVPA) and more time sedentary than healthy controls despite advances in the multidisciplinary management of JIA [6–8, 10, 11, 13, 14].

The World Health Organization (WHO) recommends children with and without disabilities to do a minimum of 60 min of MVPA daily [15]. Previous studies indicate that patients with JIA meet these recommendations less frequently than healthy controls [6–8, 10]. Vigorous PA (VPA) is considered more beneficial for health outcomes than moderate PA (MPA) [16, 17]. Knowledge is sparse on objectively measured PA levels and intensities in patients with JIA diagnosed in the era of biologics and whether their PA behavior is optimal to gain health benefits. Furthermore, these patients seem to participate more in unorganized than in organized PA [18, 19], but PA facilitators and barriers need to be identified [20]. Also, little is known about participation in physical education (PE) in school. Increased knowledge about PA participation is needed to help health professionals promote a physically active lifestyle for patients with JIA.

Thus, the objectives of this cross-sectional study were to 1) compare objectively measured levels and intensities of PA between JIA subgroups (oligo- and polyarticular) diagnosed in the era of biologics and an age- and sex-matched control population; 2) to assess differences in PA between JIA subgroups and examine associations between PA and disease variables and 3) to explore participation in PA and PE and facilitators and barriers for PA in the patients and the matched controls.

Methods

Study participants

The inclusion criteria for patients were: (A) age 10–16 years, (B) disease duration > 6 months (to ensure that patients had started anti-inflammatory medication if needed), (C) JIA classified as persistent oligoarthritis or polyarticular disease (extended oligoarthritis and polyarticular RF +/−) according to the International League of Associations for Rheumatology (ILAR) criteria [21], and (D) home address in the geographical area served by the South-Eastern Norway Regional Health Authority. This area has a denominator population of 2.8 million (57% of the Norwegian population).

Patients were excluded if they had comorbidities associated or potentially associated with, impaired cardiopulmonary fitness (e.g heart- or lung disease), severe orthopedic conditions, recent surgery or inability to walk. These exclusion criteria were applied because the patients were also included in a parallel study with compulsory exercise tests.

We consecutively recruited eligible patients with a planned routine visit at Oslo University Hospital (OUS), during 2015 until the predefined number of 30 in each subgroup was reached.

Individually age- and sex-matched controls from the general population (living in or nearby Oslo) were randomly selected from the National Registry (a registry of all individuals living in Norway), and were invited to participate by mail. Exclusion criteria for the controls were inflammatory rheumatic or autoimmune disease, severe heart or lung disease, or other diseases involving mobility problems.

All participants provided written informed consent/assent. The study was approved by the Norwegian South East Regional Ethics Committee for Medical Research (2014/188).

Data collection and clinical examination

All patients were clinically examined in conjunction with their routine visit at OUS between January and August 2015. All controls were examined during a one-day program between November 2015 and March 2016 at OUS. Height and bodyweight were measured to the nearest 0.1 cm and 0.1 kg, respectively, with participants wearing light clothes and no shoes. Body mass index (BMI) was calculated and the age- and sex-specific BMI cut-off values were used to categorize the children as normal weight, overweight or obese [22] . Pain and fatigue were assessed with the following questions: “How do you rate your pain/fatigue in the previous week?” and “How do you rate your current pain?” We used the numeric rating

scale (NRS) 0–10, where 0 = no pain/fatigue and 10 = worst possible pain/fatigue [23]. ESR and CRP were analyzed according to hospital routine.

Objectively measured physical activity

Volume and intensity of PA were measured using Actigraph GT3X+ accelerometers (ActiGraph, Pesacola, FL, USA), which measures bodily acceleration. Participants were instructed to wear the accelerometer for seven consecutive days during waking hours, except during swimming, bathing, and other water activities since the device is not waterproof. The accelerometer was worn on an elastic belt at the waistline on the right side of the hip. The participants noted time spent on swimming, cycling and skiing, as the accelerometer does not capture these physical activities accurately. Movement is detected as a combined function of the frequency and intensity of movement. Vertical axis count data were exported from the device in 10-s epochs using the ActiLife 6 software (ActiGraph, Pesacola, FL, USA). The raw data were converted to mean *counts per minutes* (cpm) (our main outcome) and mean *steps per day* to reflect the general level of PA. We applied the most used cut-off points regarding PA intensities in children; sedentary time (< 101 cpm), light PA (LPA) (≥101 to ≤2295 cpm), moderate PA (MPA) (≥2296 to ≤4011 cpm) and vigorous PA (VPA) (> 4011 cpm) [24]. Non-wear periods were defined as consecutive strings of zero counts lasting at least 10 min. In order for a day to be deemed valid, participants had to accumulate at least 8 h of valid wear. Only participants who had worn the accelerometer for at least 3 days were included in the analyses.

Subjectively measured physical activity

To explore participation in PA and PE, and facilitators and barriers for PA participation, a senior physiotherapist (KR) performed a structured 15–20 min interview with all participants individually. The participants could choose if they wanted parent(s) to be present during the interview. The interview guide was developed for this study by two physiotherapists and one nurse (all experienced in pediatric rheumatology), based on literature review and clinical experience. The questions included were: 1) Do you participate in any organized and/or unorganized physical activity? If yes, which activity/activities? 2) Do you perceive barriers to being physical active? If yes, how? 3) Do you perceive facilitating factors to being physical active? If yes, which? and 4) Do you participate in physical education classes in school? If yes, how often? If the participants replied positively to the initial question, follow-up questions were asked. If needed, the interviewer provided some examples during the follow-up questions. The responses were written down during the interviews.

Assessment of disease variables in patients

Disease activity was assessed by the Juvenile Arthritis Disease Activity Score 71 (JADAS 71) [25]. The children's score of the patients/(parents) global assessment was used to calculate the JADAS 71 score. The joint assessments were performed by a senior physical therapist (KR). Clinical inactive disease (CID) was defined according to the Wallace criteria [26]. Disease duration and medication history were obtained from the patients' medical records. The Childhood Health Assessment Questionnaire (CHAQ) was used to measure functional ability [27, 28]. The children completed the CHAQ, with assistance from their parents if needed.

Statistical analysis

Continuous data were expressed as mean (standard deviation (SD) or median (25th–75th percentile) as appropriate and categorical data as n (%). Independent sample t tests, analyses of covariance, Mann Whitney U tests or chi-square tests were used to assess differences between patients and controls and between patient subgroups as appropriate. Linear regression analyses were used to identify correlates of cpm, vigorous PA and sedentary time in patients. Disease related variables that were associated ($p < 0.15$) with the outcome variables in univariate analyses, were evaluated in the multivariate analyses (method enter), adjusted for age, sex, and accelerometer wear time. To be able to perform frequency analyses, variables for PA and PE participation, facilitators and barriers were categorized and coded as reported (1) and not reported (0) according to the participant's responses. Statistical tests were conducted using SPSS version 23.0 (SPSS, Chicago, Illinois, USA). P values < 0.05 were considered statistically significant. Due to multiple statistical analyses, p-values close to 0.05 should be interpreted with caution. Effect size for difference in PA categories was determined by using the partial Eta Squared value, and were defined as small = 0.2, medium = 0.5 or large = 0.8.

Results

Study participants

Of all patients who were invited to participate, 60/96 (63%) accepted (Fig. 1); this included 10/22 (45%) of the invited boys and 50/74 (68%) of the invited girls. The JIA patient cohort consisted of 60 consecutive patients, 30 with oligoarthritis and 30 with poly JIA. In the poly JIA group, 15 patients had poly JIA from disease onset (14 of these were RF÷, and one was RF+) and 15 had an extended oligo JIA (Fig. 1).

Health related measures in patients and controls

Measures of height, weight and BMI did not differ between patients and controls (Table 1). Two patients and six controls were categorized as overweight, while two

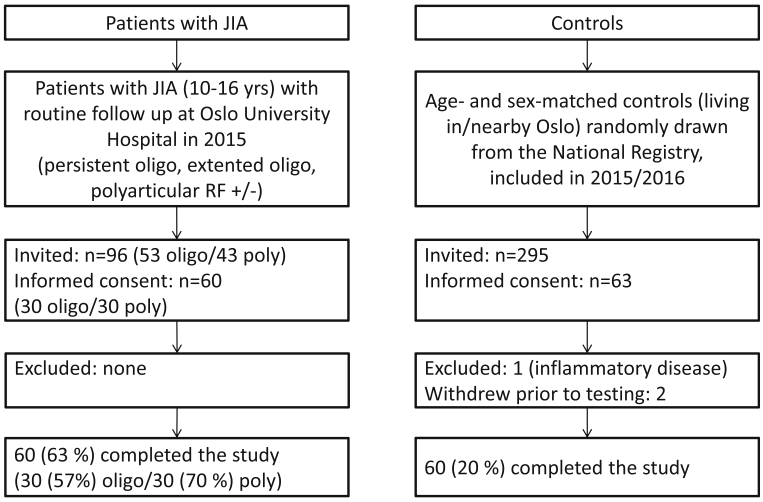

Fig. 1 Flowchart over participant inclusion. *JIA* juvenile idiopathic arthritis, *RF* rheumatoid factor

Table 1 Characteristics of patients with JIA and controls

	Oligo JIA ($n = 30$)	Poly JIA ($n = 30$)	*P*-value oligo vs poly JIA	JIA total ($n = 60$)	Controls ($n = 60$)	*P*-value JIA total vs controls
Age (yrs)	13.5 (2.2)	13.7 (2.2)	0.62	13.6 (2.2)	13.5 (2.6)	0.86
Female sex, n (%)	27 (90)	23 (77)	0.17	50 (83)	50 (83)	1.00
Height (cm)	157.1 (11.8)	158.7 (13.6)	0.64	157.9 (12.6)	161.2 (12.6)	0.16
Weight (kg)	47.0 (10.1)	51.5 (16.2)	0.21	49.3 (13.8)	53.5 (15.4)	0.12
BMI (kg/m^2)	18.8 (2.1)	20.1 (4.4)	0.17	19.4 (3.5)	20.2 (3.5)	0.26
NRS current pain (0–10), n (%) with score > 0	12 (40)	11 (37)	0.76	23 (38)	18 (30)	0.34
NRS pain previous week (0–10)	0.0 (2.0–3.3)	1.0 (0.0–3.5)	0.58	1.0 (0.0–3.0)	1.0 (0.0–3.0)	0.67
NRS fatigue previous week (0–10)	3.5 (2.0–6.3)	3.0 (2.0–5.3)	0.61	3.0 (2.0–6.0)	3.0 (1.0–3.5)	0.09
CRP > 4 mg/l, n (%)	1 (3)	2 (7)	1.00	3 (5)	0 (0)	0.24
Physiotherapy regularly, n (%)	3 (10)	10 (33)	0.03	13 (22)	4 (7)	0.04
Disease duration (yrs)	7.6 (3.9)	7.3 (4.0)	0.74	7.5 (3.8)	NA	
JADAS 71 (0–101)	3.3 (0.8–4.8)	3.2 (1.4–4.6)	0.80	3.3 (1.1–4.8)	NA	
CHAQ (0–3)	0.1 (0.0–0.3)	0.0 (0.0–0.4)	0.62	0.0 (0–1.4)	NA	
Off medication, n (%)	10 (33)	2 (7)	0.02	12 (20)	NA	
NSAIDs regularly, n (%)	9 (30)	7 (23)	0.56	16 (27)	NA	
Synthetic DMARDs, n (%)	18 (60)	22 (73)	0.27	40 (67)	NA	
MTX, n (%)	17 (57)	21 (70)	0.28	38 (63)	NA	
Sulfasalazine, n (%)	1 (3)	1 (3)	1.00	2 (3)	NA	
Biologic DMARDs, n (%)	5 (17)	20 (67)	< 0.001	25 (42)	NA	
TNFi, n (%)	5 (17)	18 (60)	0.001	23 (38)	NA	
IL-6i, n (%)	0 (0)	2 (7)	0.49	2 (3)	NA	
Synthetic+biologic DMARDs, n (%)	5 (17)	14 (47)	0.01	19 (32)	NA	
Active disease, n (%)	18 (60)	22 (73)	0.27	40 (67)	NA	
Clinical inactive disease, n (%)	12 (40)	8 (27)		20 (33)	NA	

Numbers are mean (SD) or median (25th -75th percentile) unless otherwise indicated

JIA juvenile idiopathic arthritis, *Oligo JIA* persistent oligoarticular JIA, *Poly JIA* extended oligoarticular JIA and polyarticular JIA RF +/–, *JIA total* persistent oligoarticular JIA, extended oligoarticular JIA and polyarticular JIA RF +/–, *RF* rheumatoid factor, *BMI* body mass index, *NRS* numeric rating scale, *CRP* C-reactive protein, *JADAS* juvenile arthritis disease activity score, *CHAQ* childhood health assessment questionnaire, *NSAIDs* non-steroid anti-inflammatory drugs, *DMARDs* disease modifying anti-rheumatoid drugs, *MTX* methotrexate, *TNFi* tumor necrosis factor inhibitors, *IL-6i* interleukin-6 inhibitor, *NA* not applicable

patients and two controls were categorized as obese. Patients and controls reported comparable levels of current pain and similar levels of pain and fatigue during the previous week. Only three patients and none of the controls had CRP > 4 mg/l, whereas all patients and controls had normal range ESR values.

Disease characteristics and treatment in the JIA cohort

The patients in both JIA subgroups had relatively modest disease activity (Table 1), and their functional limitations were in the range of no to mild measured by CHAQ [29]. Fifteen (25%) of the patients had active joint disease (range one-two joints), with affliction of lower extremities in nine patients, the upper extremities in five, the neck in one, and the temporomandibular joint in one. Current treatment is shown in Table 1. Twenty-five (42%) of patients used biologic DMARDs, most commonly TNFi; of the 35 (58%) patients not on biologics, 25 had oligo- and 10 polyarticular JIA. None of the patients were on corticosteroids.

Objectively measured physical activity

One patient did not return the accelerometer and four patients and four controls had less than three valid wear days and were therefore excluded from the analyses. Thus, acceptable data from the accelerometers were retrieved in 55 patients (47 girls and eight boys) and 56 controls (47 girls and nine boys) (Table 2). We found no differences between patients and controls regarding cpm, steps daily, sedentary time, LPA, MPA or proportion achieving the WHO recommendations for MVPA. However, the patients spent less time in daily VPA than the controls, mean (SE) 21 (2) min vs 26 (2) min respectively, $p = 0.02$. The effect size was small (partial Eta Squared = 0.05). Adjusting the analyses for wear month did not alter any findings. Self-reported time spent on swimming, bicycling and skiing were generally of short duration and were not significantly different between patients and controls, and therefore not included in the analyses.

No significant differences in accelerometer variables were found between the included JIA subsets (Table 2). Thus, the regression analyses were conducted for the JIA sample as one group. Also, no significant difference was found between patients with CID and controls for cpm; mean (SD) 465 (215) vs 479 (132), $p = 0.74$.

Correlates of physical activity in patients with JIA

For cpm, use of biological medication and participation in organized PA were identified as correlates, in addition to lower age (Table 3). For VPA, only participation in organized PA was identified as a correlate. For lower sedentary time, lower age and using biological medicine were significant correlates, in addition to accelerometer wear time. Disease variables that were not associated with the outcome variables in univariate analyses ($p > 0.15$) included: use of any medication, use of methotrexate, CRP, ESR, having active joints, having active joints in the lower extremities, JADAS 71, CHAQ, disease duration, current pain, and pain and fatigue during the previous week.

Participation in physical activities and physical education

Participation in organized and unorganized PA were not significantly different between patients and controls (Table 4). The most commonly practiced organized and unorganized modes of PA are shown in Table 4. Nearly all the patients (58 (97%)) and the controls (59 (98%)) reported that they participated regularly in PE (Table 4). However, 25% of the patients reported that they occasionally needed some modification of the activities in PE at school.

Facilitators and barriers for physical activity

Barriers for participating in PA were reported by 26 (43%) patients and 19 (32%) controls. The most reported

Table 2 Physical activity measured by accelerometers in patients with JIA and controls

Accelerometer variables	Oligo JIA ($n = 28$)	Poly JIA ($n = 27$)	*P*-value oligo vs poly JIA	JIA total ($n = 55$)	Controls ($n = 56$)	*P*-value JIA total vs controls
Counts per minute [a]	437 (140)	478 (233)	0.43	457 (91)	479 (132)	0.48
Steps daily [a]	8932 (2307)	9563 (2951)	0.38	9242 (2637)	9694 (2572)	0.36
Sedentary PA daily (min) [b]	580 (11)	573 (11)	0.63	577 (7)	573 (7)	0.86
Light PA daily (min) [b]	186 (9)	192 (9)	0.65	190 (6)	182 (6)	0.38
Moderate PA daily (min) [b]	32 (2)	34 (2)	0.44	33 (2)	36 (2)	0.09
Vigorous PA daily (min) [b]	21 (2)	20 (2)	0.88	21 (2)	26 (2)	0.02
Achieves 60 min MVPA daily, n (%)	10 (36)	8 (30)	0.63	18 (33)	27 (48)	0.10
Accelerometer wear time (min) [a]	812 (60)	827 (34)	0.25	819 (49)	816 (46)	0.71

JIA juvenile idiopathic arthritis, *Oligo JIA* persistent oligoarticular JIA, *Poly JIA* extended oligoarticular JIA and polyarticular JIA RF +/−, *JIA total* persistent oligoarticular JIA, extended oligoarticular JIA and polyarticular JIA RF +/−, *RF* rheumatoid factor, *PA* physical activity, *MVPA* moderate-to-vigorous physical activity
[a]Mean (SD). [b] Mean (SE) adjusted for accelerometer wear time

Table 3 Correlates for physical activity in patients with JIA ($N = 55$)

	Univariate Analyses		Multiple Regression Analyses	
	Unstandardized B (95% CI)	*P*-value	Unstandardized B (95% CI)	*P*-value
Counts per minute [a]				
Age	−31.5 (− 54.1, − 8.9)	0.007	−25.2 (−46.0, − 4.4)	0.02
Female sex	100.2 (− 44.7, 245.2)	0.17	20.4 (111.7, 152.4)	0.76
Participation in organized PA	141.0 (38.7, 243.2)	0.008	105.7 (9.2, 202.2)	0.03
Use of biologic medication	150.5 (53.5, 247.5)	0.003	117.5 (24.2, 210,7)	0.02
Disease duration	−9.5 (− 22.7, 3.7)	0.15		
R^2 adjusted			0.37	
Vigorous physical activity [b]				
Age	0.4 (−1.0, 1.9)	0.57	0.5 (−0.9, 1.9)	0.41
Female sex	7.2 (−0.9, 16.1)	0.08	5.69 (−2.8, 14.2)	0.19
Participation in organized PA	8.4 (2.3, 14.5)	0.008	7.6 (1.3, 13.9)	0.02
Use of biologic medication	5.0 (−1.1, 11.2)	0.10		
Accelerometer wear time	0.03 (−0.04, 0.09)	0.41	0.03 (−0.04, 0.09)	0.41
R^2 adjusted			0.11	
Sedentary time [b]				
Age	21.2 (14.7, 27.6)	< 0.001	17.4 (12.1, 22.6)	< 0.001
Female sex	−33.4 (18.6, −85.5)	0.20	−8.9 (−41.0, 23.3)	0.32
Participation in organized PA	−30.2 (−68.5, 8.1)	0.12		
Use of biologic medication	−43.8 (−79.6, −8.0)	0.02	−31.0 (−53.9, − 8.0)	0.01
Arthritis in lower extremities	46.3 (−2.4, 95.1)	0.06		
Disease duration	4.0 (−0.7, 8.7)	0.09		
Accelerometer wear time	0.8 (0.4, 1.1)	< 0.001	0.6 (0.4, 0.8)	< 0.001
R^2 adjusted			0.65	

JIA juvenile idiopathic arthritis, *CI* confidence interval, *PA* physical activity
[a]Results from the final model of multiple linear regression analysis (method enter) controlled for age and sex. [b] Results from the final models of multiple linear regression analyses (method enter) controlled for age, sex and accelerometer wear time

barrier was pain in patients and time in controls (Table 5). The most frequently reported facilitators for PA in both groups were enjoyment and becoming fit.

Discussion

The main finding of our study was that the general level of PA in patients with JIA was comparable with age- and sex-matched controls, but patients spent less time in vigorous PA. The use of biologics was associated with higher levels of PA. Also, patients engaged in similar physical activities as controls, almost all participated in PE, and enjoyment was the most frequently reported facilitator. To our knowledge, this is the first study to a) directly compare PA and PE in patients with JIA diagnosed in the biologic era with matched controls examined in the same time period and b) comprehensively measure PA objectively, and assess correlates, facilitators and barriers for PA in the same study population.

Regarding representativeness of our patients, the included JIA categories constitute 75% of patients with JIA included in our hospital-based registry; thus, the results cannot be extrapolated to the categories not included. However, a previous study found no differences across all ILAR categories when assessing PA by accelerometry [7]. The proportion of girls in our cohort was slightly higher compared to other studies on PA in JIA [6, 7]. We believe the reason for this is twofold; most ILAR categories which were not included have a less female predominance than included categories and the study participation rate was higher among eligible girls than boys. We cannot rule out that the patients enrolled might be biased towards more physically active patients with a milder disease than those who declined participation. However, we are not allowed to report data on patients declining to participate.

The controls were randomly selected from the National Registry, and were examined within a year after the patients, thereby avoiding bias due to changes in patterns of

Table 4 Participation in physical activity and physical education in patients with JIA and controls

	Patients with JIA ($n = 60$)	Controls ($n = 60$)	p-value
Participation in PA (organized and/or unorganized)	51 (85)	56 (93)	0.14
Participation in organized PA	38 (63)	47 (78)	0.11
Frequency of organized PA			0.14
None	22 (37)	13 (22)	
1–3 h/week	16 (27)	12 (20)	
4–6 h/week	12 (20)	24 (40)	
7–9 h/week	8 (13)	6 (10)	
> 10 h/week	2 (3)	5 (8)	
The most reported organized PA			
Dancing	14 (23)	9 (15)	0.25
Soccer	10 (17)	16 (27)	0.18
Handball	5 (8)	5 (8)	1.00
Cross-country skiing/biathlon	4 (7)	5 (8)	0.73
Swimming	3 (5)	4 (7)	0.70
Horse riding	4 (7)	2 (3)	0.34
Athletics	1 (2)	4 (7)	0.36
Fight sports (taekwondo, kickboxing, boxing)	0 (0)	5 (8)	0.06
Participation in unorganized PA	41 (68)	42 (70)	1.00
Frequency of unorganized PA			0.79
None	19 (32)	18 (30)	
1–3 h/week	30 (50)	34 (57)	
4–6 h/week	11 (18)	8 (13)	
The most reported unorganized PA			
Jogging/running	10 (17)	14 (23)	0.36
Training in fitness center	11 (18)	10 17)	0.81
Strength exercising at home	10 (17)	8 (13)	0.61
Walking/hiking	5 (8)	10 (17)	0.17
Ball activities	3 (5)	4 (7)	0.70
Cross-country skiing	4 (7)	2 (3)	0.68
Swimming	3 (5)	1 (2)	0.62
Participation in PE			< 0.001
Always (without modifications)	42 (70)	59 (98)	
Always (occasionally with modifications)	16 (27)	0 (0)	
Sometimes	2 (3)	1 (2)	

Numbers are n (%)
JIA juvenile idiopathic arthritis, *PA* physical activity, *PE* physical education

PA. The levels of PA and PA participation in our controls were comparable to recent, population-based studies of Norwegian children [30, 31], indicating that the controls were representative.

We found that most objectively measured PA parameters, including overall cpm, MPA, LPA, sedentary time and proportion achieving the WHO recommendations for MVPA were not significantly different in patients and controls. These findings are in contrast to other studies reporting that patients with JIA have lower cpm [6, 7, 10], and spend less time in MPA and LPA [6, 7] and more in sedentary time [10] than controls. However, in most of these studies, included patients were diagnosed both before and after the introduction of biological medications. We applied the most widely used PA intensity thresholds [24]; in lack of international consensus it is challenging to directly compare our data with PA intensity data from other studies. Adjusting

Table 5 Facilitators and barriers for being physically active in patients with JIA and controls

	Patients with JIA ($n = 60$)	Controls ($n = 60$)	*P*-value
Facilitators for being physically active			
Enjoyment	40 (67)	45 (75)	0.32
Become/stay fit	12 (20)	21 (35)	0.07
Social setting/be with friends	1 (2)	13 (22)	0.001
Less pain	4 (7)	0 (0)	0.12
Barriers for being physically active			
Pain	18 (30)	8 (13)	0.03
Time	3 (5)	11 (18)	0.04
Disease activity	4 (7)	0 (0)	0.12
Lack of energy	2 (3)	2 (3)	1.00

Numbers are n (%)
JIA juvenile idiopathic arthritis, *PA* physical activity

our analyses for wear month did not alter our results, indicating that seasonality did not have a major impact on PA.

Similar to other studies, the time devoted to VPA was lower in our patients than in controls [6, 7, 10]. Even if the effect size for the difference was small, it may be of clinical importance when aiming to optimize the health benefits of PA. Patients with JIA have increased risk for early subclinical atherosclerosis [32]. VPA is particularly important to reduce the risk of cardiovascular diseases [16, 17]. Therefore, patients with JIA should be recommended to include VPA in their PA behavior, but until now, we have not provided specific advice on VPA. Since our patients spent nearly 10 h in daily sedentary time, it seems reasonable to also focus on limiting sedentary behavior to reduce the risk of cardiovascular diseases.

Our identified correlates of objectively measured PA in patients were mostly in line with studies in healthy children. Lower age was associated with higher cpm and lower sedentary time [33], and participation in organized PA was associated with higher cpm and VPA [31, 34]. In healthy children, boys have higher PA levels than girls [33]. We found no association with sex, which must be interpreted with caution due to a low proportion of boys. Interestingly, the use of biological medication was associated with higher cpm and lower sedentary time. This may reflect the effectiveness of these medications, but also that patients using biologics have regular contact with health professionals who repeatedly encourage them to be physically active. Other disease related variables were not identified as correlates; this included also pain which is in accordance with other studies [5–7, 10] and fatigue, which is contrary to another study [35]. Interestingly, our patients and controls reported similar low levels of pain and fatigue.

Participation in organized and unorganized PA were not significantly different between patients and controls. A higher proportion of our patients participated in organized PA than previously reported [19], which may be favorable because of its association with higher cpm and VPA. Also, we found higher PE participation compared to recent studies [8, 35, 36]. However, PE participation has been categorized differently in previous studies, making comparisons difficult. The types of physical activities our patients reported are comparable to activities reported in a national sample of healthy Norwegian children and adolescents [31].

Enjoyment was the most frequently reported facilitator for PA participation in both patients and controls who were regularly physically active, followed by becoming fit. The importance of enjoyment for PA participation has also previously been highlighted in patients with JIA [37] and healthy children [33]. Having less pain was a facilitator in some of our patients, supporting existing results [37]. Both patients and controls reported barriers for PA participation. More patients reported pain, while more controls reported time as a barrier, and none of the study participants reported fatigue as a PA barrier. Disease activity was a barrier in only a few patients (7%). Taken together, disease related barriers (i.e. pain and disease activity) were more common than regular barriers (i.e. time) in patients, similar to findings in other studies [37, 38].

We believe the main reasons for our positive results are two-fold: Firstly, the health care system in Norway has from year 2000 allowed for relatively early introduction of biologics, securing that the patients are aggressively treated following international recommendations [2]. All patients were diagnosed after 2000 and 42% was currently treated with biologics. They seem well treated, supported by measures of modest disease activity, low functional disability and low inflammatory parameters. Interestingly, a recent study measuring PA levels with a questionnaire reported comparable overall PA levels

between patients with JIA (with low disease activity treated with a treat-to-target approach) and controls [39]. Secondly, the physiotherapy management of all patients newly diagnosed with JIA at OUS includes individualized tailored patient education regarding the importance and safety of PA. They have from 2003 been encouraged to participate in PA and PE like their healthy peers without any general restrictions (even if they have active arthritis). Specific exercise programs are not used anymore because patients have improved functional ability and our experience is that there is poor adherence to such programs, which is in line with previous research [40, 41]. To facilitate PA and PE participation, there is also a close collaboration between health professionals at OUS, local physiotherapists, PE teachers and patients and parents.

The cross-sectional design does not allow for the assessment of the causal relation between study outcomes and explanatory factors. Also, measuring a complex behavior like PA at one time point may not provide a complete picture of an individual's PA behavior. Furthermore, to our knowledge, disease-specific facilitators and barriers are not addressed in standardized questionnaires. Therefore, we used a structured interview to assess these factors and PA participation, which may have limited the generalizability of the results. Another limitation is that no formal power analyses were performed for the outcomes; we have a relatively small sample size, which might have introduced type 2 errors.

Conclusions

Even though most PA levels and PA participation were comparable between older children and adolescents with oligo- and polyarticular JIA diagnosed in the biologic era and controls, patients spent less time in VPA. Health professionals should take the patient's preferences about enjoyable activities and disease symptoms like pain into account when encouraging a physically active lifestyle, including more VPA to optimize the health benefits of PA.

Abbreviations

BMI: Body mass index; CHAQ: Childhood health assessment questionnaire; Cpm: Counts per minute; CRP: C-reactive protein; DMARDs: Disease-modifying anti-rheumatic drugs; ESR: Erythrocyte sedimentation rate; IL-6i: Interleukin-6 inhibitor; ILAR: International League of Associations for Rheumatology; JADAS: Juvenile arthritis disease activity score; JIA: Juvenile idiopathic arthritis; LPA: Light physical activity; MPA: Moderate physical activity; MVPA: Moderate-to-vigorous physical activity; NRS: Numeric rating scale; NSAIDs: Non-steroid anti-inflammatory drugs; OUS: Oslo University Hospital; PA: Physical activity; PE: Physical education; RF: Rheumatoid factor; TNFi: Tumor necrosis factor inhibitors; VPA: Vigorous physical activity; WHO: World Health Organization

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Availability of data and materials

The dataset generated and analyzed during the current study is not publicly available due to strict ethical regulation of health related data in Norway. The consent to participate does not include permission to make the data available to a third party.

Authors' contributions

KR, AMS, ØM, HD and HS contributed to the design and conception of the study. KR was responsible for acquisition of data. BHH analyzed the raw accelerometer data. KR and HS performed the statistical analyses and drafted the manuscript. All authors revised the manuscript critically. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Norwegian South East Regional Ethics Committee for Medical Research (2014/188). All participants provided written informed consent/assent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author details

[1]Section for Orthopaedic Rehabilitation, Oslo University Hospital, Rikshospitalet, Postboks 4950 Nydalen, 0424 Oslo, Norway. [2]Department of Health Sciences, Institute of Health and Society, Faculty of Medicine, University of Oslo, Oslo, Norway. [3]Department of Sports Medicine, Norwegian School of Sports Sciences, Oslo, Norway. [4]Department of Rheumatology, Oslo University Hospital, Rikshospitalet, Oslo, Norway. [5]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway. [6]National Advisory Unit on Rehabilitation in Rheumatology, Diakonhjemmet Hospital, Oslo, Norway. [7]Norwegian National Advisory Unit on Rheumatic Diseases in Children and Adolescents, Oslo University Hospital, Rikshospitalet, Oslo, Norway. [8]Bjørknes University College, Oslo, Norway.

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III

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Pediatric Rheumatology

RESEARCH ARTICLE Open Access

Measurement properties and performance of an eight-minute submaximal treadmill test in patients with juvenile idiopathic arthritis: a controlled study

Kristine Risum[1,2*], Elisabeth Edvardsen[3,4], Anne M. Selvaag[5], Hanne Dagfinrud[2,6] and Helga Sanner[5,7,8]

Abstract

Background: Poor cardiorespiratory fitness is previously reported in patients with juvenile idiopathic arthritis (JIA) measured both by maximal and submaximal exercise tests, but a submaximal exercise test with acceptable measurement properties is currently lacking for both clinical and research purposes in this patient population. The objectives of this study were to evaluate the measurement properties and performance of a submaximal treadmill test in patients with JIA, and to compare the results with those obtained in controls.

Methods: Fifty-nine patients (50 girls), aged 10–16 years, with oligo- ($n = 30$) and polyarticular ($n = 29$) JIA, and 59 age- and sex-matched controls performed an eight-minute submaximal treadmill test for estimating peak oxygen uptake (VO_{2peak}) followed by a maximal treadmill test measuring VO_{2peak} directly. During the submaximal treadmill test, the study participants walked with no inclination at a speed between 3.2–7.2 km/h for four minutes, and then continued to walk at the same speed for four minutes with five % inclination. VO_{2peak} was directly measured during a continuous graded exercise test on treadmill until exhaustion. Thirty-seven patients participated in the evaluation of the reliability. Criterion validity and reliability were evaluated with interclass correlation coefficient (ICC); measurement errors by Bland-Altman plot, standard error of measurement and smallest detectable change.

Results: In patients with JIA, the ICC (95% CI) for criterion validity was acceptable at group level 0.71 (0.51, 0.82), but not at individual level. The test-retest reliability and inter-rater reliability were acceptable at individual (0.84 (0.71, 0.91) and 0.92 (0.83, 0.96), respectively) and group levels (0.91 (0.83, 0.96) and 0.96 (0.91, 0.98), respectively). The measurement errors (for test-retest reliability/inter-rater reliability) were large. Bland-Altman plots showed no systematic differences, but a large variability for both the validity and reliability. The performance of and estimated VO_{2peak} from the submaximal test were not associated with disease variables and were comparable between patients and controls.

Conclusion: The submaximal treadmill test is valid for use in patients with JIA on group level, but not on individual level. The reliability is acceptable. Due to large measurement errors, the submaximal treadmill test is not optimal for use in daily clinical practice to estimate VO_{2peak} in individual patients.

Keywords: Juvenile idiopathic arthritis, Cardiorespiratory fitness, Exercise testing, Validity, Reliability, Measurement properties

* Correspondence: krisum@ous-hf.no
[1]Division of Orthopaedic Surgery, Section for Orthopaedic Rehabilitation, Oslo University Hospital, Rikshospitalet, Postboks 4950 Nydalen, 0424 Oslo, Norway
[2]Department of Health Sciences, Institute of Health and Society, Oslo, Faculty of Medicine, University of Oslo, Oslo, Norway
Full list of author information is available at the end of the article

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Background

Juvenile idiopathic arthritis (JIA) can affect physical function and cardiorespiratory fitness (CRF). CRF is important for general health, and high CRF has been shown to decrease cardiovascular disease in general pediatric and adult populations [1–3]. Previous studies have shown that patients with JIA have poor CRF measured with both maximal and submaximal exercise tests [4–6]. Contrary to these results, we have recently reported that patients with oligo- and polyarticular JIA diagnosed in the era of biologics have comparable levels of CRF as age- and sex-matched controls from the general population, measured directly as peak oxygen uptake (VO_{2peak}) [7]. We believe our positive results may be explained by advances in the multidisciplinary management of JIA in the era of biologics, as well as differences in study populations. Importantly, 20–30% of both our patients with JIA and controls had poor CRF.

The gold standard method to measure CRF is through a cardiopulmonary exercise test (CPET) with direct measurement of VO_{2peak}, using a treadmill or bicycle to maximal exhaustion [8]. However, a CPET is time consuming, requires advanced and expensive equipment in a laboratory setting and extensive experience to encourage individuals to achieve maximal effort. Furthermore, performing a maximal exercise test may be uncomfortable and unpleasant for patients.

In contrast, indirect submaximal tests do not require the individuals to exercise to exhaustion, are easier to perform, require less advanced equipment, and are therefore frequently used in research and clinical practice to measure CRF [9]. The disadvantage of submaximal tests is less precise measurements of CRF compared to direct measurement of VO_{2peak}. Submaximal tests are usually developed to provide estimation of VO_{2peak} or to assess the distance covered in a given period of time or the time taken to cover a given distance. The most commonly used submaximal test in chronic pediatric conditions is probably the 6-min walk test (6MWT), even if the measurement properties vary largely among chronic pediatric conditions [10]. In JIA, the 6MWT has been suggested as a possible field test to measure walking ability, but is shown to be a poor predictor of VO_{2peak} [6, 11]. To the best of our knowledge, no submaximal walking tests aiming to estimate VO_{2peak} have been validated in pediatric populations.

An eight-minute submaximal treadmill test has been developed to estimate VO_{2peak} in healthy adults [12], and is proven valid for women with rheumatic diseases [13], who may experience similar symptoms as patients with pediatric rheumatic diseases. However, in healthy adults the test seems to either under- or overestimate VO_{2peak} depending on the chosen intensity [14]. The validity of this test is unknown for patients with JIA and healthy children. Also, knowledge about the reliability of the test is essential for both clinical practice and research purposes. Knowledge about how the performance of the test relate to disease variables is also warranted.

The objectives of the study were to evaluate the criterion validity and reliability of the eight-minute submaximal treadmill test in patients with JIA; also to investigate if the performance of the submaximal treadmill test is influenced by disease characteristics or differ from controls.

Methods

Study participants

This study is part of a larger study examining physical activity and physical fitness in patients with JIA diagnosed in the era of biologics [7, 15]. From January to August 2015, consecutive patients aged 10–16 years with polyarticular (extended oligoarthritis and polyarticular RF +/–) and oligoarticular JIA according to the ILAR criteria [16] with a planned routine follow-up at Oslo University Hospital (OUS) were recruited (JIA validity sample). We included these JIA categories to be able to compare homogenous JIA subgroups in the physical fitness and physical activity studies. Other inclusion criteria were disease duration > 6 months and a home address in the geographical area served by the South-Eastern Norway Regional Health Authority. Exclusion criteria for patients were comorbidities associated with, or potentially associated with, impaired cardiopulmonary fitness (e.g heart- or lung disease, severe orthopedic conditions or recent surgery) or inability to walk. In addition, age- and sex-matched controls from the general population (living in or nearby Oslo) were randomly selected from the National Registry, and were included from November 2015 to March 2016 (controls validity sample). Exclusion criteria for the controls were inflammatory rheumatic or autoimmune disease, severe heart or lung disease, or other diseases involving mobility problems.

To evaluate the reliability of the submaximal treadmill test, patients living in or nearby Oslo and patients with a planned follow-up at OUS within 4 weeks, also performed the submaximal treadmill test 1–4 weeks after the initial test (JIA reliability sample). In general, a sample size of 50 participants is considered to be adequate when assessing reliability and validity [17].

Our study was conducted in compliance with the Helsinki Declaration and all participants provided written informed consent (the children themselves if aged ≥16 years and the parents/guardians of children aged < 16 years together with the children's assent). The study was approved by the Norwegian South East Regional Ethics Committee for Medical Research (2014/188).

Assessment of demographic and disease-related variables

Height and bodyweight were measured to the nearest 0.1 cm using a stadiometer and 0.1 kg on a digital scale, respectively, with participants wearing light clothes and

no shoes. Body mass index (BMI) was calculated. Waist circumference was measured at the midpoint between the bony markers of the ribs and the superior iliac crest in a standing position at the end of expiration with a measuring tape at the height of umbilicus to the nearest 0.1 cm. Current pain, pain and fatigue during the previous week were assessed by numeric rating scale (NRS) 0–10, where 0 = no pain/fatigue and 10 = worst possible pain/fatigue [18]. In patients, disease activity was assessed by the Juvenile Arthritis Disease Activity Score 71 (JADAS 71) [19]. The Wallace criteria were used to determine if patients had active disease or clinical inactive disease [20]. The Childhood Health Assessment Questionnaire (CHAQ) was used to measure functional disability [21, 22]. The patients completed the CHAQ themselves, with parental assistance if needed.

Submaximal treadmill test

We used the submaximal treadmill test developed by Ebbeling et al. [12] to estimate VO_{2peak} (Technogym, Rimini, Italy). During the first four minutes of the test, the participant walked with no inclination at a speed between 3.2 km/h (2.0 mph) and 7.2 km/h (4.5 mph) corresponding to a heart rate (HR) between 50 to 70% of age-predicted peak HR (HR_{peak}) of 220-age [23]. If possible, we aimed for a HR close to 70% of the predicted HR_{peak} and the speed was gradually increased until this intensity was reached. If a HR close to 70% of predicted HR_{peak} was not reached at the speed of 7.2 km/h (4.5 mph), the participant's HR at this intensity was recorded. After four minutes, the treadmill elevation was then gradually increased (within 15–20 s) to five % for the next four minutes. HR was measured at the end of each stage with a heart rate monitor (Polar Sports Watch, Kempele, Finland). Participants rated their perceived exertion (RPE) using the Borg Scale $_{6–20}$ [24] at three and eight minutes. The Borg Scale $_{6–20}$ is a subjective measure of a person's exertion during exercise, ranging from 6 to 20, where 6 = no exertion at all and 20 = maximal exertion. The HR and walking speed achieved after eight minutes of walking were then recorded for entry into the previously developed equation to estimate VO_{2peak} ($mL{\cdot}kg^{-1}{\cdot}min^{-1}$) based on the following equation [12]:

$$\begin{aligned} &15.1 + (21.8 \times \text{speed [mph]}) \\ &\quad - (0.327 \times \text{HR [bpm]}) \\ &\quad - (0.26 \times \text{speed [mph]} \times \text{age [yrs]}) \\ &\quad + (0.00504 \times \text{HR} \times \text{age}) \\ &\quad + (5.98 \times \text{sex [female} = 0; \text{male} = 1]) \end{aligned}$$

We also recorded the total walking distance (m) the participants walked during the submaximal treadmill test. Evaluation of the submaximal treadmill performance included HR and RPE at three and eight minutes, speed and walking distance.

Maximal treadmill test

CRF was directly measured as VO_{2peak} ($mL{\cdot}kg^{-1}{\cdot}min^{-1}$) during a maximal treadmill test (Woodway, Würzburg, Germany). The test protocol and procedure are described previously [7]. Briefly, gas exchange and ventilator variables were measured continuously breath-by-breath as the participants breathed into a two-way breathing mask (2700 series; Hans Rudolph, Inc., Shawnee KS, USA). The gas exchange variables were reported as 30 s averages using a gas analyzer (Vmax, SensorMedics, Yorba Linda, CA, USA). The highest achieved oxygen uptake averaged over a 30-s period was defined as VO_{2peak}. The highest respiratory exchange ratio (RER) measured before or corresponding to the highest minute ventilation was reported. RER is the ratio between the VCO_2 and VO_2, and increases with exercise intensity. The HR was recorded every minute using Polar Sports Watch (Kempele, Finland) and the HR_{peak} was reported. The RPE was rated by Borg Scale $_{6–20}$ [24], and the participants also gave reason for terminating the test. The test was terminated when the participant was unable to continue, even with encouragement.

Standardization of the conditions for treadmill testing

Both validity samples (JIA and controls) performed the submaximal treadmill test prior to the maximal treadmill test on the same day, separated by approximately 30–60 min rest between each test. Both validity samples performed the submaximal treadmill test at 9.30 AM at the earliest, thereby most likely avoiding issues with morning stiffness. If unfamiliar with treadmill walking, participants practiced until they felt comfortable to start the submaximal treadmill test. The JIA reliability sample performed the submaximal treadmill test twice on the second test day after school, separated by approximately 15 min rest between each test. The same physiotherapist (KR) conducted all maximal and submaximal treadmill tests used to evaluate criterion validity and test-retest reliability. To test inter-rater reliability, KR and a second physiotherapist, both with more than 13 years of clinical experience in pediatric rheumatology, conducted the submaximal treadmill tests on the second test session.

Statistical analyses

A power analysis was performed to estimate the required sample size for reliability testing of the submaximal treadmill test to achieve an ICC of 0.85 with a 95% confidence interval (CI) and an interval width of 0.2 (0.75 and 0.95). This calculation resulted in a sample size of 31 participants.

Descriptive data are presented as percentages, means (SD) and medians (25th–75th percentile) as appropriate.

The COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) panel recommendations for measurement properties were followed for the evaluation of validity and reliability [17]. The observed VO_{2peak} from the maximal treadmill test was considered the criterion measurement.

Paired t tests were used to examine potential differences between the observed and estimated VO_{2peak} and between the estimated VO_{2peak} values from the three submaximal treadmill tests. Criterion validity and reliability were evaluated with two-ways mixed interclass correlation coefficient$_{agreement}$ (ICC). ICC > 0.70 was considered acceptable [17]. Limits of agreement (LoA) (Bland and Altman method), standard error of measurement ($SEM_{agreement}$) and smallest detectable change (SDC_{95}) were calculated to evaluate the measurement errors of the submaximal treadmill test. The $SEM_{agreement}$ represents the standard deviation of repeated measures in one patient, and was calculated with values from a two-way ANOVA. The SDC represents the minimal change that a patient must show on the scale to ensure that the observed change is real and larger than the measurement error. The SDC was calculated as $1.96 \times \sqrt{2} \times SEM_{agreement}$ to obtain 95% CI. The SDC values at the group level (SDC_{group}) were calculated as $1.96 \times \sqrt{2} \times SEM_{agreement}/\sqrt{n}$.

The Bland and Altman method was used to assess whether there was any systematic disagreement between the submaximal and maximal treadmill test and between the submaximal treadmill tests for both test-retest reliability and inter-rater reliability through a Bland and Altman plot. LoA were calculated as the mean difference in scores ± (1.96 × SD of the difference).

Differences between patients and controls were tested with independent sample t tests and correlations with Spearman's rho correlation coefficients.

All statistical analyses were conducted using SPSS version 23 for windows package (SPSS, Chicago, IL, USA) with the level of significance set at $P < 0.05$.

Results

Characteristics of patients and controls

The flow of study participants is shown in Fig. 1. Demographic characteristics of the validity samples of patients and controls and the JIA reliability sample are displayed in Table 1. A total of 59 patients (50 girls) with oligo- (n = 30) and polyarticular (n = 29) JIA and 59 matched controls with complete data on the maximal and submaximal treadmill tests were included in the analyses to evaluate the criterion validity. Mean age (SD) was 13.6 (2.2) years in patients and 13.5 (2.6) years in controls. In patients, disease activity was moderate with a median (25th -75th percentile) JADAS of 3.2 (1.1–4.8), and 42% used biologic DMARDs (Table 1). Twenty-nine patients reported morning stiffness, but morning stiffness lasting 60–120 min or > 120 min was only reported by four patients and one patient, respectively. There was no clinical indication of cardiopulmonary side effects from synthetic or biologic DMARDs considered to be of importance for CRF. The JIA reliability sample included 37 patients (30 girls).

Criterion validity in patients and controls

All participants were able to perform both the submaximal and maximal treadmill tests according to the test protocols for each test. None of the study participants experienced any adverse events during the treadmill testing. The results from the maximal and submaximal treadmill tests are shown in Table 2. For the maximal treadmill test, the mean HR_{peak}, RER and RPE (Borg scale$_{6-20}$) indicate that the participants exercised at their maximal capacity. This is underlined by the fact that all participants reported exhaustion as the reason for terminating the maximal treadmill test. As previously published [7], there were no significant differences between patients and controls for any variables from the maximal treadmill test. For the submaximal treadmill test, the HR and RPE reported during and immediately after the test indicate that both patients and controls exercised at submaximal intensity. In total, 44 (75%) patients and 41 (70%) controls reached the target HR of 70% of predicted HR_{peak} during the submaximal treadmill test. The remaining patients and controls reached a HR between 60 and 70% of predicted HR_{peak}.

In patients, no significant difference was found between the observed and estimated VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$); 44.8 (8.8) vs 43.2 (10.3), respectively, $P = 0.18$. The ICC (95% CI) at group level was acceptable; 0.71 (0.51, 0.82), while the single ICC value at individual level between the observed and estimated VO_{2peak} was not acceptable; 0.55 (0.34, 0.70). LoA showed large variation between the observed and estimated VO_{2peak} (− 16.4 to 19.4 $mL \cdot kg^{-1} \cdot min^{-1}$), with no systematic bias (Fig. 2a).

In controls, no significant difference was found between the observed and estimated VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$); 46.53 (8.47) vs 44.60 (7.92), respectively, $P = 0.12$. Neither the ICC (95% CI) value at group level nor individual level were acceptable; 0.52 (0.21, 0.71) and 0.35 (0.11, 0.56), respectively. LoA showed large variation between the observed and estimated VO_{2peak} (− 16.3 to 20.1 $mL \cdot kg^{-1} \cdot min^{-1}$), with no systematic bias (Fig. 2b).

Reliability in patients

Paired t tests showed no significant differences in estimated VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$) when comparing the results from the submaximal treadmill tests (Table 3). Both the test-retest reliability and inter-rater reliability were acceptable at group level (ICC (95% CI) 0.91 (0.83, 0.96) and 0.96 (0.91, 0.98), respectively) and at individual level (0.84 (0.71, 0.91) and 0.92 (0.83, 0.96), respectively). The measurement errors were

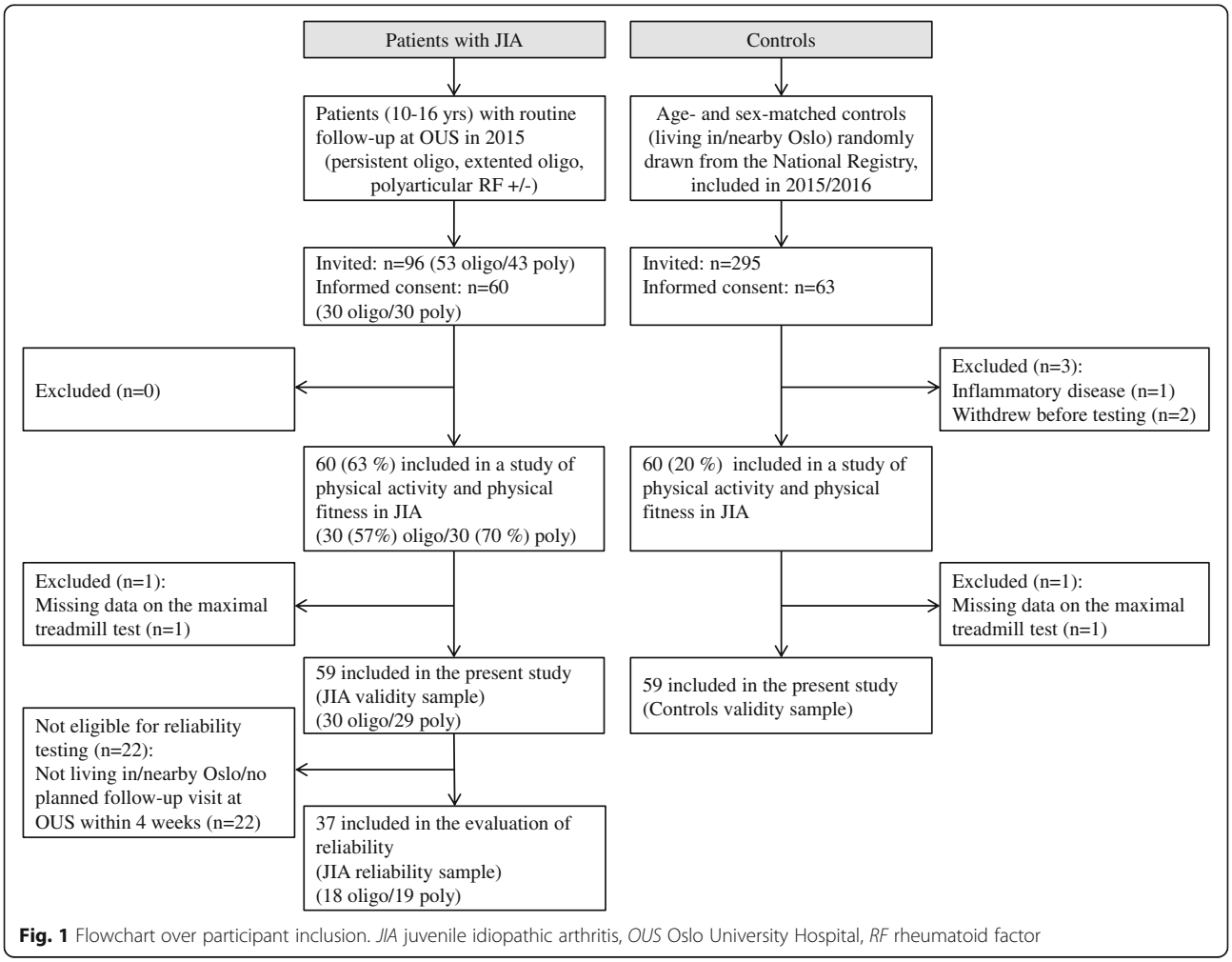

Fig. 1 Flowchart over participant inclusion. *JIA* juvenile idiopathic arthritis, *OUS* Oslo University Hospital, *RF* rheumatoid factor

large for both test-retest reliability and inter-rater reliability (Table 3). The SDC_{95} values indicate that a change greater than 11.4 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ for the test-retest reliability and 8.6 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ for the inter-rater reliability would be required to be 95% certain that a change would not be the result of measurement error, but of a real change. The $SDC_{95group}$ (at group level) values indicated that a change of greater than 1.5 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ for the test-retest reliability and 1.1 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ for the inter-rater reliability, would be required to be 95% certain that a change would not be the result of measurement error, but of a real change.

The Bland and Altman plots showed no systematic differences, but the LoA confirmed the large variability of agreement in estimated VO_{2peak} for both test-retest reliability and inter-rater reliability (Fig. 2c and d).

Estimated VO_{2peak} and performance of the submaximal treadmill test between patients and controls, and correlation with disease variables

Estimated VO_{2peak} ($mL{\cdot}kg^{-1}{\cdot}min^{-1}$) and performance of the submaximal treadmill test did not differ significantly between patients and controls, all P's > 0.15 (Table 2). Estimated VO_{2peak} ($mL{\cdot}kg^{-1}{\cdot}min^{-1}$) and performance of the submaximal treadmill test were also comparable between patients with persistent oligo- and polyarticular JIA and between patients with active and clinical inactive disease (data not shown). In patients, there were no correlations between any disease variables and estimated VO_{2peak} or walking distance (Table 4).

Discussion

This is the first study to examine criterion validity and reliability of the eight-minute submaximal treadmill test aiming to estimate VO_{2peak} in patients with JIA. The results showed acceptable measurement properties on group level for both validity and reliability. The reliability was acceptable measured by ICC, but the measurement errors were large. On individual level, the validity was not acceptable, with large limits of agreement, and with no systematic bias. In controls, the validity of the submaximal treadmill test was not acceptable neither on group nor individual level. Patients with JIA and

Table 1 Characteristics of patients with JIA and controls

	Patients with JIA validity sample ($n = 59$)	Patients with JIA reliability sample ($n = 37$)	Controls validity sample ($n = 59$)
Age (yrs)	13.6 (2.2)	13.6 (2.1)	13.5 (2.6)
Female sex, n (%)	50 (85)	30 (81)	50 (85)
Height (cm)	157.6 (12.5)	158.5 (13.0)	160.8 (12.3)
Weight (kg)	48.3 (11.8)	49.5 (12.7)	53.1 (15.2)
BMI (kg/m^2)	19.2 (3.0)	19.4 (3.3)	20.1 (3.5)
Waist circumference (cm)	70.5 (9.8)	70.2 (8.9)	69.3 (9.2)
Pubertal status (pre-, mid-, and postpubertal %)	24/61/15	22/65/13	17/68/15
NRS current pain (0–10), n (%) score > 0	23 (38)	16 (43)	18 (30)
NRS pain previous week (0–10)	1.0 (0.0–3.0)	1.0 (1.0–3.5)	1.0 (0.0–3.0)
NRS fatigue previous week (0–10)	3 (2.0–6.0)	3.0 (2.0–6.0)	3.0 (1.0–5.0)
Oligo/poly, n (%)	30 (51) / 29 (49)	18 (49) / 19 (51)	NA
Disease duration (yrs)	7.5 (3.8)	7.5 (3.9)	NA
JADAS 71 (0–101)	3.2 (1.1–4.8)	3.0 (1.0–4.7)	NA
CHAQ score (0–3)	0.0 (0.0–0.3)	0.1 (0.0–0.4)	NA
Off medication, n (%)	12 (20)	9 (24)	NA
Synthetic DMARDs, n (%)	39 (66)	24 (65)	NA
Biologic DMARDs, n (%)	25 (42)	15 (41)	NA
Active disease, n (%)	20 (34)	12 (32)	NA
Inactive disease, n (%)	39 (66)	25 (68)	NA

Numbers are mean (SD) or median (25th – 75th percentile) unless otherwise indicated. *JIA* juvenile idiopathic arthritis, *BMI* body mass index, *NRS* numeric rating scale, *JADAS* juvenile arthritis disease activity score, *CHAQ* childhood health assessment questionnaire, *DMARDs* disease modifying anti-rheumatic drugs, *NA* not applicable

Table 2 Data characteristics of the submaximal and maximal tests used for the evaluation of criterion validity in patients with JIA and controls

		Patients with JIA ($n = 59$)	Controls ($n = 59$)
Maximal test			
VO_{2peak} (mL·kg^{-1}·min^{-1})		45.1 (8.5)	46.5 (8.5)
Running distance (m)		909 (236)	968 (190)
Peak HR (beats/min)		196 (9)	197 (7)
Borg $_{6–20}$		18.9 (1.9)	18.5 (1.0)
Respiratory exchange ratio		1.27 (0.12)	1.23 (0.10)
Test time (sec)		527 (99)	554 (76)
Speed (km/h)		8.3 (0.9)	8.5 (0.7)
Gradient (%)		11.5 (1.7)	11.8 (1.4)
Submaximal test			
Estimated VO_{2peak} (mL·kg^{-1}·min^{-1})		43.6 (9.9)	44.6 (7.9)
Walking distance (m)		751 (91)	739 (67)
Speed (km/h)		6.2 (0.8)	6.2 (0.6)
3 min	HR (beats/min)	134 (9)	132 (9)
	Borg $_{6–20}$	9.6 (2.0)	9.4 (2.2)
8 min	HR (beats/min)	163 (14)	159 (14)
	Borg $_{6–20}$	13.0 (2.2)	12.4 (2.2)

Numbers are mean (SD). *JIA* juvenile idiopathic arthritis, *HR* heart rate, *VO_{2peak}* peak oxygen uptake

controls had similar estimated VO_{2peak} and submaximal treadmill test performance, and we found no associations with disease variables.

Compared to our results, studies on healthy adults [14] and women with rheumatic diseases [13] showed better validity. However, these studies applied different statistical methods than ours, making comparisons challenging. We applied ICC and Bland and Altman plots to evaluate criterion validity and reliability, statistical analyses methods recommended for these purposes by the COSMIN panel [17].

In the original study of the submaximal treadmill test, Ebbeling et al. [12] reported that there were no significant differences between the estimated and observed VO_{2peak} values in healthy adults, suggesting that the test has good predictive validity. We found similar results in both patients with JIA and controls when comparing estimated and observed VO_{2peak} mean values using paired t tests. The ICC value for evaluation of criterion validity at group level was acceptable in patients, but not in controls. However, our agreement analyses in both patients and controls showed large variation between the observed and estimated VO_{2peak}, but with no systematic differences between the observed and estimated VO_{2peak}. Agreement analyses were not conducted in the original article [12] or in other studies [13, 14]. However, a study of healthy adults [14] has reported a systematic overestimation of

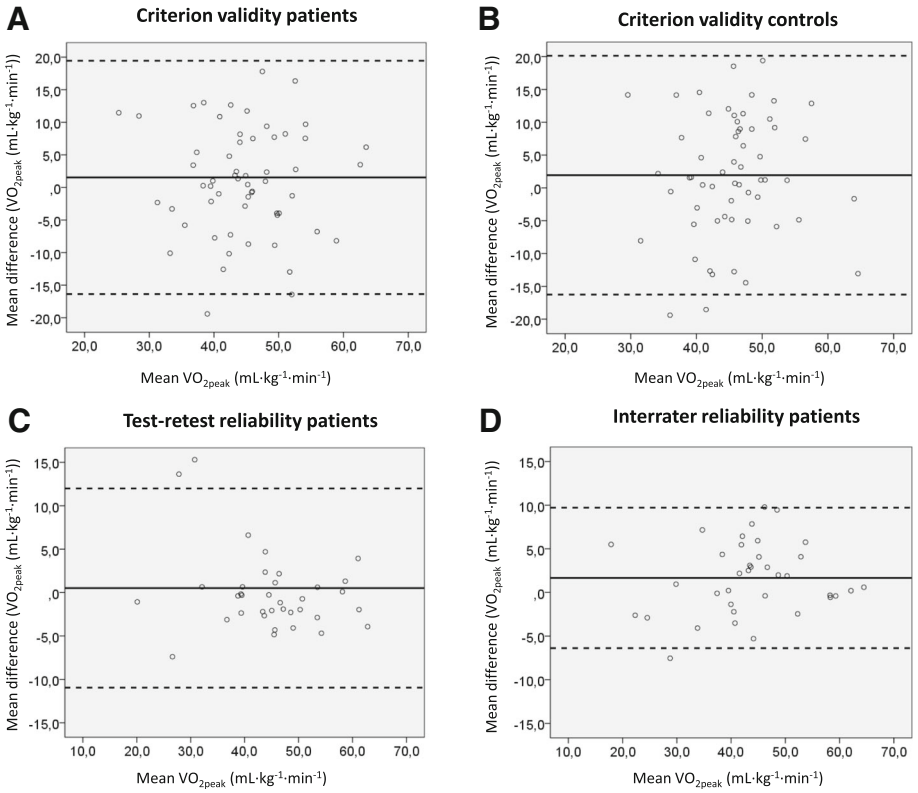

Fig. 2 Bland and Altman plots with the mean scores [(observed+estimated VO_{2peak})/2] on the x-axis and mean difference between scores (observed-estimated VO_{2peak}) on the y-axis for criterion validity in patients with JIA (**a**) and controls (**b**), and the mean scores [(test+retest)/2 and (Tester 1 + Tester 2)/2] on the x-axis and mean difference between scores [(test-retest) and (Tester 1-Tester 2)] on the y-axis for test-retest (**c**) and inter-rater reliability (**d**) in patients with JIA, respectively. *JIA* juvenile idiopathic arthritis, *VO_{2peak}* peak oxygen uptake

VO_{2peak} by 3.5 mL·kg^{-1}·min^{-1} when testing at the moderate intensity (70% of the predicted HR_{peak}) and an underestimation of VO_{2peak} by 3.5 mL·kg^{-1}·min^{-1},when testing at the low intensity (50% of the predicted HR_{peak}). The authors therefore suggested that if the purpose of using the submaximal treadmill test is to evaluate changes in CRF, all test sessions for the individual should be conducted at the same HR rather than the same speed. Thus, we aimed to test the participants at the same HR intensity (close to 70% of predicted HR_{peak}) when conducting the submaximal tests. With this approach, the SDC was large for both test-retest and inter-rater reliability in our patients.

At group level, a change of more than 1.5 mL·kg^{-1}·min^{-1} and 1.1 mL·kg^{-1}·min^{-1} would be required to be 95% certain that a real change has occurred for test-retest- and inter-rater testing, respectively. These small SDC_{group} values suggest that the submaximal treadmill test is reliable on group level in patients, which is important for research purposes. When mean scores of a group of patients are used instead of individual patient scores, the measurement error becomes smaller and subsequently, the measure is more reliable [17]. If the submaximal treadmill test is used for evaluating change in individual patients in clinical settings, the large measurement errors must be taken

Table 3 Reliability and measurement error of the submaximal treadmill test in patients with JIA

	Test*	Retest*	Difference*	$SEM_{agreement}$	SDC_{95}	$SDC_{95group}$
Est VO_{2peak} (mL·kg^{-1}·min^{-1})	44.9 (9.4)	44.3 (11.0)	0.5 (5.9)	4.1	11.4	1.5
	Tester 1*	Tester 2*	Difference*	$SEM_{agreement}$	SDC_{95}	$SDC_{95group}$
Est VO_{2peak} (mL·kg^{-1}·min^{-1})	44.3 (11.0)	42.7 (10.5)	1.6 (4.1)	3.1	8.6	1.1

*Values are mean (SD). *JIA* juvenile idiopathic arthritis, *SEM* standard error of measurement, *SDC* smallest detectable change, *Est* estimated, *VO_{2peak}* peak oxygen uptake
N = 37

Table 4 Correlation between disease variables and estimated VO_{2peak} and walking distance in patients with JIA

Disease variable	Estimated VO_{2peak}	*p*-value	Walking distance	*p*-value
Use of any medication	−0.07	0.59	−0.10	0.47
Use of synthetic DMARDs	0.04	0.79	−0.04	0.76
Use of biologic DMARDs	−0.03	0.80	0.02	0.81
JADAS 71 (0–101)	−0.03	0.84	0.08	0.54
CHAQ (0–3)	−0.13	0.35	−0.18	0.17
Active joints	0.10	0.48	0.21	0.16
Active joints in the lower extremities	0.09	0.46	0.20	0.13
Disease duration (years)	−0.13	0.34	0.00	0.97
Pain, current (NRS 0–10)	−0.21	0.11	−0.13	0.31
Pain, previous week (NRS 0–10)	−0.16	0.24	−0.02	0.88
Fatigue, previous week (NRS 0–10)	−0.07	0.58	−0.02	0.87

JIA juvenile idiopathic arthritis, *DMARDs* disease modifying anti-rheumatic drugs, *JADAS* juvenile arthritis disease activity score, *CHAQ* childhood health assessment questionnaire, *NRS* numeric rating scale, *VO_{2peak}* peak oxygen uptake

into consideration. Specifically, a change of more than 11.4 $mL \cdot kg^{-1} \cdot min^{-1}$ and 8.6 $mL \cdot kg^{-1} \cdot min^{-1}$ are required to be 95% certain that a real change in a single individual has occurred, for test-retest- and inter-rater testing, respectively.

Submaximal tests are based on the assumption that there is a linear relationship between HR, oxygen consumption, and exercise intensity [8]. Therefore, an accurate age-predicted HR_{peak} is of importance. We used the same prediction of HR_{peak} as Ebbeling et al. [12] when they developed the test. This equation is proposed to underestimate HR_{peak} with increasing age and other equations in adult populations have been suggested [25, 26]. In our study participants, the mean predicted HR_{peak} was 207 in both patients and controls, while the mean HR_{peak} observed from the maximal treadmill test was 196 and 197 $beat \cdot min^{-1}$ in patients and controls, respectively, suggesting overestimation of the predicted HR_{peak} when using the 220- age formula. In particular, as HR_{peak} varies between individuals, children with low HR_{peak} have probably been exercising at higher intensities than 70%. Importantly, there are many factors that may affect HR (e.g. hydration, caffeine, pain and anxiety). Nevertheless, the RPE and HR during the submaximal test indicate that the submaximal treadmill test is a test of submaximal intensity in these participants at group level. The formula by Tanaka et al. (208–0.7 x age) [25] was better for predicting HR_{peak} in both patients and controls than the formula by Nes et al. (211–0.64 x age) [26] and the 220-age formula [23] (data not shown). The formula by Tanaka et al. was also preferable over the 220-age formula in another study involving children [27].

The estimated VO_{2peak} and the performance of the submaximal treadmill test were comparable between patients with JIA and controls. This is in line with our previous findings studying the same cohort; directly measured VO_{2peak} was comparable between patients with JIA and controls [7]. Furthermore, we observed no correlation between disease variables and estimated VO_{2peak} and walking distance in patients. We have previously also reported that disease variables were not associated with any components of physical fitness in our patient cohort [7]. Taken together, our results suggest that disease variables are less important for physical fitness, including submaximal performance, in patients treated with a modern multidisciplinary management of JIA.

Our study has several strengths; we applied the COSMIN recommendations for evaluating the criterion validity and reliability of the submaximal treadmill test and the gold standard test was used as criterion measurement. Also, both physiotherapists conducting the submaximal tests for evaluation of reliability were experienced in pediatric rheumatology and one of these physiotherapists also conducted all maximal and submaximal treadmill tests used to evaluate the criterion validity. Also, the sample size was adequate. However, some limitations need to be considered. The equation to estimate the VO_{2peak} was developed in healthy adults aged 20–59 years, and it can be questioned if the formula is valid to use in patients with JIA and controls aged 10–16 years. Our JIA cohort seems well treated with low disease activity and functional disability, thus the findings may not be generalized to patients with higher disease activity or JIA categories not included in the current study. Additionally, the majority of the individuals included in the present study were females, which also could have hampered the generalizability of the results, although the formula used to estimate VO_{2peak} takes sex into account. Thus, future research should include other JIA categories and more males to improve the generalizability of the results.

Conclusions

In patients with JIA, the submaximal treadmill test shows acceptable criterion validity at group level but not at individual level. The reliability of the test is acceptable, but with large measurement errors for both test-retest- and inter-rater reliability. Our results support that the submaximal treadmill test is valid and reliable for research purposes (on group level), but not optimal to estimate VO_{2peak} in individual patients. Estimated VO_{2peak} and performance of the submaximal treadmill test did not differ between patients and controls and were not associated with disease variables, probably reflecting the positive effect of modern multidisciplinary management of JIA.

Abbreviations

6MWT: 6-min walk test; BMI: Body mass index; CHAQ: Childhood health assessment questionnaire; COSMIN: The COnsensus-based Standards for the selection of health Measurement INstruments; CPET: Cardiopulmonary exercise test; CRF: Cardiorespiratory fitness; DMARDs: Disease-modifying antirheumatic drugs; HR: Heart rate; HR_{peak}: Peak heart rate; ICC: Interclass correlation coefficient; ILAR: International League of Associations for Rheumatology; JADAS: Juvenile arthritis disease activity score; JIA: Juvenile idiopathic arthritis; LoA: Limits of agreement; NRS: Numeric rating scale; OUS: Oslo University Hospital; RF: Rheumatoid factor; RPE: Rated perceived exertion; SDC: Smallest detectable change; SEM: Standard error of measurement; VO_{2peak}: Peak oxygen uptake

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Availability of data and materials

The dataset generated and analyzed during the current study is not publicly available due to strict ethical regulation of health related data in Norway. The consent to participate does not include permission to make the data available to a third party.

Authors' contributions

KR, AMS, HD and HS contributed to the design and conception of the study. KR was responsible for acquisition of data. KR performed the statistical analyses. KR, HD and HS and drafted the manuscript. All authors revised the manuscript critically. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Norwegian South East Regional Ethics Committee for Medical Research (2014/188). All participants provided written informed consent (the children themselves if aged ≥16 years and the parents/guardians of children aged < 16 years together with the children's assent).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author details

[1]Division of Orthopaedic Surgery, Section for Orthopaedic Rehabilitation, Oslo University Hospital, Rikshospitalet, Postboks 4950 Nydalen, 0424 Oslo, Norway. [2]Department of Health Sciences, Institute of Health and Society, Oslo, Faculty of Medicine, University of Oslo, Oslo, Norway. [3]Department of Pulmonary Medicine, Oslo University Hospital, Ullevål, Oslo, Norway. [4]Department of Physical Performance, Norwegian School of Sports Sciences, Oslo, Norway. [5]Department of Rheumatology, Oslo University Hospital, Rikshospitalet, Oslo, Norway. [6]National Advisory Unit on Rehabilitation in Rheumatology, Diakonhjemmet Hospital, Oslo, Norway. [7]Norwegian National Advisory Unit on Rheumatic Diseases in Children and Adolescents, Oslo University Hospital, Rikshospitalet, Oslo, Norway. [8]Bjørknes University College, Oslo, Norway.

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Errata

Page 23 (line 25-27): “Inter-rater reliability refers to the agreement of repeated measurements in the same rater while intra-rater reliability refers to the agreement of repeated measurements between different raters” is corrected to “Intra-rater reliability refers to the agreement of repeated measurements in the same rater while inter-rater reliability refers to the agreement of repeated measurements between different raters.”

Page 58 (line 20-21): “The ICC (95 % CI) at group level was acceptable for criterion validity in patients, 71 (0.51-0.82),...” is corrected to “The ICC (95 % CI) at group level was acceptable for criterion validity in patients, 0.71 (0.51-0.82),...”

Page 70 (line 14): “Z score values ≤ 2“ is corrected to “Z score values ≤ - 2”

Page 71 (line 22): “the area of biologics” is corrected to “the era of biologics”

Page 87 (reference 201): “Flato B, Sorskaar D, Vinje O, Lien G, Aasland A, Moum T, et al. Measuring disability in early juvenile rheumatoid arthritis: evaluation of a Norwegian version of the childhood Health Assessment Questionnaire. J Rheumatol. 1998;25(9):1851-8” is changed to “Selvaag AM, Ruperto N, Asplin L, Rygg M, Landgraf JM, Forre Ø, Flatø B; Paediatric Rheumatology International Trials Organisation. The Norwegian version of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ). Clin Exp Rheumatol. 2001 Jul-Aug;19(4 Suppl 23):S116-20.”

Paper III (abstract, methods and abbreviations): “Interclass correlation coefficient (ICC)” should read “Intraclass correlation coefficient (ICC).”

Paper III (results, paragraph 3): “In patients, no significant difference was found between the observed and estimated VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$); 44.8 (8.8) vs 43.2 (10.3), respectively, P = 0.18” should read “In patients, no significant difference was found between the observed and estimated VO_{2peak} ($mL \cdot kg^{-1} \cdot min^{-1}$); 45.1 (8.5) vs 43.6 (9.9), respectively, P = 0.18.”