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OROFACIAL ASPECTS OF JUVENILE IDIOPATHIC ARTHRITIS IN CHILDREN

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OROFACIAL ASPECTS OF JUVENILE IDIOPATHIC ARTHRITIS IN CHILDREN
Thesis for Doctoral Degree (Ph.D.)

By

Malin Collin

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There is nothing more deceptive than an obvious fact

Sir Arthur Conan Doyle

Dedicated to Kenneth and Elliot

Popular science summary of the thesis

Imagine that your child suddenly develops a chronic joint disease. A disease that is painful and forces them to quit football training and prevents them from opening their mouth big enough to take a bite of a hamburger or an apple. This is a real possibility for the 130-230 children that every year develop juvenile idiopathic arthritis (JIA) in Sweden. JIA is a childhood rheumatic disease, with an onset before the age of 16. It is an autoimmune disease, in which the body's immune system mistakenly attacks healthy tissues in the body. The children will suffer from joint inflammations that cause pain, stiffness and swelling and often prevents the child from participating in normal daily activities at home and at school. The inflammation can cause permanent damage to the joints leading to misalignment and asymmetry. JIA can affect all joints of the body; knee and ankle inflammations are common, but it becomes challenging from a dental perspective when it involves the jaw joint.

This thesis investigates the impact JIA has on the jaw joint, on jaw function and what to include in an orofacial examination in order to make sure to identify children with jaw joint involvement. In addition, saliva as a potential carrier of information on JIA disease activity was investigated as a part of the thesis. The overall purpose was to improve the already existing Swedish dental health care program for children with JIA.

Here we followed a group of children with JIA for two years and observed and measured orofacial characteristics. In addition, X-rays of their jaw joints were taken with two different techniques.

What we found was that jaw joint destruction was common in children with JIA; this despite the children appearing to have low disease activity and being treated with modern antirheumatic drugs. The signs of jaw joint involvement seen were, joint noises, pain at jaw movement as well as jaw joints and facial muscles being tender to pressure. We also found self-reported pain to be an important factor for identifying jaw joint involvement. The children reported pain and dysfunction in their jaw joints to a high degree and this self-reported pain coincided with findings of jaw joint destructions on X-rays. There were overall subtle changes in orofacial characteristics over the two-year observation period.

A new classification system for grading jaw joint deformities on X-rays was applied and evaluated. The X-ray technique with a lower radiation dose (panoramic imaging) proved to distinguish, with high certainty, between a healthy jaw joint and a jaw joint with deformities due to JIA. The technique that provides diagnostically acceptable information at the lowest radiation dose should always be used in children who are radiosensitive. This can be an important contribution to the health care program, if confirmed in other studies.

One part of the thesis is an exploratory study on inflammatory JIA disease markers in saliva. We could confirm that inflammatory disease markers indeed were present in the saliva samples collected but that there were no differences between children with JIA and a group of age matched, healthy children. We conclude that at present, the scientific support for using saliva to screen for disease activity in JIA is not sufficient. An interesting secondary find was that saliva flow rate was reduced in children self-reporting orofacial pain regardless of being healthy or having a diagnosis of JIA. However, the mechanisms behind this were not investigated.

Taken together, the findings in this thesis suggests that jaw joint involvement, as well as self-reported jaw pain is common in children with JIA. There may be a pattern in orofacial characteristics in children with JIA and jaw joint deformations. However, the deviation from what is normal is subtle. When adding that the natural difference between individuals is large; interpreting clinical findings alone will often be inconclusive. The key is to regularly repeat clinical examinations and observe change over time. In addition, we found panoramic imaging to be a reliable and safe method for detecting jaw joint deformities in children with JIA.

For a comprehensive assessment of jaw joint involvement in JIA we recommend including self-reported pain and dysfunction, clinical and X-ray findings, facial features, knowledge on overall disease activity and pharmacological treatment.

Abstract

Aims: This thesis, which investigates orofacial aspects and temporomandibular joint (TMJ) involvement in juvenile idiopathic arthritis (JIA), aims to improve knowledge about the variables to include in a clinical examination, radiographic imaging techniques, and whether saliva can be used as a medium for disease monitoring.

Material and methods: In a prospective longitudinal study comprising 59 children diagnosed with JIA, clinical and radiological data were collected. Demographic data and data on patient history of localized pain and dysfunction were recorded. Clinical examinations were performed according to the Research Diagnostic Criteria for Temporomandibular Disorders at baseline and repeated after one year and after two years. Radiological examinations were performed with panoramic imaging (PAN) and cone beam computed tomography (CBCT) at baseline and at the two-year follow-up. A classification system for how to grade TMJ morphology on PAN and CBCT was proposed and evaluated using radiological data from this longitudinal study.

In a case control study, stimulated whole saliva was collected from 30 children with JIA and 30 healthy age-matched controls. Self-reported orofacial pain was recorded, and saliva flow rate calculated. Saliva samples were analyzed for presence and concentration of 21 immunological active proteins using the Luminex system and customized R&B bead-based immunoassay.

Results: The result from the longitudinal study showed a higher proportion of TMJ deformities in children self-reporting TMJ pain and dysfunction. However, self-reported pain was not predictive of change in TMJ status over time. TMJ deformities were associated with a smaller maximum unassisted mouth opening (MUO), palpatory TMJ pain, and TMJ crepitations, but palpatory muscle pain, although common, did not correlate with TMJ deformities. Predictive of finding TMJ deformities was number of years with disease and a smaller MUO.

When using the proposed classification system for TMJ morphology, PAN and CBCT recognized presence of TMJ abnormality equally well. The reliability of PAN to distinguish between normal and abnormal TMJ morphology was good, and CBCT was found to be superior for assessing the severity of TMJ abnormality.

Regarding presence of immunological biomarkers in saliva, 14 of 21 examined proteins were found in the saliva samples. However, no significant differences in concentrations were found between children with JIA and healthy children. No difference in saliva flow rate was observed between children with JIA and controls, but there was an association between lower salivary flow rate and children reporting orofacial pain regardless of group.

Conclusion: In children with JIA, self-reported TMJ pain and dysfunction were common. A high degree of TMJ deformities were found, but clinical variables only showed subtle variations from what is considered normal. No single clinical variable was found to predict or indicate TMJ involvement in JIA. Regarding radiological methods evaluated, the technique that provides diagnostically acceptable information at the lowest radiation dose should be used. The result showed that PANs can be used to determine whether TMJ deformities are present in children with JIA; however, this finding needs to be confirmed in future studies. Furthermore, with the current level of knowledge and based on the results presented, saliva cannot be recommended as a medium for monitoring disease activity in JIA.

List of scientific papers

I. Temporomandibular joint involvement in children with juvenile idiopathic arthritis-Symptoms, clinical signs and radiographic findings
Collin M, Hagelberg S, Ernberg M, Hedenberg-Magnusson B, Christidis N.
Journal of Oral Rehabilitation 2022;49(1):37-46

II. Salivary biomarkers in children with juvenile idiopathic arthritis and healthy age-matched controls: a prospective observational study
Collin M, Ernberg M, Christidis N, Hedenberg-Magnusson B.
Scientific Reports 2022 Feb 25;12(1):3240

III. Panoramic imaging may detect morphologically abnormal temporomandibular joints in children with juvenile idiopathic arthritis
Collin M, Christidis N, Ernberg M, Wiklander L, Arvidsson L, Larheim T, Hedenberg-Magnusson B
Pediatric Dental Journal 2023;33:52-60

IV. Orofacial manifestations in children with JIA - a prospective cohort study
Collin M, Christidis N, Hagelberg S, Arvidsson L, Larheim T, Ernberg M, Hedenberg-Magnusson B
In manuscript

Contents

List of abbreviations

ACPA	Anti-citrullinated protein antibodies
ANA	Anti-nuclear antibody
ANOVA	Analysis of variance
CBCT	Cone beam computer tomography
CCL	Chemokine (C-C motif) ligand
CD4	Cluster of differentiation 4, a co-receptor on a T-cell
CD8	Cluster of differentiation 8, a co-receptor on a T-cell
CT	Computer tomography
CTR	Controls
CXCL	Chemokine (C-X-C motif) ligand
DC/TMD	Diagnostic criteria for temporomandibular disorders
DMARDs	Disease-modifying antirheumatic drugs
bDMARDs	Biological disease-modifying antirheumatic drugs
sDMARDs	Synthetic disease-modifying antirheumatic drugs
HLA	Human leucocyte antigen
IL	Interleukin
ILAR	The international league of associations for rheumatology
IQR	Inter quartile range
JIA	Juvenile idiopathic arthritis
JIAs	Systemic juvenile idiopathic arthritis
LTR	Laterotrusion
MMPs	Matrix metalloproteinases
MRI	Magnetic resonance imaging
MTX	Methotrexate
MUO	Maximum unassisted mouth opening
NRS	Numerical rating scale
NSAIDs	Non-steroid anti-inflammatory drugs
PAN	Panoramic imaging
PTR	Protrusion

RDC/TMD	Research diagnostic criteria for temporomandibular disorders
RF	Rheumatoid factor
SD	Standard deviation
TMD	Temporomandibular disorder
TMJ	Temporomandibular joint
TNF	Tumor necrosis factor
3Q/TMD	Three validated screening questions regarding temporomandibular disorders
Q1	Do you have pain in your temple, face, jaw, or jaw joint once a week or more?
Q2	Do you have pain once a week or more when you open your mouth or chew?
Q3	Does your jaw lock or become stuck once a week or more?

Standardized terminology and Assessment for Orofacial Conditions in Juvenile Idiopathic Arthritis: International, Multidisciplinary Consensus-based Recommendations[1]

TMJ arthritis	Active inflammation in the TMJ
TMJ involvement	Abnormalities presumed to be the result of TMJ arthritis
Dentofacial deformity	Abnormality in growth, development, structure, and/or alignment of the facial bones and dentition
TMJ deformity	Abnormality in growth, development, or structure of the osseous and/or soft-tissue components of the TMJ

Introduction

From an orofacial viewpoint, this thesis highlights different questions about juvenile idiopathic arthritis (JIA). The literature review covers JIA as one of many rheumatic diseases that can affect children, normal growth patterns and growth disturbances due to JIA, immunological markers of interest in JIA, and saliva as a medium for detection and monitoring of these biomarkers. In addition, background information is provided on the temporomandibular joint (TMJ) and clinical and radiographic examination techniques used in dentistry for detection of TMJ involvement in JIA.

Although JIA is the most common of rheumatic diseases in children,[2] its etiology is not fully elucidated. Moreover, JIA is an autoimmune/autoinflammatory disease that can affect all joints of the body including the TMJ.[3,4] Advancements in pharmacological treatment in the last decades have improved long-term disease outcome, but JIA is a chronic disease that can continue into adulthood.[5] Goals in management and treatment of children with JIA are to relieve symptoms, maintain growth, and preserve function. To achieve these goals, early identification and treatment are crucial.

The evaluation of disease activity in children with JIA is primarily based on clinical examination, imaging, and conventional variables of inflammation. Effective evaluation requires the expertise of several medical professions such as pediatric rheumatologists, physiotherapists, radiologists, ophthalmologist, and, for assessing orofacial health, dentists. Effective evaluation also requires tools such as validated examinations techniques with established cut-off values and reference standards for distinguishing between normal findings and pathology. Although a great deal of research has been done on TMJ involvement in children with JIA, few longitudinal studies have been published and even fewer have been published that reflect the last decades of improvement in pharmacological treatment. To date, most studies lack comprehensive and validated examination protocols for orofacial evaluation of children with JIA. In addition, there is no consensus on what variables to include in a clinical examination (and how to interpret said variables) or which imaging technique to use. Evidence on how to predict TMJ involvement or progression of TMJ involvement in JIA is also lacking. This knowledge gap needs to be filled and methods for identifying and managing TMJ involvement in JIA need to be developed to ensure that children with JIA receive proper care and maintain good quality of life.

This thesis investigates progression of TMJ involvement in JIA and what clinical and radiographic examination techniques to use for detection of TMJ deformities. In addition, this thesis investigates saliva as a potential carrier of information on disease activity.

1 Literature review

1.1 Rheumatic disease in children

Pediatric rheumatic disease is an umbrella term including a large group of connective tissue and musculoskeletal disorders (summarized in Figure 6 at the end of the literature review). All these diseases are autoimmune or autoinflammatory diseases with an onset during childhood. All pediatric rheumatic diagnoses are mutually exclusive, and each has its own set of signs, symptoms, and diagnostic criteria. Many of these diseases show joint involvement, but other organs and parts of the body can also be affected, including eyes, skin, blood vessels, muscles, and internal organs such as the gastrointestinal tract. Although there are undoubtedly genetic predispositions and environmental triggers for these diseases, no single factor can explain the pathogenesis or the diversity of the clinical patterns they display. In some cases, the rheumatic disease is short lived and easily treated, but often the disease is lifelong. Rheumatic disease in children affects not only the quality of life of the children but also of their families.

1.2 Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) is a complicated disorder and an exclusion diagnosis that covers arthritis that persists for more than 6 weeks, has an onset before the age of 16 years, and are of unknown etiology.[3] The current classification system was published in 2004 by The International League of Association for Rheumatology (ILAR).[6] The classification is based on clinical characteristics presented during the first six months of disease and are divided into seven mutually exclusive sub types: systemic arthritis (sJIA), oligoarthritis (persistent an extended), polyarthritis rheumatoid factor (RF) positive, polyarthritis RF negative, enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis.[6] There are three main criteria for JIA (Figure 1) and specific mutually exclusive criteria for each subgroup (Figure 2).

Figure 1. Criteria for the diagnosis of juvenile idiopathic arthritis (ILAR 2004)[6]

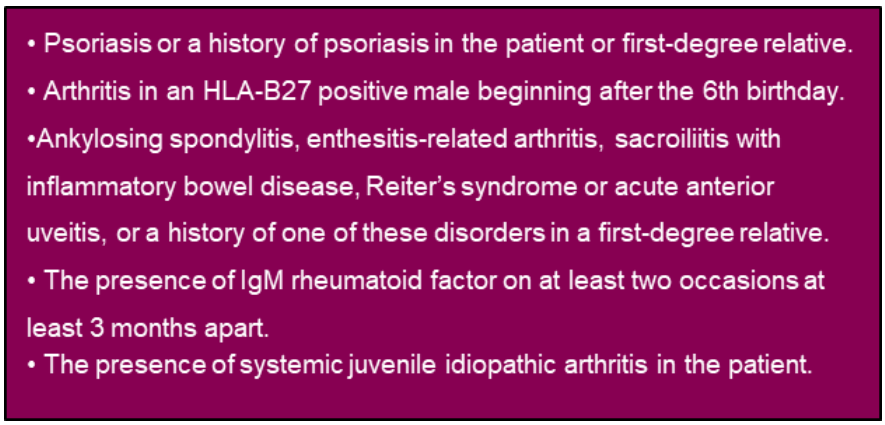

Figure 2. Mutual exclusion criteria for respectively subtype of juvenile idiopathic arthritis (ILAR 2004)[6]

Current research and understanding points in the direction that JIA might not be a single distinct disease. The ILAR criteria have been criticized as there is evidence that some of the JIA subgroups represent heterogenic conditions while other subgroups do not.[7] This evidence indicates that the current classifications of JIA subtypes actually represent a mix of different diseases with a common clinical feature, namely arthritis with onset in childhood.[7] Nevertheless, ILAR criteria are still the best available diagnostic system and are used daily throughout the world.

1.2.1 Clinical manifestations

Many children affected by JIA are very young at disease onset. Symptoms often appear in a remitting-relapsing pattern and parents and children may report pain, limping, swelling and tenderness of joints, morning stiffness, fever, weight loss, and fatigue.[8] Large joints are more frequently involved, especially the knee and the ankle, but any joint might be affected. A careful physical examination is essential since it may reveal more joints affected than those mentioned by the patients or their parents. The clinical skills required for musculoskeletal examination of children include knowledge of growth and expected development of the musculoskeletal system and the subtle range of normality and abnormality. JIA also commonly affects the uvea and the iris, and children should regularly be examined by an ophthalmologist.[8,9] Untreated JIA can cause destruction of joint tissue, growth impairment, skeletal malalignments, and deformities and, if the eyes are affected, blindness.

As JIA often varies in severity and degree of inflammation over time, treatment and medication must be closely monitored. There are risks for long-term consequences from the disease as well as from applied medication such as growth impairment, low

bone mineral density/osteoporosis, as well as a decreased muscle mass.[10-14] Pain is a common symptom and self-report early disease related pain is predictive of ongoing or development of persistent pain and unfavorable disease outcome.[15]

In 1999, biologic disease-modifying antirheumatic drugs (bDMARDs) were introduced in the JIA treatment regime and a dramatic improvement in treatment outcome in children with JIA followed.[5] Long-term prediction of disease outcome can now be made with acceptable precision[16] and evidence suggests that early aggressive treatment may alter the course of the disease as well as improve long-term prognosis.[17-19] Today, children with JIA have a significant chance of recovering but a substantial portion continues to have active disease into adulthood.[20,21] The chance to lifelong remission varies depending on subtype and 30%–50% of the children are expected to achieve remission off medication.[20-24]

1.2.2 Epidemiology

Although the distribution of JIA appears to be worldwide, reported incidence and prevalence vary between contries and regions. These differences can be explained by the fact that this is a heterogenic group of patients, the use of different classification systems, accessibility to health care, differences in study techniques, as well as differences in genetics and ethnicity of the source population. The annual incidence rate of JIA varies between less than 1 child per 100 000 in Japan to more than 20 per 100 000 in Norway.[25] In Sweden, the incidence of JIA is 11–15 per 100 000 children based on two longitudinal prospective population studies by Anderson-Gäre and co-workers (1999) and Berntson and co-workers (2003), which means that in Sweden approximatly 200–250 children every year develop JIA.[26,27]

There is a pattern of female predilection in all subgroups of JIA except in sJIA and enthesitis-related arthritis.[7,25,28] Overall twice as many girls than boys receive a diagnosis of JIA. There is a also a tendency for earlier disease onset in girls than in boys.[25,28] Proportions and typical age of onset in each subtype of JIA are presented in (Table 1).

Table 1. ILAR classification of juvenile idiopathic arthritis: categories, frequency, and age distribution.[6]

ILAR category	Frequency	Age of onset
Oligoarthritis	30%–60%	Early childhood
Rheumatoid factor-positive polyarthritis	3%–7%	Late childhood or adolescence
Rheumatoid factor-negative polyarthritis	10%–25%	Biphasic distribution: early peak at <6 years and late peak at >6 years
Enthesitis-related arthritis	5%–10%	Late childhood or adolescence
Psoriatic arthritis	3%–10%	Biphasic distribution: early peak at <6 years and late peak at >6 years
Systemic arthritis	5%–15%	Any pediatric age
Undifferentiated arthritis	10%–20%	-

1.2.3 Growth impairment

Bone formation and skeletal growth takes place during childhood and adolescents; later in life, bone is continually resorbed and formed in a normal turnover to maintain healthy tissue and to adapt to function. This process is regulated by factors such as insulin-like growth hormones, growth hormones, locally produced cytokines, and mechanical loading. Chronic inflammatory diseases are often associated with shorter stature due to growth failure.[29] Inflammation can also cause local acceleration of growth in an affected limb, for example, unilateral knee arthritis is known to cause length discrepancies of legs.[30]

1.2.4 Genetics

Although there is a clear genetic susecptibility in JIA,[29] linking the clinical phenotypes to specific genetic markers has been challenging. There are no single common genetic risk factors identified so far, but different subtypes of JIA show slightly different gene patterns and studies have found association to several HLA alleles.[29,31] The ILAR classification of JIA subtypes fails to fully reflect this underlying disease biology.[31] Several studies have established relationship between JIA and both HLA class I (HLA A-2 & HLA B27) and HLA class II (HLADRB1 & HLA DP).[32-34] Furthermore, presence of HLA-B27 together with a later disease onset predict a more extended disease.[35]

In addition to the HLA alleles identified, evidence suggests an association between non-HLA single-nucleotide polymorphisms and a risk of developing JIA.[31] There is also a risk of unfavorable long-term disease outcome associated with these non-HLA single-nucleotide polymorphisms.[36] Several reasons explain both the lack of one universal as well as the multitude of genetic risk factors found, but it mostly indicates, as mentioned before, that JIA is not one single disease and genetics are not the only explanation.[7,31]

1.2.5 Pathogenesis

The pathogenesis of JIA is still not fully explained and there are no disease specific markers identified. JIA is a complex autoimmune disease, and the theory is that a combination of environmental factors can trigger an autoimmune response in children that are genetically predisposed. What role environmental factors play in JIA immune pathogenesis is still not clear although there are reports that indicate that infections, alterations in gut-microbiota, and exposure to antibiotics are risk factors.[37,38]

1.2.6 Immunopathophysiology

Genetic changes in HLA alleles are relevant for understanding the pathogenesis of JIA and underscores the importance of the adaptive part of the immune response. The main function of HLA molecules is to present processed antigens to CD4 and CD8 T cells and any disturbances in this function can potentially change the immune response.

Arthritis as well as other manifestations of JIA are caused by changes in the innate immune response as well as a loss of immunological tolerance in the adaptive immune response; the first causing autoinflammation and the second resulting in auto reactive T- and B-cells and production of autoantibodies. In the joints, JIA is typically associated with persistent inflammation of the synovial membranes, pannus formation, and, if not treated, irreversible joint damage.[25,39,40]

The immune response is facilitated by proteins released from cells of the innate and adaptive immune system: cytokines and chemokines. These proteins mediate the immune and inflammatory response by binding to cellular receptors thus starting and modulating the cellular response.[25,28,41,42] Both pro- and anti-inflammatory cytokines are

essential in the pathogeneses of JIA as they drive the immune response. Some of these molecules are part of the innate immune response, e.g., TNF-alpha, interleukin-1 (IL-1), and IL-6, and IL-10[42-45], while others are part of the adaptive immune response, e.g., IL-2.[40,43] Some cytokines such as IL-12 play roles in both innate and adaptive immune response.[46]

TNF-alpha, IL-1, IL-6, and IL-8 have been shown to be pro-inflammatory,[43,45,47,48] while TNF receptor-2 (TNFs RII/ TNFRSF1B), soluble IL-1 receptor antagonist (IL1-RII), and IL-10 down regulates the immune response and have anti-inflammatory properties.[49-51]

In recent years, research on a group of myeloid-related proteins called S100A has shown that they can be used to monitor and possibly predict disease course and treatment outcome in JIA.[52] Other studies have shown that the same can be said for IL-1β, IL-6, and IL-12 [53]. All these biomarkers are interesting to monitor since levels might change during disease flare and remission. The different subtypes of JIA also have different cytokine profiles.[54]

Immunological biomarkers that are clinically relevant are anti-nuclear antibodies (ANA), RF, and anti-citrullinated proteins (ACPA). Presence of ANA is slightly more frequent in girls than in boys[55] and positive ANA correlates with elevated risk of developing uveitis (chronic iridocyclitis).[56] Five percent of children with JIA have positive RF and this is predominantly seen in older children with polyarthritis. Positive RF in children is thought to indicate childhood onset of adult rheumatoid arthritis.[57] ACPA is a highly specific biomarker and part of the diagnostic criteria for rheumatoid arthritis in adults.[58] In children, the presence of ACPA is uncommon but it has a high specificity for JIA and, when present, it is a marker for severe bone involvement.[59,60] There have been suggestions that ACPA be included in future classification system of JIA.[61]

1.2.7 Treatment

Treatment of JIA requires a multi-disciplinary approach involving a team of medical specialists. Longtime goals of treatment are to control symptoms, prevent structural damage, and ensure physical functioning as well as monitor and facilitate growth and development. In Sweden, guidelines for pharmacological treatment are published and regularly updated by Svensk Barnreumatologisk Förening (accessed 20220921,

https://reuma.barnlakarforeningen.se/wp-content/uploads/sites/11/2022/01/Farm-beh-2022-01-25.pdf). There has been considerable improvement in pharmacological treatment of JIA the last two decades, the introduction of biological disease modifying antirheumatic drugs (bDMARDs) being the most important one.[5,20,22] Despite the medical advancements made, JIA is still a challenge to treat.

1.3 The stomatognathic system

The stomatognathic system consists of the temporomandibular joints, bones around the oral cavity, muscles involved in chewing and swallowing, teeth, and soft tissues such as gingiva, mucosa, tongue, lips, cheeks, and salivary glands.

1.3.1 The temporomandibular joint

The TMJ is just one of the joints affected by JIA; however, in this thesis, it is the center of attention. This part of the introduction will cover anatomy, healthy growth pattern, changes in growth pattern when the TMJ affected by JIA, symptoms, and clinical picture as well as clinical and radiographic examination techniques.

Anatomically the TMJ consists of two articulating surfaces–one on the temporal bone and one on the mandibular bone (Figure 3). A thin layer of fibrocartilage covers the articulating surfaces of the joint. Interposed between these articulating surfaces is a fibrocartilage disc situated and held in position by retrodiscal tissue. The disc divides the joint cavity into two compartments–the inferior and the superior joint space. A normal disc is biconcave where the thin central segment serves as the articulating part during mandibular movement and the thicker surrounding part helps hold the disc in place. The joint is enclosed by a fibrous capsule with a synovial membrane, which lines all non-force-bearing surfaces of the joint. The synovial membrane secrets synovial fluid, which lubricates the joint. Although the TMJs anatomically are two separate joints, they function together as one unit as both condyles are part of the mandibular bone. Another unique aspect of the TMJs is that during mouth opening two movements occur in the joint–rotation and translation.

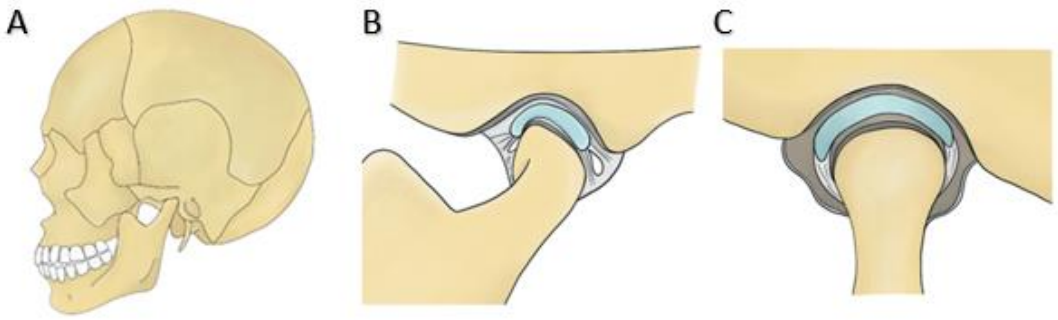

Figure 3. Illustrations of A) a lateral view of the head B) A lateral view of the TMJ, demonstrating the relationship between the condyle, fossa, articular eminence, and the articular disc C) A sagittal view of the TMJ, showing the articular disc, condyle, and fossa. Figure by Johanna Svedenlöf, adapted from illustrations from "Bettfysiologi – orofacial smärta och käkfunktion" (Nikolaos Christidis, Gothia, 2020) with permission from the publisher.

1.3.2 Growth

Orofacial skeletal growth is of two different types–displacement and remodeling (endochondral ossification)–and the growth rate changes over time.[62] In the mandible, the growth is of both types; the mandible is progressively displaced in an anterior, inferior direction, away from the condyle and the articular surface, and at the same time, the condyle and the ramus is remodeled in the opposite posterior, superior direction.[63]

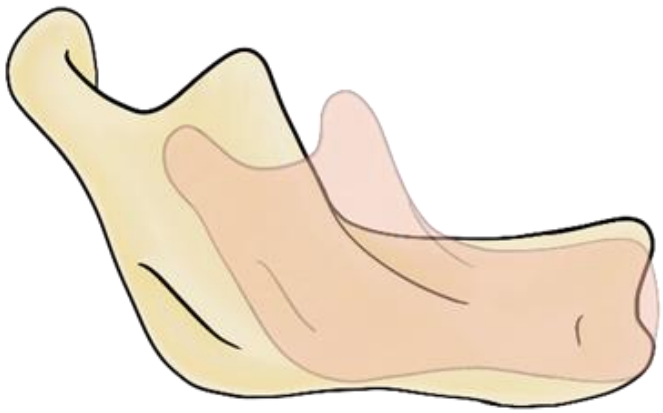

Figure 4. Showing the mandibular and condylar growth pattern. Figure by Johanna Svedenlöf.

During childhood, formation of new bone on the mandible occurs mainly on the caput and ramus parts of the bone.[11] In the condyle head, the growth plate is situated at the surface and under a thin layer of fibrocartilage.[64] Growth occurs in this area from the

prenatal period until just after puberty.[64] Growth velocity peaks before the age of three, and then slowly diminishes by middle to late teens. The TMJ reaches 50% of mature size by the time of completed eruption of the primary dentition (around 2.5 years of age).[65]

TMJ structural changes, both in volume and character, occur during growth.[11,65,66] In children, the condyle is rounded[67] and then normally grow more in medio-lateral direction than in antero-posterior,[68,69] resulting in an adult condyle in the form of a cylinder. In young individuals, the cortical bone enclosing the condyle is not continuous and compact. During adolescence, the cortical bone begins to form around the periphery of the condyle, but the cortical bone is not fully developed until the age of 20–22.[70,71] These morphological changes can make it a challenge to interpret TMJ imaging of children.

1.4 Temporomandibular joint involvement in juvenile idiopathic arthritis

TMJ involvement in children with chronic arthritis was first described by Still in 1897.[72] In the literature, the TMJ has been called the silent joint since TMJ arthritis was thought to be rare and, when present, frequently asymptomatic. Today, we know that TMJ involvement is common, but due to differences in examination methods, definition used, and the populations studied the reported incidence and prevalence vary. In studies using panoramic imaging, the prevalence of unilateral TMJ deformities in children is reported to be high (about 40%).[73-75] In older patients, TMJ deformities will develop into a more bilateral and symmetric condition.[76]

The fact that TMJ involvement often are clinically silent despite magnetic resonance imaging (MRI) or computed tomography (CT) findings has been confirmed in several studies.[77-79] Some studies have found a higher rate of TMJ involvement in JIA subgroups with polyarticular involvement,[74,80,81] but other studies show that presence of antigen HLB-B27 seems to be protective.[80,81] There is also evidence that the TMJ may be the first as well as the only joint affected.[82,83] However, there is still no single marker that specifically predicts TMJ involvement in JIA.

1.4.1 Clinical manifestations

The common belief has been that in many children with JIA TMJ involvement starts and then evolves without any symptoms. Several studies show that TMJ arthritis are not linked to medical history or physical findings such as joint noises, pain, localized tenderness, or jaw asymmetry.[78,79,84]

However, a study by Larheim from 1982 showed that restricted mouth opening was associated with morphological changes in the TMJ in children with JIA [75]. In addition, recent studies show that pain and jaw function limitation are common and affect the quality of life in children with JIA.[80,85] Symptoms of TMJ involvement include limited maximal mouth opening, functional pain such as chewing pain and pain on movement,[86,87] as well as ear pain and headache.[28] One study from 2012 showed that mouth opening deviation was highly predictive of TMJ arthritis.[88] Reduction in biteforce has also been associated with TMJ involvement in JIA.[89] The introduction of bDMARDs for management of JIA has led to a great improvement in disease outcome.[90] Nevertheless, prospective longitudinal studies have shown that self-reported orofacial pain and functional disability[86,91] as well as dentofacial deformities are still common[4] and that TMJ involvement according to MRI is highly prevalent in JIA children both with and without symptoms.[92] However, to accurately identify TMJ involvement in JIA by clinical examination alone is still a challenge TMJ.

1.4.2 Changes in growth in the TMJ and the facial skeleton due to JIA

In addition to general growth disturbances that are common in JIA due to disease activity and medication, inflammation in the TMJ during the growth period cases typically changes in growth patterns.[93-95] Changes in the TMJ are characterized by deformation and morphological variations such as flattening of the condyle and fossa/eminence and widening of fossa and condyle anteroposteriorly [96] whereas classical surface erosions are rare.[97] These characteristic in TMJ morphology in JIA are likely a result of growth disturbances due to inflammation[98] and not the equivalence of what is seen in TMJ involvement in adults with rheumatic disease. The position of the growth center in the condyle makes it vulnerable for inflammation and trauma.

Dentofacial morphology in children with JIA is characterized by a mandible that is overall smaller, more retrognathic, and with steeper mandibular angulation. There is also a typical pattern of Class II malocclusion, frontal open bite, and dental crowding.[99-101] Changes in proclination and protrusion in upper and lower incisors are also common.[99,100,102] In unilateral deformities of the TMJ, facial asymmetry might occur[73,103]; in bilateral deformities of the TMJ, micrognathia with reduced posterior airway space are seen.[76,104]

All these changes have life-long negative functional and aesthetic consequences, with a debut at a psychologically sensitive age.[78] The severity of these orofacial alterations is linked to JIA subtype and are most prominent in the polyarticular subtype.[86] The time of disease onset has a strong impact on the severity of mandibular growth deviations; early onset increases the risk for adverse effects on growth.[99] All these consequences are difficult to treat when already present. Today, it is not possible to with any certainty single out individuals who might be at a higher risk for growth disturbances. TMJ deformities may improve over time if disease activity is low,[86] but they may also persist and progress from childhood into adulthood.[105,106]

1.5 Diagnostic methods

As TMJ historically belongs to odontology rather than medicine per se, it has been overlooked. Over the last decade, joint efforts have been done to establish recommendations for diagnostic and therapeutic management of TMJ involvement in JIA. The network EuroTMjoint (now Temporomandibular Joint Juvenile Arthritis Working Group), initiated in Oslo 2010 is now a global network, and has provided at platform for collaborations for researchers at dental and medical centers. This network aims to facilitate research on TMJ arthritis in JIA, provide support and educational material on TMJ arthritis and craniofacial development in JIA for physicians and other health care professionals, and in the end improve the therapeutic management of JIA patients with TMJ arthritis.

In Sweden, guidelines for dental assessment and management of children with JIA was established in 2003. These guidelines were drawn up according to best scientific knowledge available by a group of specialists with expertise on JIA. Since these

guidelines were introduced, they have been used at the Department of Orofacial Pain and Jaw Function at Folktandvården Eastmaninstitutet.

1.5.1 Clinical examination

To evaluate oral health in a consistent way, a reliable examination protocol is required. In dentistry, many pathological conditions are well defined such as caries, different types of malocclusions, and periodontal disease. However, variables such as mandibular range of motion in children do not have well defined cut-off values for pathology. Orofacial pain is traditionally used as an important diagnostic marker for myalgia and arthritis, but previous studies on JIA show that pain is a poor predictor of TMJ involvement.[78,79] To evaluate temporomandibular disorders (TMD) and the TMJ, examination protocols such as the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) have been developed. Since first published in 1992, the RDC/TMD has created common ground for researchers in the field.[107] It consists of an examination protocol and a strict key for diagnosing different types of temporomandibular disorders such as myalgia, different types of disc disorders, as well as osteoarthritis and osteoarthrosis of the TMJ. However, the RDC/TMD has weaknesses. It was developed for otherwise healthy adults and consequently does not consider either the impact of rheumatic disease, age, or growth. Despite this, the RDC/TMD has been used numerus times in research on adults with rheumatic diseases as well as in studies on older children and adolescents.[108-111]

1.5.2 Imaging of the temporomandibular joint

TMJs are difficult to depict in one single radiologic projection.[112] The TMJ is located slightly below and behind protrudin parts of the temporal and zygomatic bone, which tend to superimpose in images of the joint (Figure 3). As the joint is a three-dimensional structure, a two-dimensional image is insufficient. Different techniques have been used to overcome these obstacles, and today cone beam computed tomography (CBCT) and MRI are best suited for obtaining detailed information about TMJs. As previously mentioned, TMJ morphology differs between adults and children in several aspects such as dimensions and angulations, and the cortical outlining of the condyles is thinner in children.[68]

With prolonged arthritis of the TMJ comes joint changes that need to be assessed such as cartilage destruction, bone erosion, and joint malalignment. Radiographs show the skeletal changes and MRIs show changes in soft tissue as well as effusion in the joint space. New atlases and MRI scoring system for the TMJ in JIA are under development[42,113] and MRIs are the gold standard diagnosing arthritis in the TMJ. Lately, a risk of false positive results for TMJ arthritis has been reported[96,114] as well as a risk for gadolinium deposition in the brain.[115] Consequently, MRI as the gold standard method has been questioned. CBCT is superior to MRI when looking at morphological changes in the osseous joint components.[96]

When selecting imagining technique, it is important to remember that children have more radiosensitive tissues than adults. In clinical practice, one should always use the modality that provides acceptable images at a radiation dose as low as diagnostically acceptable. Therefore, all radiographic examinations should be done on strict indication.[116] Other factors that influence the choice of imaging techniques can be availability of machinery or whether the examination may be challenging for a child. In this project, two imaging techniques were used: CBCT and panoramic imaging (PAN).

1.5.2.1 Panoramic Imaging

PAN, a low-dose radiological method,[96,117] is used for examination of TMJs in children with JIA.[98] PAN provides a broad overview of the maxilla, mandible, and surrounding structures. The method is easily available, and a successful examination can be performed in seconds. The diagnostic value of PAN compared to CBCT is considered low and this is clearly demonstrated in many studies on adults.[118–120] For children, there seems to be no previous comparative studies of PAN and CBCT on this issue. However, studies that have followed children with JIA longitudinally via PAN examinations have reported that deformities of the mandibular condyle can be observed and assessed.[86,106] Gross osseous changes in the condyle can be identified but a panoramic projection cannot detect mild osseous changes on the condyle and only marked changes in the articular part of the joint. For a more detailed image of the TMJ, other techniques are required.

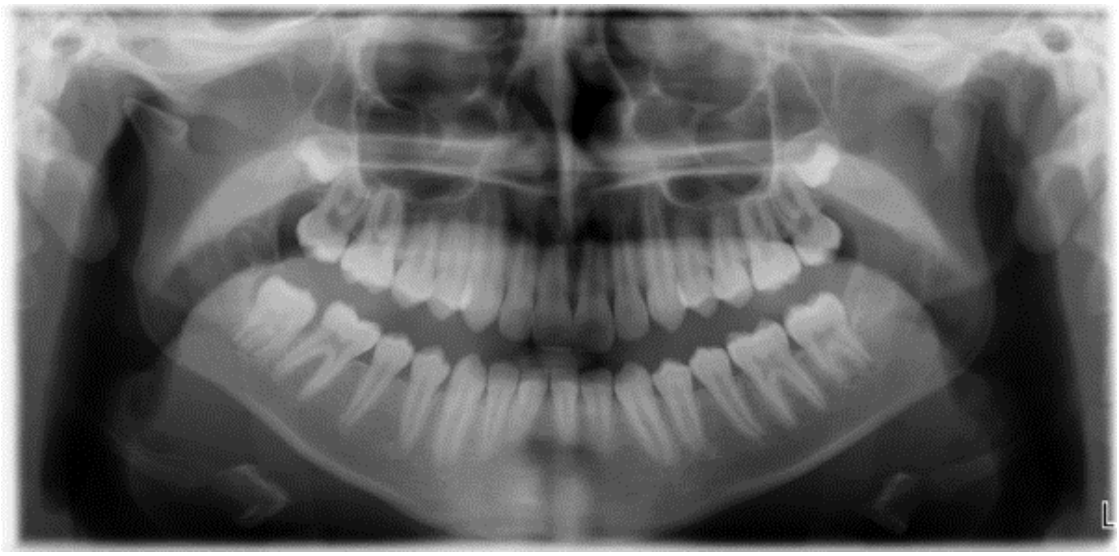

Figure 5. A panoramic image of a 16-year-old boy with oligoarthritis since the age of 2 years. Despite no history of TMJ arthritis the right TMJ shows a Grade 3 abnormality.

1.5.2.2 Cone beam computed tomography

Since CBCT was introduced in odontology in the late 1990s, it has quickly reached wide acceptance and is today accepted as the superior method for assessing bony components of the TMJ.[96] The CBCT technique produces volumetric images that allow reconstruction of a thin section that can be viewed in multiple planes. CBCT makes it possible to reliably depict the complicated topography of the TMJ with a minimum of distortion. CBCT is currently considered the best method for assessing bony TMJ components.[96] The disadvantages of using CBCT, especially when dealing with pediatric care, is that it is relatively sensitive for movement distortion and has a higher radiation dosage than PAN.[96,117]

CBCTs are available in Sweden but not at every dental clinic. The Swedish Radiation Safety Authority licenses clinics to operate CBCT machines. The licensed clinics must meet certain requirements regarding staff competence, radiation safety, and responsibility. As not all countries have the same strict regulations, CBCTs are more readily available in these countries. Concerns have been raised that easy access to CBCT might lead to overuse for radiological examinations where intraoral imaging or PAN could be equally informative.[121] The method can be used for TMJ examinations in patients with JIA.[122,123]

1.6 Orofacial management of JIA

The goal for dental assessment and management of children with JIA is to maintain oral health, oral functions, and dentofacial development. This encompasses the entire spectrum that dental care offers, from help with oral hygiene and caries prevention to providing timely diagnosis of TMJ involvement. Early diagnosis and treatment of TMJ arthritis is central to avoid permanent joint damage and impaired growth. In cases with TMJ involvement, the management goals are reduction of TMJ inflammation, reduction of TMJ- and TMD-related symptoms and dysfunctions, normalization of dentofacial development, and addressing dentofacial deformities.[124,125] In addition, it is well established that TMJ involvement in JIA has negative influence on quality of life and this aspect of the disease must also be included in management and treatment.[91,126,127]

1.7 Saliva

1.7.1 Saliva–function, secretion, content

Saliva is a biofluid with multiple roles such as protecting teeth and the oral mucosa, initiating digestion, and facilitating mastication and swallowing. The secretion of saliva, an autonomic response, is mainly produced by three pairs of large salivary glands: the parotid, submandibular, and sublingual glands. The composition of saliva varies depending on glandular origin. The parotid glands produce serous saliva, and the sublingual and submandibular glands produce a mixture of serous and mucous saliva. In the resting state, about two-thirds of the volume is produced by the submandibular glands and during stimulation 50% of the saliva derives from the parotid glands.[128] Normally, the salivary glands produce 0.5–1.5-liter saliva per day, which consists to 99% of water and contains many kinds of minerals, proteins, and peptides.[129] There are diurnal variations in saliva flow and content and saliva flow is influenced by both psychological and physiological factors.[130–132] The composition also differs between men and women and it changes with age.[133]

1.7.2 Methods for saliva sampling

Saliva can be collected in several ways and different methods will produce different volumes and types of saliva. Saliva flow can be stimulated mechanically and by applying

citric acid to the tongue.[134] Saliva can also be collected as one whole volume or as separate volumes collected from each gland.[135,136] Different sampling techniques provide different proteomic profiles and consistency in technique is important.[137] Saliva sampling techniques are noninvasive and mostly pain-free.

1.7.3 Salivary biomarkers as a diagnostic tool

Saliva mirrors the content of blood but contains lower concentrations of some analytes.[138] It also contains an abundance of large/heavy proteins synthesized in the salivary glands (mucins, cystatins, and proline-rich peptides). Advancements made in methodology and analytical techniques have made saliva useful for diagnostics and for disease monitoring.[139–142] Saliva has successfully been used for detection of pro-inflammatory cytokines in immune diseases[143] and to study biomarkers in rheumatic disease in adults.[141,144] As previously described, specific biomarkers are of interested in JIA and some, but not all, have been studied in saliva as well as other biofluids beside serum and plasma.

Studies in adults have shown both similarities and discrepancies in biomarker expression in different biofluids such as saliva, serum, plasma, and urine.[140–142] In children with JIA, saliva has been studied regarding factors vital to maintaining good oral health, such as saliva flow rate, pH, salivary oxidants, and bacterial components.[145,146] There are also studies showing that metalloproteinases can be detected in saliva in children with JIA and both increased and decreased levels have been reported.[145,147,148]

A biofluid that can be collected noninvasively (i.e., saliva) has great potential for providing clinicians and researchers valuable information in diseases such as JIA.[54,145,147–150] Consequently, saliva has the potential of becoming important in JIA diagnostics and research.

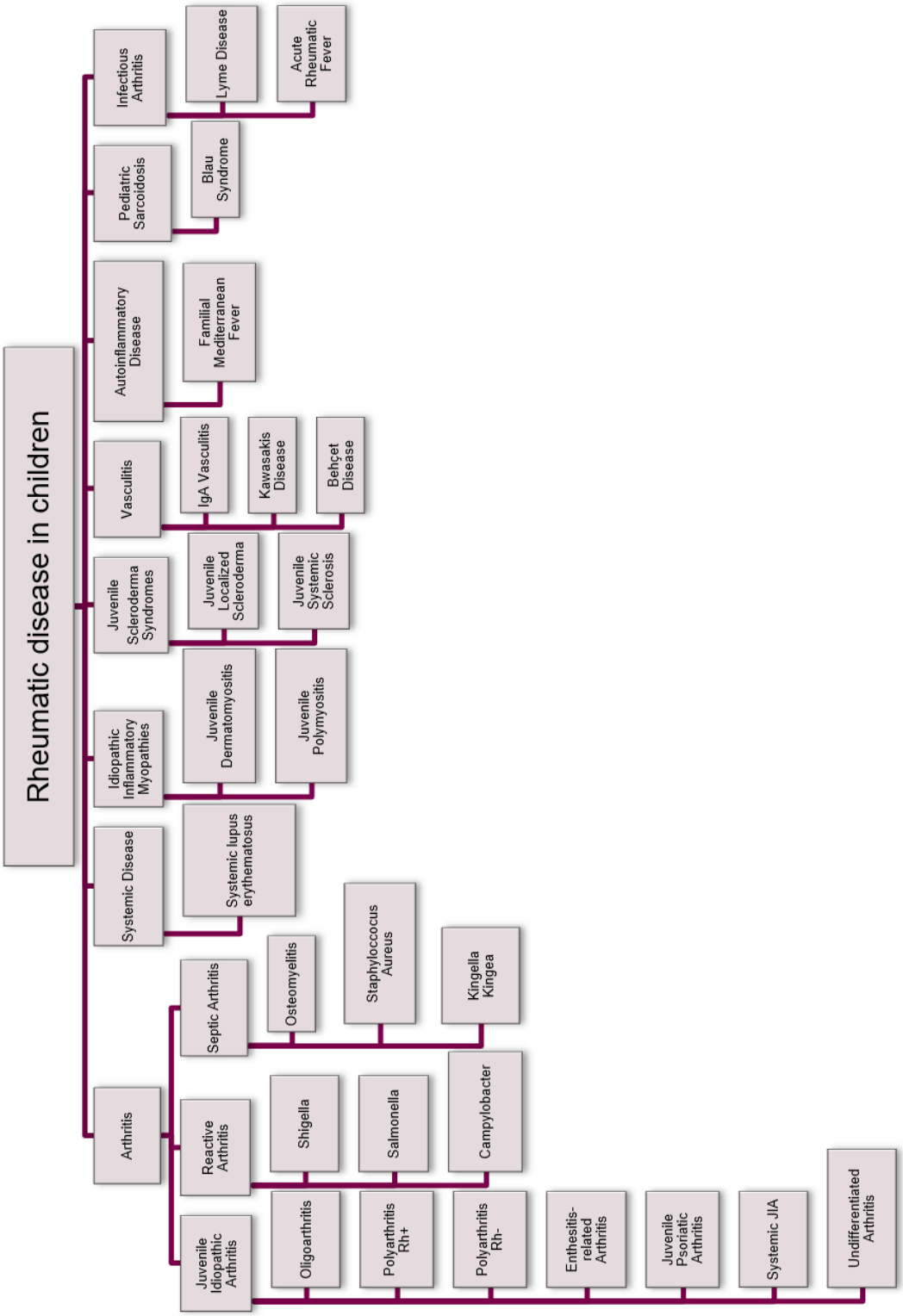

Figure 6. Pediatric rheumatic diseases, a schematic overview of some of the different subtypes. (After Textbook of Pediatric Rheumatology, sixth edition. Cassidy, Petty, Laxer & Lindsley and the7th EULAR / PRES Online Course in Paediatric Rheumatology)

2 Research aims

This thesis aims to gain a better understanding on orofacial manifestations in children with JIA, including what clinical variables imply TMJ involvement, which radiologic technique to use to exclude TMJ involvement, and finally whether saliva can be used to detect immunological biomarkers of relevance in JIA. Moreover, this thesis aims to find valid and reliable methods for examining and detecting TMJ involvement in children with JIA and contribute to improvement of the Swedish national care program for orofacial health in children with JIA.

The objectives were:

Study I & IV: To investigate if self-reported symptoms or clinical variables indicate or predict TMJ deformities or change in TMJ deformities over time.

Study I & IV: To investigate the associations between clinical variables and TMJ deformities

Study II: To compare detectability and concentration of a set of salivary biomarkers in children with JIA compared to a control group of healthy children.

Study II: To investigate salivary flow rate in relation to presence of JIA and/or orofacial pain.

Study III: To validate a modified classification system for radiological assessment of grade of TMJ deformities in a sample of children with JIA.

Study III: To investigate, using the modified classification system, the reliability of PAN to assess abnormal TMJ morphology, with CBCT as gold standard, in a sample of children with JIA.

Specific aims and hypotheses

S*tudy I*: This study aimed to investigates if findings from patient history and clinical examination, using the RDC/TMD, can diagnose TMJ involvement in children with JIA. The hypothesis was that self-reported pain on mouth opening in combination with reduced contralateral excursion is more common in children with JIA-associated TMJ abnormalities.

Study II: This study aimed to investigate the detectability and concentration of cytokines and chemokines in saliva in children with JIA and matched controls. In addition, saliva flow and the influence of orofacial pain on saliva flow was investigated. The hypotheses were that the expression of inflammatory mediators in saliva differs between children with JIA and healthy controls and that salivary flow rate is related to orofacial pain in children with JIA.

Study III: This study aimed to investigate, using a modified classification system, the reliability of PAN to assess abnormal TMJ morphology, with CBCT as gold standard, in a sample of children with JIA. The hypothesis was that the reliability of PAN for identification of abnormal TMJ morphology in this subset of children (age 7–14 years and with JIA) is good.

Study IV: This study's aim was twofold: to evaluate a set of clinical variables and their ability to identify and/or predict development of TMJ involvement over time using CBCT as outcome variable and to investigate the predictive value of self-reported TMJ pain for presence and for development of TMJ abnormalities over time. The hypothesis was that self-reported TMJ pain and dysfunction and clinical variables such as mandibular range of motion and palpatory findings can detect and/or predict TMJ involvement JIA.

3 Materials and methods

3.1 Study design

This thesis is based on one observational cohort study with a prospective longitudinal design (Figure 7) and one observational prospective case-control study. The studies were performed at the Department of Orofacial Pain and Jaw Function at Folktandvården Eastmaninstitutet.

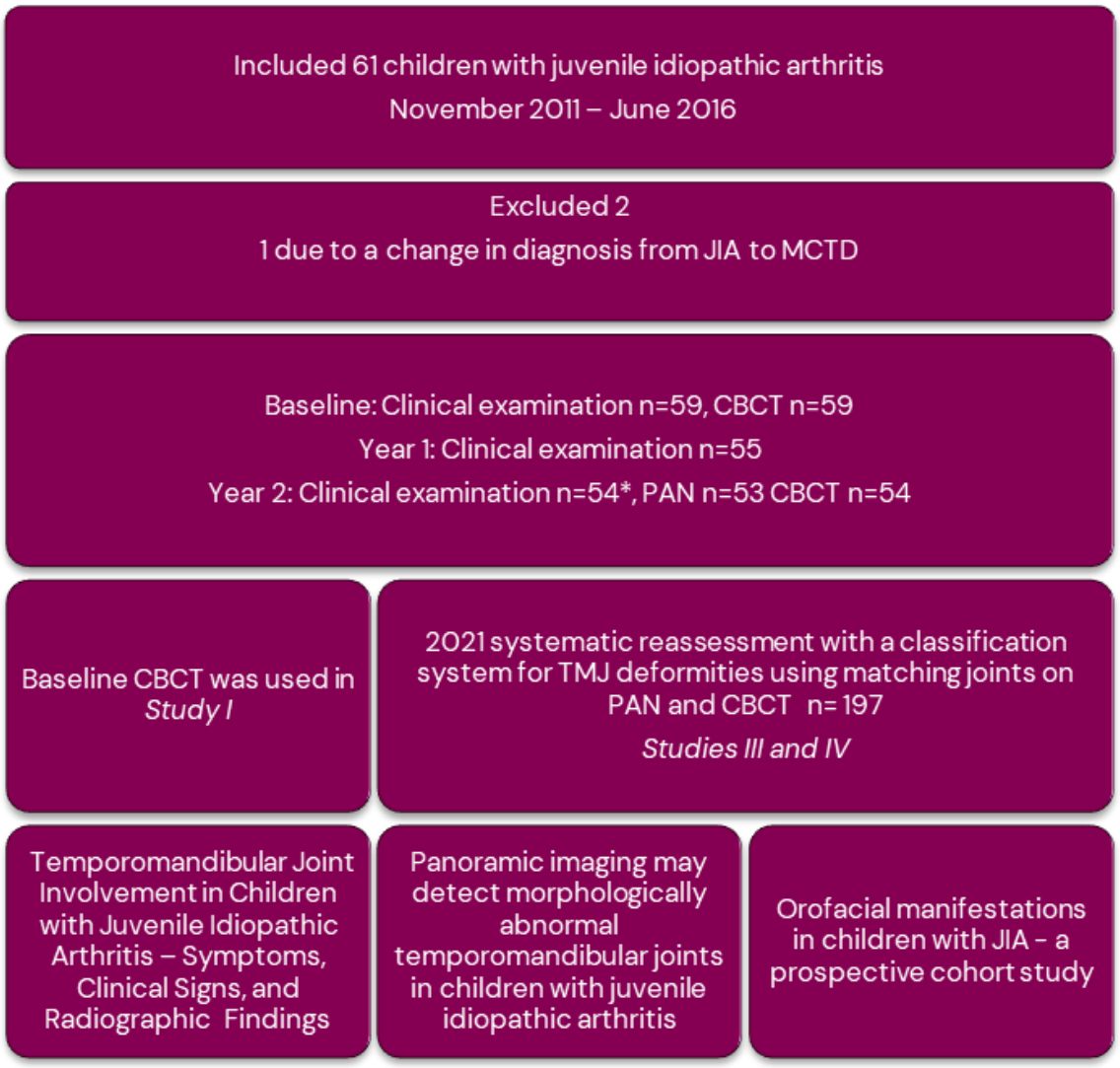

Figure 7. Illustration of how clinical and radiographic data were collected and reported in Studies I, III, and I.

*Three of the children missing at clinical examination year 2 were the same as those missing at clinical examination year 1. JIA: juvenile idiopathic arthritis; MCTD: Mixed connective tissue disease; PAN: panoramic imaging; CBCT: cone beam computed tomography TMJ: temporomandibular joint.

3.2 Study population

All participants were recruited through their contact with Folktandvården Stockholms län AB. Healthy controls were recruited from Folktandvården Vasastan and participants with JIA from the Department of Orofacial Pain and Jaw Function at Folktandvården Eastmaninstitutet.

All participants and their parents received written and verbal information on research objectives and procedures and signed an informed consent form before participation.

3.2.1 Participants with a diagnosis if JIA

In Study I, 59 participants (44 girls and 15 boys) with JIA were included between November 2011 and June 2015 (Table 2). Inclusion criteria were age 7 to 14 years, a diagnosis of JIA according to ILAR, a referral from Astrid Lindgren Children's Hospital at Karolinska, Solna, or Sachsska's Children and Youth Hospital at Södersjukhuset, Stockholm. Children who were under regular medical supervision and treatment were included, but children perceived to be in long-time remission without pharmacological treatment did not meet inclusion criteria. Exclusion criterion was a concomitant diagnosis of any other autoimmune or autoinflammatory disease.

In Study II, 30 participants (22 girls and 8 boys) with JIA were included between November 2014 and July 2017 (Table 2). Inclusion criteria were age 7 to 14 years, a diagnosis of JIA according to ILAR, a referral from Astrid Lindgren Children's Hospital at Karolinska, Solna, or from Sachsska's Children and Youth Hospital at Södersjukhuset, Stockholm and ongoing disease with joint symptoms (pain, swelling, and stiffness) within the last two weeks. Exclusion criteria were other systemic conditions or diseases that influence the inflammatory response present or earlier, diagnosis of current malignancies, intake of antibiotics the last three months, ongoing orthodontic treatment, or nicotine use. An inclusion questionnaire was used.

A power calculation was done based on a study from an adult population[137] since there were no previous studies on salivary biomarkers in children. According to the power calculation, 25 participants would be sufficient to detect a statistically significant difference of 20% (SD 25%) in biomarker level between samples with a power of 80% at a significance level of 5%. To compensate for dropouts, five additional participants were included.

In Study III, radiographic examinations from the population described in Study I were systematically reassessed during 2021. Data from 106 PANs and 108 CBCTs from 54 children were included. During the reading process, ten of the included PANs were found to

only show one of the TMJs and for these examinations data are reported for just one TMJ; 394 of the radiographs showed corresponding joints on PANs and CBCTs resulting in 197 matching pairs of examinations.

In Study IV, a combination of data on self-reported symptoms, medical history, and clinical data collected over a two-year period from the cohort described in Study 1 and data on radiographic findings from Study 3 were used. Data from 54 children are reported.

3.2.2 Healthy participants

A group of 30 healthy individuals (19 girls and 11 boys) participated in Study II (Table 2). Participants were matched according to age and sex and inclusion began in June 2017 and was completed in April 2018. Mean (SD) age was 11.0 (2.1) years. Inclusion criterion was age 7 to 14 years and exclusion criteria were other systemic conditions or diseases that influence the inflammatory response present or earlier, diagnosis of current malignancies, intake of antibiotics the last three months, ongoing orthodontic treatment, or nicotine use. An inclusion questionnaire was used.

Table 2. The distribution in number (n) of participants included in Studies I–IV, mean age, and years with a diagnosis of JIA.

	I	II	III & IV
Healthy participants			
All (n)	-	30	-
Girls	-	19	-
Boys	-	11	-
Age (years)			
All	-	11.0 ± 2.1	-
Girls	-	10.9 ± 2.3	-
Boys	-	11.2 ± 1.7	-
Children with JIA			
All	59	30	54
Girls	44	22	39
Boys	15	8	15
Age (years)			
All	10.7 ± 2.1	11.1 ± 2.0	10.7 ± 2.1
Girls	10.7 ± 2.0	11.6 ± 2.3	10.8 ± 2.1
Boys	10.6 ± 2.3	10.9 ± 1.8	10.6 ± 2.3
Years with diagnosis of JIA (years)			
All	4.2 ± 3.6	-	4.1 ± 3.5
Girls	4.2 ± 3.8	-	4.2 ± 3.7
Boys	3.9 ± 3.2	-	3.9 ± 3.2

JIA: juvenile idiopathic arthritis

3.3 Methods

3.3.1 Medical history

Information on medical history, specifics on diagnosis, general disease activity, medication, and previous medical treatment were obtained from medical records by pediatricians.

3.3.2 Self-reported symptoms

Information on self-perceived disease activity (i.e., current joint pain, joint stiffness, or joint swelling) was obtained through questions, visual aids, and confirmation by examiner. Data on self-perceived disease activity were reported in Studies I and IV and used as inclusion criteria in Study II.

3.3.3 Self-reported TMJ involvement

In Study I and IV, self-reported TMJ pain and dysfunction were recorded. Two questions on presence of orofacial pain during mandibular movement and visual aid and pain drawings were used: 1) "Point to all areas you have had pain before or currently have pain at rest" and 2) "Point to all areas where you currently have pain during maximal mouth opening and clenching". The areas were recorded on a pain drawing and the child (and parent) confirmed. Pain intensity was assessed with a 0–10 numerical rating scale (NRS).

3.3.4 3Q/TMD

To identify temporomandibular pain and dysfunction (TMD) in participants in Study II, three validated screening questions (3Q/TMD) were used.[151,152] The 3Q/TMD questions are as follows: Q1: Do you have pain in your temple, face, jaw, or jaw joint once a week or more? Q2: Do you have pain once a week or more when you open your mouth or chew? Q3: Does your jaw lock or become stuck once a week or more?[152]

3.3.5 Clinical examination

In the longitudinal prospective cohort study, clinical examinations were performed at baseline and repeated after 12 and 24 months. Data form this cohort are presented in Study I (baseline) and in Study IV (longitudinal data). The clinical examinations were performed by three dentists, specialist in orofacial pain and jaw function (MC, BHM, NCh). The RDC/TMD protocol was used, and the examiners were repeatedly calibrated to a gold standard examiner. The RDC/TMD examination protocol includes mandibular range of motion and pain on jaw movement, presence of TMJ sounds, and palpatory pain over the TMJ and masticatory muscles. Some deviations were made from the RDC/TMD protocol and only Axis I was used. Maximum assisted mouth opening was not used at all and maximum unassisted mouth opening (MUO) with and without pain was defined as the vertical distance in millimeters between the incisal edges of the maxillary and mandibular central incisors plus the vertical overbite. The terminology defined by the RDC/TMD protocol[107] is used in Study I.

In addition to the RDC/TMD protocol, data on occlusion and relation of malocclusion according to Angle[153] were recorded. Sagittal relations were registered at the position of the first molar. Postnormality (Angle Class II) was defined as the maxillary first molar being in line with or anteriorly positioned relative to the mandibular first molar, the deviation from neutral position half a cusp or more.

3.3.6 Radiological examination

CBCTs and PANs were taken at baseline and at the two-year follow-up. All radiological examinations were performed by specially trained dental nurses and under supervision of a specialist in oral and maxillofacial radiology at the Department of Oral and Maxillofacial Radiology at Eastmaninstitutet, Folktandvården Stockholm AB. The CBCTs were performed using one of three machines: the NewTom 3G (QR, Verona, Italy) settings: 110 kV, 5–6 mA, 5.4 s; ProMax 3D Classic (Planmeca Oy, Helsinki, Finland), settings: 90 kV, 9–10 mA, 12.3 s; and the most recent CBCTs in the study were taken with a 3D Accuitomo 170 (Morita, Kyoto, Japan), settings: 85 kV, 7 mA, 17.5 s. The PANs were taken with Proline interface, Proline Dimax 2/3 PCI interface, and ProMax Ethernet Interface (Planmeca Oy, Helsinki, Finland), settings: 74 kV 6–7mA, 12.6–18 s. All images

were studied as anonymized DICOM files. Imaging software used were RadiAnt DICOM Viewer, version 2020.2.3 (Medixant, Poznan, Poland) and Romexis, versions 5.3.1 & 5.3.4 (Planmeca Oy, Helsinki, Finland). The CBCT examinations were performed using thin (0.625–1.25 mm) sections, a bone algorithm, and axial sections parallel to the hard palate.

After all participants had completed their two-year follow-up, radiological examinations were transferred to a separate database. At this time, the examinations were anonymized and assigned randomly produced identification numbers.

The evaluation of the radiological examinations was made by three experienced maxillofacial radiologists (L. Z. Arvidsson, Associate Professor, Institute of Clinical Dentistry, University of Oslo, T. A. Larheim, Professor emeritus, Institute of Clinical Dentistry, University of Oslo, and L. Wiklander, Senior Consultant, Department of Oral and Maxillofacial Radiology, Eastmaninstitutet, Folktandvården Stockholm AB). Data are presented in Studies I, III, and IV.

In 2018, baseline radiological examinations were analyzed. PANs and CBCTs were evaluated together and in random order. Before analyzing the radiographic material, meetings were held to discuss what type of grading system to use. The grading system for TMJ deformities proposed by Arvidsson et al.[154] developed for PANs and lateral transcranial radiography of TMJs were chosen. The classification system divided TMJ deformities into four groups, based on morphology of the condyle and the temporal part of the joint. Some additional specifications were made to the written criteria of the proposed grading system to allow for analysis of CBCTs. A calibration meeting was held in December 2017 at which, all three readers together graded and discussed a selected material of PANs and CBCTs with TMJs with various degrees of deformities. After this, the three readers separately reviewed all radiographic examinations during the first half of 2018. No consensus meetings were held. To decide on whether a TMJ was normal or abnormal, the reading protocols were dichotomized, after with a majority decision was made. Information from the radiological review in 2018 of baseline CBCT examinations is presented in Study I.

In Studies III and IV, all radiographic examinations were reevaluated in 2021. At this time, some additional changes were proposed to the grading system. Adjustments were made based on the grading system initially used by Arvidsson et al.[106] and the work done

for Study I in 2018. The written criteria were revised and reference images for each grade of TMJ deformity were added (Table 3; Figures 8 and 9). Additional findings such as cortical erosions, presence of double contour of the caput, condylar sclerosis, bone apposition in the fossa, and condylar osteophyte change of ramus height were also defined in the written criteria (Table 4).

Table 3. Classification system* for temporomandibular joint morphology in juvenile idiopathic arthritis on panoramic imaging and cone beam computed tomography.

Grade		Description
PAN	*CBCT*	
0	0	**Normal:** Normal bone structures, shape and size of condyle and fossa/eminence. Condyle is smooth and rounded or slightly flat. Fossa/eminence is s-shaped.
1	1	**Small abnormality:** Condyle has a slightly abnormal shape (parts of, or entire condyle slightly flattened). Fossa/eminence normal or slightly abnormal in shape (widened/flattened).
2	2a	**Moderate condylar abnormality:** Parts of, or entire condyle moderately abnormal in shape (flattened/remodeled). Condyle may be larger or smaller than normal. Fossa/eminence normal or slightly abnormal in shape (widened/flattened).
2	2b	**Moderate condylar and fossa/eminence abnormality:** Parts of, or entire condyle moderately abnormal in shape (flattened/remodeled). Condyle may be larger or smaller than normal. Fossa/eminence moderately abnormal in shape (widened/flattened).
3	3	**Extensive abnormality:** Entire condyle extensively abnormal in shape or size (small, large, wide, flat) and condyle/condylar neck short. Fossa/eminence moderately or extensively abnormal in shape (widened/flattened).

*Modified after Arvidsson et al. (2009).[106] On panoramic imaging there is no differentiation into grade 2a and 2b since the fossa/eminence cannot be evaluated.

Table 4. Written criteria for additional findings in temporomandibular joints on panoramic radiographs and cone beam computed tomography of children with juvenile idiopathic arthritis.

Additional findings	Description
Erosion in condyle and/or fossa/eminence	Clear interruption of articular surface without a cortical bone-like delineation towards trabecular bone; may be difficult to assess when cortical surface is not yet fully formed; Erosion 1 = total area <=1 mm in any direction; erosion 2 = total area > 1 mm in any direction
Irregular cortical/articular surface	Irregular but intact surface. Cannot be registered together with erosion
Double contour of condyle	Extra cortical outline, usually posteriorly
Osteophyte of condyle	Bony outgrowth anteriorly
Sclerosis of condyle	Subcortical density similar to cortical bone
Bone apposition in fossa	New bone formation/extra cortical outline
Anteriorly positioned condyle	Condyle below apex of eminence at teeth in occlusion

In the reevaluation of radiological examinations in 2021, 106 PAN (two examinations were lost during data transfer) and 108 CBCT examinations were included. For ten (about 9%) of the PAN examinations only one joint could be interpreted due to superimposition and/or inferior image quality of the contralateral joint, which was excluded from analysis. This resulted in 197 matching pairs of PAN and CBCT examinations.

The reading of the radiographic examinations was made in steps. First, calibration meetings for PANs were held to discuss written criteria, perform calibration exercises, and choose reference images for proposed gradings of TMJ abnormality (Figures 8 and 9). Next, all PANs were graded separately by the three readers within four weeks. This process was then repeated with the same timetable for the CBCTs.

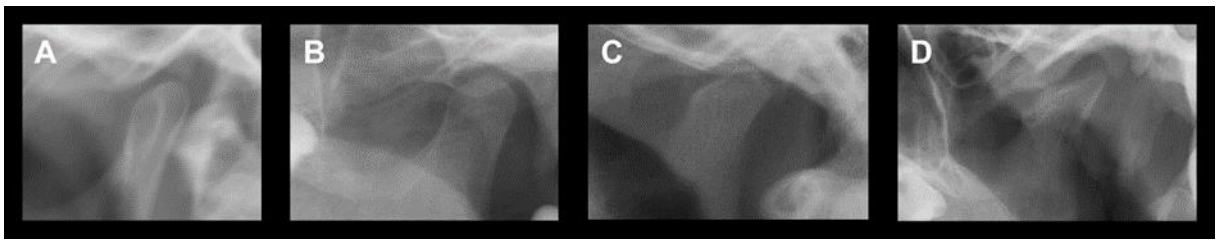

Figure 8. Reference images for PANs. A, Grade 0, normal; B, Grad 1, small abnormality; C, Grade 2, moderate condylar abnormality; D, Grade 3, Extensive abnormality.

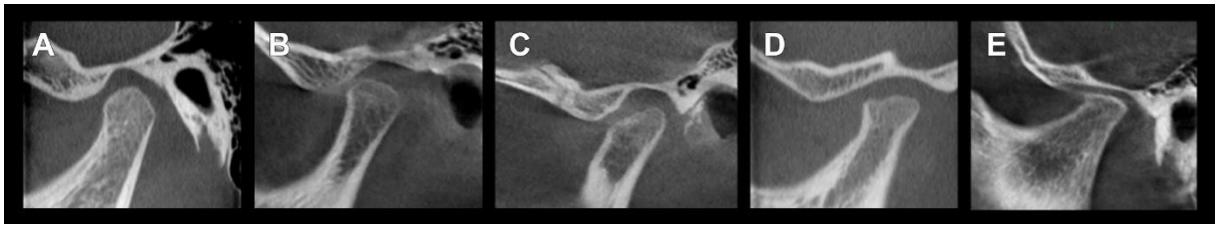

Figure 9. Reference images for CBCT. A, Grade 0, normal; B, Grad 1, small abnormality; C, Grade 2a, moderate condylar abnormality; D, Grade 2b, moderate condylar and fossa/eminence abnormality; E, Grade 3, extensive abnormality.

To assess intrareader agreement, 15 randomly selected PANs and CBCTs were reexamined 3–4 weeks after the CBCTs had been graded. After finishing the individual readings of radiological examinations, TMJs on both the PANs and the CBCTs received a final grading and validation of additional findings during consensus meetings.

3.3.7 Saliva collection

Stimulated whole saliva was collected for Study II. Samples were collected during the same circumstances for healthy controls and participants with JIA. To avoid circadian variance, we collected saliva samples between 8 and 11 am.

The participants were instructed to chew a piece of paraffin gum (Paraffin Pellets, Ivoclar Vivadent, Germany) until it was smooth and flexible and then to swallow the saliva present in the mouth. The participants were then asked to start chew again and for 5 minutes expectorate all produced saliva into a sterile polypropylene tube.[135,146] The saliva sample collected was placed on ice, the volume measured, and salivary flow calculated. The sample was then centrifuged (Centrifuge 5702, Eppendorf, Hamburg, Germany) at 1500 rpm for 15 minutes after which the supernatant was stored in 500 microliter Eppendorf tubes at −80 ºC in Karolinska Institutet's Tandvårdsbiobank (reg nr 737) in Huddinge, Sweden.

3.4 Biomarker analysis

A literature search produced several biomarkers (cytokines and chemokines) implicated in the pathophysiology of inflammatory joint disease and potentially measurable in saliva.[48-50,140,149,155,156] The following biomarkers were chosen: TNF-alpha, TNFRII/TNFRSF1B, MMP-1, MMP-2, MMP-3, MMP-13, IL-1 alpha, IL1-beta, IL-1 RII, IL-2, IL-6, IL-6R alpha, IL-8, IL-10, IL-12, CCL2, CCL3, CCL11, CCL22, CXCL9, and S100A8.

The analysis was performed at the Plasma Profiling National Facility, Science for Life Laboratory (SciLifeLab) (Karolinska Institutet, KTH Royal Institute of Technology, Stockholm University and Uppsala University) using the Luminex system and a Human Luminex Discovery Summary (#LXSAHM-21), a customized R&B (magnetic) bead-based immunoassay (R&D SYSTEMS/Bio-Techne, Minneapolis, US). The system can simultaneously detect many targets in a single sample and give information about both the identity and concentration of the targets. The protocol for the saliva analysis was drawn up in collaboration with Head of Plasma Profiling National Facility, PhD Claudia Fredolini.

The assay used was not validated for saliva and a pilot test with pooled sample was performed to evaluate linearity and the detectability of the 21 proteins included in the kit. Two sample pools were created–one case pool and one control pool (30 individuals in each). The saliva pools were then tested in 2x, 5x, 10x, and 40x dilution. Each sample was run in duplicates. The assay was performed according to manufacturer's instructions. The initial analysis showed that 14 of 21 targeted proteins had dilution-depending curves at a dilution

of 1:2, and seven were compromised for matrix effects: MMP-1, MMP-13, IL-1 RII, IL-2, IL-6, IL-12, and CCL22 (Table 5).

Table 5. Pooled samples of saliva were assessed at different dilutions.

	1:2	1:5	1:10	1:40
Number of targets	21	21	21	21
Number of detectable targets*	14	14	14	7
Assays that show linearity	TNF alpha, TNFRSF1B, MMP 3, IL 8, IL 6R alpha, IL 1 beta, MMP 2, S100A8, IL 1 alpha, CCL2, CCL3, IL 10, CCL11, CXCL9			
Assays compromised by matrix effects	MMP 13, MMP 1, IL 2, IL 12, IL 6, CCL22, IL 1 RII			
CV (%) **(Precision)	6.0	3.1	3.1	4.4

*Above St7 and limit of detection **Average CV (coefficient of variation) based on MFI (median background) value

The main analysis was then performed (R&D systems, LXSAHM 21, Lot # L133165, 21 plex) with settings based on the pilot test on the following proteins: TNF-alpha, TNFRSF1B, MMP-2, MMP-3, IL-1 alpha, IL-1 beta, IL-6R alpha, IL-8, S100A8, CCL2, CCL3, IL-10, CCL11, and CXCL9.

3.4.1 Protein concentration analysis

To see if there were differences in total protein concentration between the saliva samples, we performed an additional analysis (Thesis). A spectrophotometer-based analyses to measure total protein concentration in the saliva samples NanoDrop technology was used (NanoDrop One/One C, Thermo Fischer Scientific, 5255 Verona Rd. Madison. WI 53711, USA). A blanking routine with sterile water was established. Saliva samples were thawed, vibrated, and then measured in duplicate. The volume of the test samples was 3 µl. The mean value for total protein concertation was calculated and then used for statistical analyses.

3.5 Statistical analysis

Statistical analyses for Studies I–IV were performed with the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 23.0, 24.0, 25.0, 26.0, 27.0 and 28.0; IBM, NY, USA). In addition, data in study III were analyzed in R Core Team (version 3.2.6) R: A language and environment for statistical computing R Foundation for

Statistical Computing, Vienna, Austria. URL https://www.R-project.org and IBM SPSS Statistics 25 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.).

In Studies I and IV, data are reported for the whole cohort as well as divided by presence of TMJ deformities on CBCT. For some analyses, the gradings of TMJ deformities (0,1, 2, 2a, 2b, 3) were dichotomized (to absent or present) due to the low number of cases in each group.

When comparing the two imaging modalities in Study III, 197 matched pairs of joints on PAN and CBCT examinations were included. For the comparison between PANs and CBCTs, CBCT grades 2a and 2b were analyzed together. Consensus evaluation of TMJ abnormalities on CBCT was used as a gold standard for calculation of sensitivity, specificity, and accuracy on reader level for both PANs and CBCTs.

Descriptive data are presented as number (n), frequencies (%), and mean and median with standard deviation (SD) and interquartile range (IQR).

Statistical inference was made with parametric and non-parametric tests depending on whether data were normally distributed. The Shapiro-Wilks test, histograms, and normal probability plots (QQ plot) were used to test for normality. In Study II, all inflammatory markers showed a skewed distribution and data were log-transformed for the analysis of distribution of protein values. Boxplots and scatter plots were used to identify outliers and Levene's test was used to test for equality of variance.

For categorical variables and variables not normally distributed, nonparametric tests were used. Mann-Whitney U-test was applied to study differences between groups and association was tested with Goodman and Kruskal's λ, Fischer's exact test, Kendall's tau-b (τb), and Risk Ratio (RR) and Odds Ratio (OR) with standard error and 95% confidence interval. Mann-Whitney U-test was applied to study differences between groups. For ordinal variables and change over time (more than two categories), the Marginal Homogeneity test was used.

For repeated measurements, the Friedman test for nonparametric continuous variables was used; when significant, post hoc test with Bonferroni correction was used. Exact Cochran's Q was used to determine differences in dichotomous variables over time and

for significant results post hoc analyses was made with multiple McNemar's exact with Bonferroni correction.

In Study III, Cohen's kappa statistic was used to evaluate intra-reader agreement and Fleiss' kappa statistic was used to evaluate inter-reader agreement for PAN and CBCT examinations, respectively. Kappa values less than 0.20 indicated poor agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 good agreement, and more than 0.80 excellent agreement. Guidelines for classification of kappa values after Maclure and Willett (1987) and Altman (1991) were applied.[157,158]

In Study IV, binominal logistic regression was performed to predict a dichotomous dependent (TMJ deformities on CBCT) variable given one or more independent variables. The ability of the binomial logistic regression model to discriminate individuals with and without the event of interest was tested with a receiver operating characteristics (ROC) curve analyses.

T-test or analysis of variance (ANOVA) vas used to test for associations for normally distributed data. For comparison with a standardized value for MUO, a one-sample t-test was performed.

In Study II, the analyses of association with group, type of diagnosis, age, gender, medication, and 3Q/TMD were done with t-test with Welch adjustment and ANOVA (for >2 groups). Association with group was analyzed with a t-test without any adjustments. A linear regression model with adjustment was applied for association with age. For all other variables in association with levels of biomarkers, ANOVA and Benjamini and Hochberg procedure were used.

The significant level for all tests (apart from post hoc testing) was set at 5%. The confidence interval was set at 95% and two-sided tests were used.

3.6 Ethical considerations

Ethical approval for Studies I, II, III, and IV was granted by the Regional Ethical Review board in Stockholm, Sweden (2011/2:1 and amendment 2014/681-3).

Before inclusion, the participants received verbal and written information about the study and different versions of written information were provided for children and parents. Information included the objective, design, and funding of the study. Participation in the study was voluntary and participants were free to withdraw at any time without questions asked or consequences. The participants were also guaranteed anonymity and confidentiality. Since all participants were children, written parental consent as well as verbal assent from the child was obtained before start of the study.

The studies followed the Declaration of Helsinki and the fundamental principle of respect for the individual, their right to self-determination, and the right to make informed decisions regarding participation in research both at inclusion and at follow-up. To ensure that all participants received proper care while participating in the study, research data on clinical variables and radiological examinations were also assigned to participants' dental records. Clinical data were assessed by a specialist in orofacial pain and jaw function and radiologic examinations were analyzed by inhouse oral and maxillofacial radiologists. All findings indicating disease, malfunction, or suffering have taken priority to research in decision making and measures were taken to ensure that all participants received whatever dental or medical care they needed.

In Study II, both healthy children and those with JIA were exposed to saliva sampling with a method that supposedly is pain-free. In this case, the possibility of advancing knowledge in the area of saliva as a medium for biomarkers justified the inconvenience that saliva sampling caused in terms of discomfort and the time allocated by children and their parents. In addition, children with JIA would benefit if techniques were developed for saliva analysis thus reducing the need for blood sampling in the future.

In research, the significance and gain of the studies must be set against the risk and the personal integrity of the research subjects. The result from the studies performed could lead to improved diagnostic tools for identification and prediction of TMJ involvement in JIA. This, in turn, can lead to a better long-term prognosis for children with JIA. However, there were no personal gains for the children participating in the study. In fact, by participating in the study, a lot of attention was focused on the fact that there is a disease, which might be stressful for a child. On the other hand, the clinical examinations performed in the studies were very similar to those regularly performed at Eastmaninstitutet. All children with JIA referred to the clinic are screened for TMJ

involvement at least once a year throughout their childhood and adolescence. At Eastmaninstitutet, the care for children is a high priority and measures are taken to, in a safe environment, provide all children treated there with the best care possible.

In Study III, two radiological imaging modalities were compared, and the diagnostic value of panoramic imaging were evaluated. With radiological examinations, it is always a matter of justification and optimization. Radiation examinations in healthcare must always do more good than harm and should only be done if the examinations contribute to the diagnosis or the treatment plan. Furthermore, the examination modality chosen should provide as low radiation dose as possible without sacrificing the diagnostic value. If a low dose x-ray imaging modality, such as PAN, is proven diagnostical acceptable, many children with JIA will benefit. In the studies, both PANs and CBCTs were taken on two occasions, a scenario, although common in day-to-day clinic work, is not something that should be done without careful consideration.

The ethical responsibility of the researcher is to consider the potential harm–physiological, social, physical, or legal–of participating in the study. Careful assessment of risks and benefits has been made and the results from the studies are expected to benefit children suffering from JIA.

4 Results

The clinical studies presented aimed to investigate several aspects of how to correctly identify and measure severity of TMJ involvement in JIA as well as investigate if JIA disease activity can be monitored through immunological biomarkers in saliva.

4.1 Participants

Dispersal of age, diagnosis, and pharmacological treatment are presented in Tables 2 (M&M), 6, and 7. The majority of the participants were diagnosed with the JIA subtypes oligoarthritis and Rh-negative polyarthritis. During the study period, a significant change in pharmacological treatment occurred, with an increase in children treated with bDMARDs (p = 0.001) and a decrease in non-steroidal anti-inflammatory drugs (NSAIDs) (p = 0.023) (Table 8).

Table 6. The distribution of individuals according to subtype of JIA in Studies I–IV.

	I n=59	**II** n=30	**III & IV** n=54
Oligoarthritis	28	18	25
Polyarthritis RF neg	19	10	18
Polyarthritis RF pos	1		1
Enthesitis-related arthritis	2	-	1
Psoriatic arthritis	5	1	5
Systemic arthritis	3	-	3
Undifferentiated	1	1	1

JIA: juvenile idiopathic arthritis; RF: rheumatoid factor

Table 7. Overview of pharmacological treatment in children with JIA in Studies I–IV.

	Study I (n=59)			Study II	Study III & IV (n=54)		
	Baseline	Year 1	Year 2	JIA group	Baseline	Year 1	Year 2
NSAID	26	20	14	5	23	20	13
sDMARDs	24	22	18	16	22	22	18
Methotrexate	24	21	16	16	22	21	16
Salazopyrine	-	1	-	-	-	1	-
Plaquenil	-	-	2	-	-	-	2
bDMARDs*	14	14	20	3	11	14	20
Cortisone	4	4	3	-	2	4	3
No medication	14	15	13	9	12	12	12
NSAID	26	20	14	5	23	20	13
sDMARDs	24	22	18	16	22	22	18
Methotrexate	24	21	16	16	22	21	16
Salazopyrine	-	1	-	-	-	1	-
Plaquenil	-	-	2	-	-	-	2
bDMARDs*	14	14	20	3	11	14	20

*bDMARD: Adalimumab (Humira/Anti-TNF alfa), Etanercept (Humira/Anti TNF-alfa), Anakinra (Kineret, Anti-IL beta), Abatacept (Orencia, Anti CD-28), Rituximab (Mabthera Anti-CD20)

Table 8. Pharmacological treatment over the 2-year study period, n=54.

Medication n (%)	Baseline	1-year follow-up	2-year follow-up	X^2/p Significance level p<0.05	Post hoc testing Significance level p<0.0167
NSAID	23	20	13	7.524/**0.023**	Baseline/year 1: 0.096 Year1/Year2: 0.039 Baseline/Year2: 0.041
sDMARDs	22	22	18	3.391/0183	
Methotrexate	22	21	16	3.130/0.209	
Salazopyrine	-	1	-	2.000/0.368	
Plaquenil	-	-	2	4.000/0.135	
bDMARDs	11 (20.4)	14 (25,9)	20 (37)	12.667/**0.001**	Baseline/year 1: 0.508 Year1/Year2: 0.031 Baseline/Year2: **0.002**
Cortisone	4	4	3	0.222/0.895	
No medication	12	12	12	0.125/0.939	

bDMARDs: Adalimumab (Humira/Anti-TNF alfa), Etanercept (Humira/Anti TNF-alfa), Anakinra (Kineret, Anti-IL beta), Abatacept (Orencia, Anti CD-28), Rituximab (Mabthera Anti-CD20)
Exact Cochran's Q-test, post hoc testing with multiple McNemar's exact with Bonferroni correction

4.2 Self-reported symptoms

4.2.1 Baseline

At baseline (n=59) examination, 33 children reported having disease activity in joints (pain, swelling, stiffness), most common were symptoms from ankles (18%) and knees (15%).

Self-reported TMJ involvement (i.e., pain or functional limitations before inclusion and at inclusion examination) were associated with TMJ deformities on CBCT at baseline, p = 0.001 and p= 0.033, respectively.

Before the RDC/TMD examination, assessments of localized pain were made for MUO and for clenching and 56% of the children reported TMJ pain during MUO and 34% during clenching. However, median NRS values (IQR) were low, 1 (4) and 0 (3), respectively.

4.2.2 Longitudinal data

At all three examinations, participants reported joint pain. At each examination (baseline, 1 year, 2 years), the mean (SD) number of painful joints were 2.4 (1.9), 1.9 (2.3), and 1.7 (2.1), respectively. Children reporting no joint pain at all increased significantly from nine to 20

individuals (p = 0.004) with the significant change taking place between baseline and the one-year follow-up. Throughout the study period, the joints most frequently reported as painful were, knees (37%), ankles (25%), and TMJs (9%) (n=54, % = % of joints reported as painful).

Self-reported TMJ pain and dysfunction before inclusion was reported by 24 (44%) children. Data show a reduction in self-reported TMJ pain and/or dysfunction over time, from 21 children at the baseline examination to 13 at both the one-year and the two-year follow-up. However, this reduction was not significant (p > 0.05). Furthermore, a multinominal logistic regression showed no predictive value of self-reported previous TMJ pain/dysfunction at baseline for developing TMJ changes over time. The frequency of self-reported pain at MUO and clenching did not change over time.

4.3 Clinical findings

4.3.1 Baseline

At baseline, all children (n=59) had mixed dentition, all with their upper permanent central incisors in place. Sagittal relations registered at the position of the first molar were neutral in 49% and postnormal in 51% of participants. Midline deviations were recorded in 27% of the children.

In Study I, mandibular range of motion and palpatory findings were presented divided by TMJ deformities or no TMJ deformities on CBCT (Table 9). Significant differences were found in MUO with pain (p = 0.018) (Figure 10) and in protrusion (PTR) (p = 0.008) between groups. However, the frequency of palpatory TMJ and masticatory muscle pain was the same for the groups.

In 70% of children with palpatory TMJ pain, the findings were the same for the lateral and posterior aspects of the TMJ. TMJ noises were found in 13 children (5 crepitations and 12 clickings).

Table 9. Mandibular range of motion and clinical findings in 59 patients with JIA divided by TMJ deformities or not. Data are presented as n (%) or mean (± SD) unless other is stated (radiologic data from 2018).

	No TMJ deformities n = 21	TMJ deformities n = 38	p-value
MUO without pain (mm)	44.0 (± 8.7)	41.3(± 8.5)	0.154
MUO with pain (mm)	50.0 (± 5.2)	45.9 (± 6.0)	**0.018**
Protrusion (mm)	9.1 (± 1.6)	7.8 (± 1.7)	**0.008**
Lateral excursion (mm)			
Right	9.9 (± 2.3)	9.5 (± 2.4)	0.797
Left	9.9 (± 1.7)	9.4 (± 2.0)	0.358
TMJ click			
Right	2 (9)	3 (8)	
Left	5 (24)	2 (5)	0.107
TMJ crepitus			
Right	0 (0)	3 (8)	
Left	0 (0)	2 (5)	0.085
Palpatory pain			
TMJ (0-4), median (IQR)	1 (± 2)	1,5 (± 3)	0.377
Muscles (0-20), median (IQR)	3 (± 9)	5 (± 10)	0.611

JIA: juvenile idiopathic arthritis; MUO: maximum unassisted (mouth) opening; TMJ: temporomandibular joint

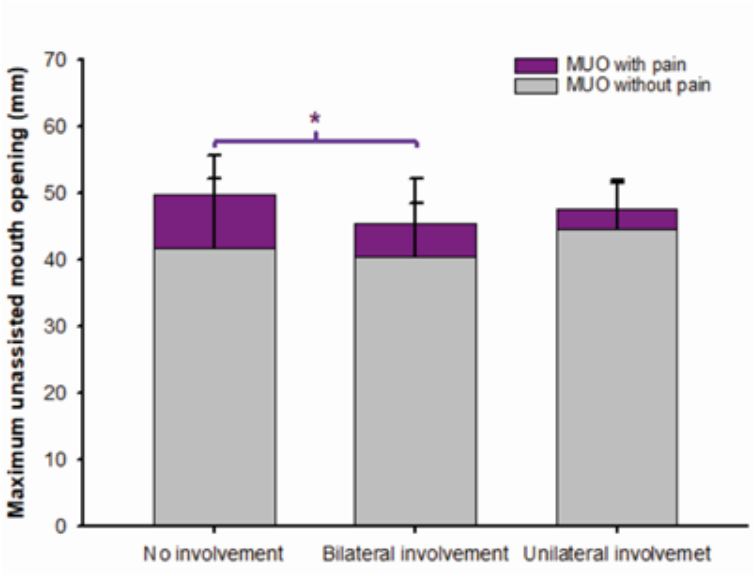

Figure 10. Graph showing the maximum unassisted mouth opening (MUO) in mm divided by presence of temporomandibular joint deformities. Baseline data.

4.3.2 Longitudinal data

Longitudinal data are reported for 54 children. There were changes in dentoalveolar relations in the children over the study period. The number of children with Angel class I increased from 48% to 60% and children with a postnormal sagittal relation decreased from 52% to 40% ($Q = 5.474$, $p < 0.065$).

Midline deviations increased over time, from 28% at baseline to 48% at two-year follow-up (Q = 9.538, p < 0.009). Despite this increase, no correlations were found between midline deviations and TMJ deformity (λ 0.039, p = 0.406).

Data were analyzed for mandibular range of motion, i.e., measurements for MUO without pain, MUO with pain, laterotrusion (LTR), and (PTR), for the whole group as well as divided by presence of TMJ deformities seen on CBCT.

An increase was observed in overall mandibular ranging of motion over the two-year study period for the whole group. MUO with pain increased from median 47.5 (7.0) mm at baseline to 50.0 (10) mm (p < 0.001) at the two-year follow-up. Laterotrusion (LTR) to the right significantly increased (p < 0.005) (Friedman test, Bonferroni post hoc test). In addition, an increase was also observed for LTR to the left; however, post hoc testing showed no significance. No other significant changes in mandibular range of motion were found (Table 10).

Table 10. Change in range of motion between baseline, year1 and year 2. Number of children = 54.

	Baseline Mean (SD)	Year 1 Mean (SD)	Year 2 Mean (SD)	χ2(2) / p	Post hoc test with Bonferroni correction[1]	
MUO without pain	42.1 (8.7)	42.1 (11.2)	44.1 (8.2)	3.482/p=0.175		
MUO with pain	47.4 (6.3)	49.0 (7.2)	50.0 (6.6)	26.662/**p<.0005**	Baseline/year1	*p*=0.100
					Year1/Year2	*p*=0.019
					Baseline/Year2	***p*<0.000**
LTR right	9.4 (2.1)	9.6 (2.2)	10.1 (1.7)	14.486/**p<0.001**	Baseline/year1	*p*=0.966
					Year1/Year2	*p*=0.088
					Baseline/Year2	**p=0.005**
LTR left	9.6 (1.9)	9.4 (2.2)	9.7 (2.1)	7.380/**p=0.025**	Baseline/year1	*p*=0.100
					Year1/Year2	*p*=0.088
					Baseline/Year2	*p*=1.000
PTR	8.3 (1.8)	8.3 (1.8)	8.8 (2.1)	2.770/*p*=0.250		

LTR: Laterotrusion; MUO: Maximum unassisted mouth opening; PTR: Protrusion[1] Friedman test

The difference between MUO without pain and MUO with pain were on average 6 mm at all three examinations. However, there were large individual differences in how MUO both with and without pain change over time (Figure 11).

When the children were divided into groups based on presence of TMJ deformities on CBCT, there were still a significant increase in MUO with pain for both groups between baseline and the two-year follow-up. In addition, LTR to the right significantly increase over time in the group without TMJ deformities (<1 mm). No other significant changes in mandibular range of motion were found.

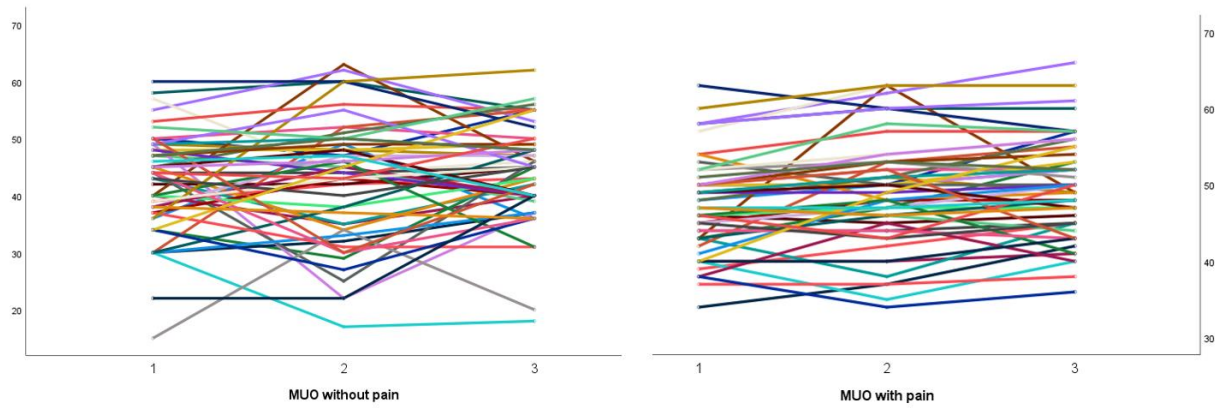

Figure 11. Figure showing individual change over time in maximum unassisted mouth opening (MUO) without pain and with pain. No pattern for change over time was found. Each line represents one child.

MUO with pain and MUO without pain for children with TMJ deformities were on average 5.5 mm larger than for children with "normal" TMJ morphology (Table 11). A weak positive association was found between the calculated difference in MUO at the follow-up examination and TMJ deformities seen on CBCT (τb=0.253, p=0.036). However, this association was not found at the baseline examination (τb=0.005, p=0.964).

Table 11. Change in range of motion from baseline to the two-year follow-up, divided by presence of TMJ deformities on CBCT at baseline (n=54).

n=54	Baseline Mean (±SD) Median (IQR)	Year 2 Mean (±SD) Median (IQR)	P[1]
TMJ deformities			
MUO without pain	38.2 (±7.2) 39.0 (12.0)	43.3 (±6.8) 42.5 (10)	**0.017**
MUO with pain	43.3 (±5.2) 43.0 (8.0)	46.7 (±6.0) 46.5 (8.0)	**0.003**
LTR right	8.9 (±2.6) 9.0 (3.0)	9.4 (±1.6) 9.5 (3.0)	0.201
LTR left	8.8 (±2.0) 9.0 (3.0)	9.5 (±1.7) 10.0 (3.0)	0.088
PTR	7.2 (±1.4) 7.0 (2.0)	8.1 (±2.0) 8.0 (4.0)	0.067
No TMJ deformities			
MUO without pain	44.6 (±8.7) 46.0 (10.0)	44.6 (±9.0) 45.5 (9.0)	0.644
MUO with pain	50.1 (±5.3) 49.0 (6.0)	52.0 (±6. 0) 52.0 (9.0)	**0.003**
LTR right	10.0 (±2.0) 10.0 (4.0)	10.7 (±1.6) 11.0 (3)	**0.019**
LTR left	10.2 (±1.7) 10.0 (2.0)	9.8 (±1.8) 10.0 (4.0)	0.200
PTR	9.0 (1±.7) 9.0 (2.0)	9.3 (±2.1) 9.0 (2.0)	0.776

MUO: maximum unassisted mouth opening; TMJ: temporomandibular joint; CBCT: cone beam computed tomography; SD: standard deviation; IQR: inter quartile range; LTR: laterotrusion; PTR: protrusion.
[1] Wilcoxon Signed rank test, significance level p<0.05

Palpatory masticatory muscle pain and TMJ pain were present at all three examinations. However, on individual level, no significant change occurred in total number of painful muscle points. In addition, no change occurred over time for palpatory findings in the masseter and temporalis muscles, or the TMJ ($p > 0.05$) (Table 12).

Table 12. Table showing clinical findings: TMJ noise and palpatory pain in m. masseter, m. temporalis, and the TMJ. Data presented as number of painful muscles and joints (n = 108).

	Baseline	Year 1	Year 2	X^2/p	p
Muscles pain on palpation					
masseter right	5	5	2	2.138/0.363	
masseter left	4	5	7	0.483/0.845	
masseter bilateral	23	20	17	1.357/0.542	
temporalis right	1	1	2	0.143/1.00	
temporalis left	2	0	3	0.111/1.00	
temporalis bilateral	9	10	7	0.571/0.840	
TMJ pain on palpation					
Right	6	4	1	3.455/0.210	
Left	9	7	4	2.714/0.295	
Bilateral	17	18	15	0.381/0.890	
TMJ noise					
Crepitus right	3	1	2	1.200/0.852	
Crepitus left	1	3	2	1.200/0.852	
Crepitus bilateral	-	4	6	4.667/0.166	
Crepitus (joint level)	4	12	16	**6.462/0.045**	Baseline/Year1 0.039 Year1/Year2 0.839 Baseline/Year2 **0.004**
Clickings right	3	3	5	1.556/0.595	
Clickings left	6	2	4	1.750/0.551	
Clickings bilateral	1	3	6	5.429/0.082	
Clicking (joint level)	11	11	15	**8.857/0.013**	Baseline/Year1 0.791 Year1/Year2 0.031 Baseline/Year2 0.076

TMJ: temporomandibular joint. Cochran's Q test, significance level $p < 0.05$ Multiple McNemar's tests (with Bonferroni correction) Significance level $p < 0.0167$

When combining palpatory findings with radiographic assessment of the TMJs, the odds for having TMJ palpatory pain was 43% higher (OR 1.425, CI 0.538, 3.774) for individuals with TMJ deformities on CBCT versus individuals without TMJ deformities on CBCT. However, a binominal logistic regression could not ascertain any effect of palpatory muscle pain (m. masseter, m. temporalis, or m. pterygoideus) on the likelihood of finding TMJ deformities on CBCT.

We found that TMJ noise increased over time. On joint level, crepitations increased significantly, from 3.7% to 14.8%, over the two-year study period ($p < 0.045$/post hoc

test p < 0.004). In addition, a corresponding increase in TMJ clickings occurred from 6.4% to 13.9 %, although this increase was not significant (p < 0.013/post hoc test p < 0.031). Crepitations were associated with TMJ deformities ($\chi 2(1) = 7.921$, p = 0.005).

4.3.3 Additional visits and treatments between follow-ups

Apart for scheduled study examinations during the two-year study period, 23 (42%) (year 1) and 15 (28%) (year 2) of the participants received additional examinations and treatments at the Department of Orofacial Pain and Jaw Function at Eastmaninstitutet, Folktandvården Stockholm AB. Two of these visits were due to ongoing TMJ arthritis and the rest of the visits were due to participants needing treatment for TMD, bruxism (teeth grinding), or for a consultation with a pediatric rheumatologist or an orthodontist (Table 13).

Table 13. Type of visits and treatment received at the specialist clinic during the study period (n=54).

Type of treatment	Year 1	Year 2	Total
Counseling/Rehab training	7	5	12
Splint	14	9	23
BASS	1	0	1
NSAID	1	1	2
Consultant with orthodontist	4	0	4
Consultant with pediatric rheumatologist	3	4	7
Intraarticular injection Eastman n=joints	1	1	2
Intraarticular injection ALB n=joints	Total number of joints: 6 Right 0 Left 2 Bilateral 4	Total number of joints: 7 Right 1 Left 2 Bilateral 4	Total number of joints:13 Right 1 Left 4 Bilateral 8

BASS: bite-jumping appliance for Class II bite correction; NSAID: nonsteroid anti-inflammatory drugs; TMJ: temporomandibular joint; ALB: Astrid Lindgren Children's Hospital, Karolinska University Hospital, Solna

During the study period, 15 joints were diagnosed with arthritis (during a relapse with multiple joints affected or confirmed with MRI or ultrasound) and subsequently treated with local corticosteroid injections (Depo-Medrol cum Lidocaine; Methylprednisolone cum Lidocaine, Pfizer, Sollentuna, Sweden). Of these injections, two were administrated by the responsible caregiver at the Department of Orofacial Pain and Jaw Function at

Eastmaninstitutet, Folktandvården Stockholm AB, and 13 by a pediatric rheumatologist at ALB Astrid Lindgren Children's Hospital, Karolinska University Hospital, Solna.

4.4 Radiological findings

Radiological examinations were performed at baseline and the two-year follow-up. CBCTs from baseline were evaluated in 2018 and reported in Study I. A reevaluation of the radiological material was made in 2021, and these data were reported in Study III as well as in Study IV. In Study III, data from both PANs and CBCTs were reported and in Study IV data from 54 baseline CBCTs and 53 CBCTs from the two-year follow-up were reported.

4.4.1 Baseline

In Study I, morphological abnormal TMJs were found in 38 (64%) children–unilaterally in 24 (40%) and bilaterally in14 (24%) of the 59 CBCTs. ANA were present in 30 (n=57) individuals but were not correlated to TMJ involvement seen on CBCT.

Using the radiological data from Study III (2021), we found that the likelihood of exhibiting TMJ deformities at baseline was predicted by number of years with disease (OR 1.23, $p = 0.023$) and a decrease in MUO without pain (OR 0.89, $p = 0.008$). In this analysis, radiographic data from Study III rather than Study I was used, a decision that is discussed later.

4.4.2 Longitudinal data

At baseline, 61% of the children had no radiographic TMJ deformities, whereas 24% showed unilateral and 15 % bilateral TMJ deformities (data from CBCT). No significant changes occurred over time in the grading of deformity on group level ($p > 0.05$). On joint level, five joints received a lower grade, while eight joints received a higher grade of deformity at the two-year follow-up examination (Figure 12).

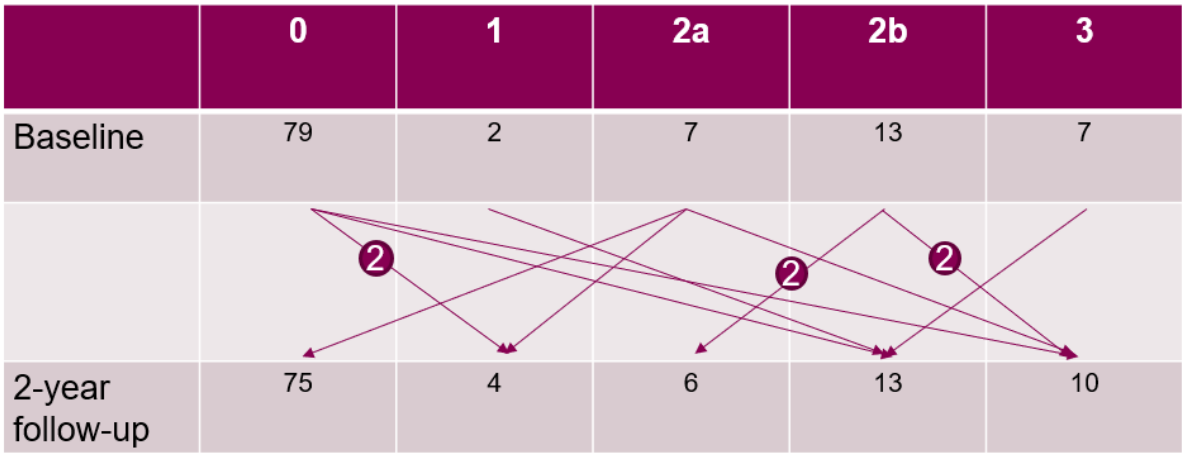

Figure 12. Flow-chart showing the change over time in grading of TMJ deformities (0, 1, 2a, 2b, 3) evaluated on CBCT. Data presented on joint level, an arrow representing one joint unless specified with a number.

An ordinal logistic regression did not show any association between a change in MUO without pain and a change in the grade of TMJ deformity over the two-year study period: OR 1.036 (95% CI, 0.925 to 1.159), Wald $\chi2(1) = 0.368$, $p = 0.543$. There was no significant difference in the proportion of TMJ deterioration or no TMJ deterioration over time in relation to a reduction in MUO without pain (Fischer's exact test, $p = 1.00$). However, a multinominal regression showed that it was more likely that the children with more involved joints at baseline would develop TMJ deformity: OR of 0.50 (95% CI, 0.25 to 0.96), Wald $\chi2(1) = 4.23$, $p = 0.04$.

An increased duration with disease ($\chi2(1) = 5.156$, $p = 0.023$) as well as a decrease in MUO without pain ($\chi2(1) = 7.077$, $p = 0.008$) were associated with an increased likelihood of exhibiting TMJ deformities (binominal logistic regression).

4.4.3 Comparison of radiological techniques

Radiological examinations were performed at baseline and at the two-year follow-up. A reevaluation of PANs and CBCTs were made in 2021 and data from this reading of the radiological material were reported in Study III. Data are presented on joint level.

How TMJ abnormalities were graded are presented in (Table 3). On CBCT, the number of joints with moderate or extensive abnormality were more frequent than on PAN (50 versus 43), whereas the number of joints with small abnormality were less frequent (5

versus 11) (Table 14). The odds ratio for detecting a morphologically abnormal TMJ on PAN vs. CBCT was 0.97. The risk of finding TMJ abnormalities on CBCT was higher than on PAN, the risk ratio (RR) being 1.05.

Table 14. Proportions of normal/abnormal TMJ morphology on PAN and on CBCT of children with JIA presented for matched pairs, on joint level, and based on consensus for three readers.

		n=197	%
PAN	Normal	143	72.4
	Abnormal	54	27.6
	1 Small abnormality	11	5.6
	2 Moderate abnormality	32	16.3
	3 Extensive abnormality	11	5.6
CBCT	Normal	142	71.9
	Abnormal	55	28.1
	1 Small abnormality	5	2.6
	2a Moderate condylar abnormality	12	6.1
	2b Moderate condylar and fossa/eminence abnormality	23	11.7
	3 Extensive abnormality	15	7.7

TMJ: temporomandibular joint; PAN: panoramic imaging; CBCT: cone beam computed tomography; JIA: juvenile idiopathic arthritis

Apart for grading TMJ abnormalities, additional findings were recorded. On PAN, recordings of additional findings were few (or nonexistent) in several of the categories, including condylar osteophytes. Only one category, condylar sclerosis, was seen more often on PAN than on CBCT. The difference in additional findings between the two imaging modalities was significant for erosion 2, erosion dichotomized, and condylar osteophyte ($p < 0.05$) (Table 15).

Table 15. Table showing proportions, odds ratio, and p-values for additional findings on joint level for matched pairs of PAN and CBCT of children with JIA. n=197*, significance level p-value < 0.05.

	PAN n (%)	CBCT n (%)	Odds ratio	95 % CI	p-value
Erosion 1	1 (0.5)	2 (1.0)	0.50	0.05, 5.53	0.5699
Erosion 2	6 (3.1)	24 (12.2)	0.23	0.090 0.57	**0.0015**
Erosion dichotomized	7 (3.6)	26 (13.3)	0.24	0.10, 0.57	**0.0012**
Irregular cortex	6 (3.1)	10 (5.1)	0.59	0.21, 1.65	0.3123
Double contour	0	4 (2.0)	0.11	0.01, 2.04	0.1377
Condylar osteophyte	0	12 (6.1)	0.04	0.01, 0.64	**0.0232**
Condylar sclerosis	6 (3.1)	4 (2.0)	1.52	0.42, 5.46	0.5245
Bone apposition fossa	0	0	-	-	-
Condylar position below apex at intercuspal position	Not recorded	5 (2.6)	-	-	-

PAN: panoramic; CBCT: cone beam computed tomography; JIA: juvenile idiopathic arthritis; CI = 95 % asymptotic confidence. * On PAN, five joints were marked undecisive; on CBCT, one joint was marked undecisive.

4.4.3.1 Sensitivity, specificity, and accuracy

In Study III, reader sensitivity, specificity, and accuracy for assessing TMJ abnormality on PAN compared to CBCT were calculated (Table 16).

Table 16. Sensitivity, specificity, and accuracy per reader for assessing normal/abnormal TMJ morphology on PAN of children with JIA using reader consensus on CBCT as gold standard.

	Sensitivity	Specificity	Accuracy
Reader 1	0.95	0.96	0.95
Reader 2	0.74	0.97	0.93
Reader 3	0.80	0.93	0.89

TMJ: temporomandibular joint; PAN: panoramic imaging; JIA: juvenile idiopathic arthritis; CBCT: cone beam computed tomography

4.4.3.2 Intrareader reliability

Intrareader reliability was calculated for the radiographic review 2021. Fifteen randomly selected PANs and CBCTs were reexamined 3–4 weeks after the main assessment of radiological examinations. Kappa values for all three readers showed excellent intrareader agreement (Table 17).

Table 17. Kappa statistics for intrareader agreement when assessing normal/abnormal TMJ morphology on PAN and on CBCT of children with JIA. Kappa values less than 0.20 indicated poor agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 good agreement, and more than 0.80 excellent agreement.

	PAN	CBCT
Reader 1	0.83 (CI 0.70-0.96)	0.81 (CI 0.71-0.92)
Reader 2	0.93 (CI 0.89-0.98)	0.94 (CI 0.90-0.99)
Reader 3	0.89 (CI 0.83-0.95)	0.84 (CI 0.76-0.91)

TMJ: temporomandibular joint; PAN: panoramic imaging; CBCT: cone beam computed tomography; JIA: juvenile idiopathic arthritis; CI = 95 % asymptotic confidence interval

Intrareader agreement for both PAN and CBCT were also calculated between the readings 2018 and the second one in 2021. Kappa values for dichotomized CBCT assessments for Readers 1 and 3 indicated moderate agreement between 2018 and 2021, whereas the kappa value for Reader 2 was excellent. Intrareader agreement for more specified evaluation on CBCT (i.e., the gradings of TMJ abnormalities) ranged from fair to good. Notably, for two of the of the maxillofacial radiologist the intrareader agreement over time was higher for PAN than for CBCT (Table 18).

Table 18. Cohen's kappa statistics for intrareader agreement on TMJ abnormality on PAN and CBCT of children with JIA, readings made 2018 and 2021. Kappa values computed for both graded assessment (0,1,2,3, and 0,1,2a,2b,3) as well as for dichotomized data assessing TMJ morphology only as normal/abnormal.

	Reader 1			Reader 2			Reader 3		
	κ	SE	CI	κ	SE	CI	κ	SE	CI
PAN 0,1,2,3	0.539	0.050	0.44-0.64	0.503	0.052	0.40-0.61	0.487	0.053	0.38-0.59
PAN dichotomized	0.607	0.055	0.50-0.72	0.646	0.057	0.53-0.76	0.784	0.050	0.69-0.88
CBCT 0,1,2a,2b,3	0.335	0.041	0.26-0.42	0.640	0.064	0.52-0.77	0.330	0.041	0.25-0.41
CBCT dichotomized	0.531	0.053	0.43-0.64	0.835	0.042	0.75-0.92	0.451	0.053	0.35-0.56

K: kappa; SE: standard error; CI: 95% confidence Interval; PAN: panoramic imaging; CBCT: cone beam computed tomography

4.4.3.3 Interreader reliability

Interreader reliability was calculated for PAN and CBCT for both gradings and for additional findings. When considering all the grades in the classification system, the interreader agreement for PAN was moderate (κ=0.545 (95 % CI, 0.49 to 0.60), p < 0.0005) and good for CBCT between the three readers (κ=0.63 (95 % CI, 0.58 to 0.68), p < 0.0005). However, when radiographic findings were categorized as "normal" or "abnormal," the interreader agreement for both PAN and CBCT was excellent (Table 19).

Table 19. The Cohen's Weighted kappa was used to evaluate the interreader agreement for TMJ abnormalities dichotomized as normal or abnormal on PAN and CBCT.

	PAN	CBCT
Reader1-Reader2	0.91 (CI 0.88–0.94)	0.94 (CI 0.92–0.96)
Reader1- Reader3	0.91 (CI 0.89–0.94)	0.90 (CI 0.89–0.93)
Reader2-Reader3	0.88 (CI 0.85–0.91)	0.92 (CI 0.90–0.94)

TMJ: temporomandibular joint; PAN: panoramic imaging; CBCT: cone beam computed tomography; CI: 95 % asymptotic confidence interval

Interreader agreement for additional findings were computed using Fleiss' kappa. For PAN, kappa values varied from moderate agreement for erosion to good agreement for both condylar osteophyte and bone apposition fossa. For CBCT, the kappa values for interreader agreement varied from moderate agreement for irregular cortex to excellent agreement for bone apposition fossa (Table 20).

Table 20: Fleiss kappa for interreader agreement of additional TMJ findings on PAN and on CBCT of children with JIA.

	PAN	CBCT
Erosion (0,1,2)	0.59 (CI 0.53-0.65)	0.60 (CI 0.58-0.65)
Erosion dichotomized	0.59 (CI 0.53-0.66)	0.63 (CI 0.58-0.69)
Irregular cortex	0.62 (CI 0.56-0.68)	0.52 (CI 0.48-0.59)
Double contour	0.68 (CI 0.61-0.74)	0.72 (CI 0.66-0.79)
Condylar osteophyte	0.71 (CI 0.64-0.78)	0.69 (CI 0.63-0.75)
Condylar sclerosis	0.63 (CI 0.57-0.69)	0.67 (CI 0.61-0.73)
Bone apposition fossa	0.71 (CI 0.64-0.78)	0.81 (CI 0.74-0.88)

TMJ: temporomandibular joint; PAN: panoramic; CBCT: cone beam computed tomography; JIA: juvenile idiopathic arthritis; CI: 95 % asymptotic confidence interval

4.5 Saliva

Study II investigated salivary flow and the presence of inflammatory biomarkers in saliva in children with JIA compared to healthy children. The groups were matched with respect to age and gender. The 3Q/TMD questions were used for detection of orofacial pain and dysfunction in both groups.

4.5.1 Orofacial pain and dysfunction

The 3Q/TMD questions showed that the children with JIA had more pain (Q1, Q2) and functional disturbances (Q3) than the healthy controls. The number of positive answers to Q1 and Q2 were significantly higher in the children with JIA than in the controls ($p = 0.010$ and $p < 0.001$, respectively), and there was a trend towards a significant difference for Q3 ($p = 0.052$) (Table 21).

Table 21. This table shows the distribution of temporomandibular symptoms according to the 3Q/TMD questions in the 30 children with a diagnosis of JIA and in the 30 healthy controls (CTR). The JIA group had significantly more orofacial and functional pain (Q1 and Q2).

Q1: Do you have pain once a week or more when you open your mouth or chew? Q2: Do you have pain once a week or more when you open your mouth or chew? Q3: Does your jaw lock or become stuck once a week or more?

	CTR (n=30)	JIA (n=30)	p-value
Q1			
No	25 (83.3%)	15 (50.0%)	**0.013**
Yes	5 (16.7%)	15 (50.0%)	
Q2:			
No	29 (96.7%)	16 (53.3%)	**<0.001**
Yes	1 (3.3%)	14 (46.7%)	
Q3:			
No	30 (100%)	25 (83.3%)	0.052
Yes	0 (0%)	5 (16.7%)	

5 Discussion

Orofacial aspects and manifestations of JIA in children have been the subject of extensive research in recent years. There are many pieces that need be put together to get a comprehensive view of how JIA affects oral health, mandibular function, and growth. This thesis investigates clinical variables indicating TMJ involvement, radiological examination techniques to identify TMJ deformities, and saliva as a potential carrier of disease-specific biomarkers for JIA.

The main findings from the longitudinal study were that that self-reported TMJ pain and dysfunction was associated with TMJ deformities. In addition, in children with TMJ deformities, compared to those without TMJ deformities, mandibular range of motion was reduced and palpatory TMJ pain as well as crepitations were more common. Regarding the reliability of PANs versus CBCT for differentiating between normal and abnormal TMJ morphology, the main observation was that normal morphology were identified equally often with PAN as with CBCT. As for saliva as a medium for detection of biomarkers in connection with JIA, the result showed that most of the investigated biomarkers were detectable in saliva by the applied method. However, no differences were found in levels of biomarkers between children with JIA and healthy controls.

5.1 Participants

The children enrolled in Studies I–IV are representative for the children diagnosed with JIA in Scandinavia with respect to age for disease onset, sex, dispersion of subtype of diagnosis, and medication.[27] This is a strength and one can assume that the results from the studies are representative for children with JIA in Europe and North America where the same diagnostic criteria are used (ILAR) and largely the same guidelines for pharmacological treatment are applied; bDMARDs and sDMARDs are more frequently prescribed than in other geographical areas.[159] To insure only children with active disease were included in the studies, no children perceived to be in long-time remission without pharmacological treatment were included. For Study II, an addition was made to the inclusion criteria: the child must have experienced joint symptoms such as increased pain, swelling, or functional limitations in the two weeks prior to inclusion.

Although these distinctions were made, there is still a degree of uncertainty regarding disease activity in the children included. JIA is a disease of variable nature with several subtypes, possibly of different genotypes and etiology and with a pattern of relapsing-remitting disease activity, making the distinction between active and inactive disease uncertain.

As always in clinical research, there are limitations in participants eligible for inclusion as well as a timeframe to consider. The inclusion time for Studies I, II and IV were 3.5 years and over that time 60 children were recruited. Sample sizes in all four studies were relatively small, especially when dividing participating children by subtype of JIA diagnosis. However, analyses based on subtype were only done in Study II.

More girls than boys were included in all studies. As mentioned, this is consistent with the prevalence of JIA and a strength. However, when considering MUO, there is also an association with height. Consequently, since boys usually are taller, expected mandibular range of motion is larger for boys than for girls.[160] This may have affected our result toward smaller numbers for MUO in Studies I and IV. The children enrolled were 7–14 years at baseline and 9–16 years at study end, implying that some have entered puberty.

For Study III, the goal was to achieve a matching control group. Although the matching was not perfect, it was deemed to be good enough for the purpose.

5.2 Localized self-reported pain and dysfunction

In children, pain assessment is challenging due to age and developmental factors. To resort to caregivers and parents' assessments of pain will only result in an estimate the child's pain.[161] No age-appropriate questionnaires specific for self-reported TMJ pain and dysfunction in children with JIA have been available. Previous studies have used scales for global health such as CHAQ[85] and others have used parental questionnaires.[79] In 2022, Stoustrup et al. (2022) published a validation of a consensus-based short patient questionnaire for assessment of orofacial symptoms in juvenile idiopathic arthritis.[162] To date, this questionnaire is only available in English and Danish. The same author has also published recommendations on what symptoms to target with questions on localized TMJ/TMD pain.[163] There is variation in the way

self-reported TMJ pain and/or dysfunction is reported in children with JIA. In some studies, signs, and symptoms of TMJ involvement are reported together,[74,78] making it difficult to distinguish between self-reported pain and pain evoked during the clinical examination. When studies use different[85,164] and often unspecified sets of questions,[165] the results are neither repeatable, nor comparable.

The previous notion of TMJ involvement in JIA being a silent condition has already been challenged.[166] Our findings support this challenge as we found the TMJ to be the third most common self-reported painful joint, both at baseline and follow-up examinations (Study IV). Previous reported prevalence numbers for self-reported pain varies. The trend is that older studies report low prevalence[77-79] and more recent studies and those using specific questions report higher prevalence of self-reported orofacial pain.[85,167]

In Study I and IV, self-reported TMJ symptoms were common. In this case, self-reported TMJ pain could be interpreted as functional pain due to TMJ deformities or TMJ arthritis, but it could also be associated with childhood TMD. It has been shown that children with JIA have higher prevalence of TMD compared to healthy children.[85,167] Other factors that predict onset of orofacial pain in children are preexisting pain conditions, female gender, and psychosocial load.[168] All these factors are more common in children with JIA and could be the explanation for the differences between the groups.[6,91] However, at baseline, significantly more children with radiologically-confirmed TMJ deformities reported previous as well as present TMJ pain and dysfunction, which suggests that self-reported TMJ pain could be associated with morphological changes in the TMJ.

In Studies I and IV, when investigating previous and present TMJ pain or dysfunction specific questions, pain drawings and physical reinforcement were used. Studies show that pain drawings can be of value in clinical diagnosis of other pain conditions such as headache and migraine in children.[169,170] We found TMJ pain to be common and our data also showed that the number of children reporting TMJ pain decreased over the study period. However, self-reported previous pain based on recollection as in Study I should be interpreted with caution. Studies on pediatric pain have observed memory bias due to both social context and the individual pain experience.[171]

To evaluate the presence of TMD in Study II, the 3Q/TMD were used. The 3Q/TMD is a validated and cost-effective screening tool that shows good sensitivity and specificity for finding clinical TMD according to the Diagnostic Criteria for TMD (DC/TMD).[152] The first question is about localized pain, whereas questions question 2 and 3 are about functional disturbance–i.e., clicking and locking of the TMJ. However, the 3Q/TMD cannot determine the cause of TMD and not provide a specific diagnosis. In Study II, significantly more children with JIA than healthy controls answered affirmatively to Q1 (50% versus 17%) and Q2 (47% versus 3%). In comparison, a population-based study from northern Sweden found an average prevalence of less than 1% of any symptoms according to the 3Q/TMD in the age group under 10 years.[172] The result from Study II, confirms that TMD is substantially more common in children with JIA than in healthy children of the same age.

5.3 Clinical findings

The purpose of the clinical examination used is to detect patterns or signs of active TMJ arthritis as well as TMJ deformities as a consequence of previous TMJ arthritis. It should also assess growth and disturbances in growth patterns as well as longitudinal progression of orofacial pain and dysfunction in children already diagnosed with TMJ involvement.

5.3.1 Examination protocol

How to clinically assess oral health and how to identify TMJ involvement and arthritis in JIA has been subject for discussion and research for decades. Lately, some progress has been made in the area and studies with suggestions on what to include and how to perform a clinical assessment have been published.[163,173] However, there are still no validated clinical examination protocols or clinical variables with definitive cut-off values that positively can identify TMJ involvement in JIA.

At study start, the RDC/TMD examination protocol was perceived as the gold standard in TMD research. The drawback with RDC/TMD is that it was originally developed for TMD examination and diagnostics of otherwise healthy adults; that is, it does not consider factors such as growth or joint disease.[107] Nevertheless, it had been used in

several studies on adolescents[108,151] as well as in studies on adults with different rhematic diseases.[110,174] As previously mentioned, only Axis I (the clinical domain) was used as Axis II (the biobehavioral domain) was deemed not age appropriate. The RDC/TMD examinations were performed by three experienced specialists in orofacial pain who were calibrated to a reference standard. In 2014, while the study was ongoing, the new Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) were published.[175] The DC/TMD had been thoroughly validated and has high sensitivity and specificity for TMD. Therefore, it eventually replaced the RDC/TMD as the gold standard in TMD research. As with the RDC/TMD, the DC/TMD was initially developed for healthy adults, but it has in recent years (2021–2023) been adapted for children and adolescents.[176-178] A recent study concluded that the diagnostic accuracy of the DC/TMD for TMD-related pain in children was lower than previously shown adults;[179] however, more validation is pending.

Study I applied not only the examination protocol for RDC/TMD but also the diagnostic criteria. However, the accuracy of the diagnoses was questioned during the review process. Moreover, it became clear that, although a diagnosis such as myalgia could be used and made sense, diagnosis such as osteoarthrosis and osteoarthritis did not. The RDC/TMD criteria for image analyses of PAN and CT state that osseous diagnostics of the TMJ apply when there is deformation due to subcortical cyst, surface erosion, osteophyte, or generalized sclerosis.[180] This description does not match the morphological changes typically seen in JIA, which are remodulation of the condyles with various degrees of flattening (lowered condylar height) and simultaneous enlargement of the antero-posterior dimension (Study III) [98] whereas erosions are rare.[97] Based on the clinical and radiological examination made and with the knowledge of a diagnosis of JIA and that TMJ arthritis might be a silent condition, the distinction made between osteoarthrosis and osteoarthritis is questionable as well. Taken together, the RDC/TMD diagnostic criteria are not applicable when assessing TMJs in JIA.

5.3.2 Intraoral findings

The participant were children with mixed dentition, all with their permanent upper incisors in place. Data showed that all children had either Angel Class I or Angel Class II

sagittal relations. The percentage of children with Angel class II decreased from 48% at baseline to 40% at the two-year follow-up. In comparison, the expected prevalence of Angle Class II occlusion in Swedish children 7 to 13 years old is between 14% and 29%.[181,182] Angle Class II occlusion did not correlate with TMJ deformities in the examined cohort. The high prevalence of Angel class II found at follow-up might be explained by growth impairment as chronic inflammatory conditions such as JIA, often are associated with an overall growth failure.[183]

Several studies have reported facial and mandibular asymmetry in children with JIA.[11,184-187] In Study IV, midline deviations were found in 27% of the children at baseline and there was a significant increase in percentages of midline deviations over time–up to 48% at the two-year follow-up. It is known that unilateral TMJ involvement in JIA may cause uneven growth with ramus shortening and a reduction in mandibular body size on the affected side.[154,188] However, there was no correlation found between midline deviations and TMJ deformities in the current study.

An explanation for the high frequency of Angel Class II relation and midline deviation can be found in the mandibular growth pattern.[189] TMJ arthritis not only causes damage to articular structures but also affects the mandibular growth center localized in the condyle. If the growth center is affected, mandibular growth can decrease both in length and height [68,69,99,190] and therefore resulting in an overall smaller mandible, Angel Class II malocclusion, and midline deviations.

A limitation to the study is that extraoral facial or mandibular asymmetry was not assessed. It was discussed but not included in the study protocol due to difficulties defining what is normal and what is pathological in terms of facial symmetry. Mandibular asymmetry has been shown to be common in healthy children 7 and 16 years[191] and there are also contradictory findings whether facial asymmetry is correlated to TMJ deformities.[186] However, recent publications on management of orofacial manifestations of JIA recommend that frontal facial asymmetry be assessed.[163,173] It is also recommended in the Swedish orofacial health program for children with JIA to document facial shape and profile with photographs as reference for future assessments.

5.3.3 Mandibular range of motion

In children with JIA, stiffness, and limited range of motion of joints can be symptoms of active disease, but it can also indicate that the TMJs are already involved. Reduction in MUO is associated with TMJ deformities in both adults[192] and children.[85,193] Data from Studies I and IV show that the children with JIA had reduced range of mandibular motion. When TMJ deformities seen on CBCT were not considered, the overall median MUO without pain and MUO with pain at baseline were 43.5 mm and 47.5 mm, respectively. This is a clinically relevant difference compared to the healthy children. In age-matched children, expected MUO ranges from 50 to 56 mm.[194-196] Furthermore, a smaller MUO without pain at baseline was predictive of finding TMJ deformities on CBCT. However, children without TMJ deformities exhibited MUO with pain equivalent to MUO for a healthy population in the same age group.

A correlation was found between presence of TMJ deformities and a larger discrepancy between MUO with and MUO without pain. However, this correlation was only seen at the two-year follow-up. This inconsistency in correlation may be explained by the children being familiar with the questions and the examination protocol at the two-year follow-up. In addition, the children were older and cognitively more mature in their pain assessment.[197]

Previous studies have reported restricted mouth opening as the most frequent clinical symptom in children with JIA[75,198] with MUO < 35 mm in as many as 41% of the children in a study from 1982.[75] The children in Studies I and IV have better (although not quite normal) mandibular range of motion compared to the children in the Norwegian publication from 40 years ago.[75] However, the result shows that MUO was smaller in children with TMJ deformities. This finding is consistent with contemporary studies that report smaller passive and active mouth opening in children with JIA and TMJ involvement compared to healthy children[160] and that limited mouth opening correlates with severity of TMJ arthritis seen on MRI.[199]

The improvement seen in MUO compared to earlier studies on children with JIA can probably be explained by advancements in diagnostics and pharmacological treatment. A recent publication concluded that systemic treatment with bDMARDs preserve TMJ morphology and growth in children with JIA.[125] The children participating in the current study were under regular supervision and treatment by pediatricians

specialized in rheumatic disease in children. At study start, 41% were treated with bDMARDs, a number that increased significantly over the study period. An indication of the disease being well controlled in the participating children was that the overall number of self-reported painful joints decreased from baseline to the final examination after two years.

However, a note of caution is due when comparing numbers for MUO. How MUO has been defined and measured differs between studies; some studies do not describe the method at all. Furthermore, MUO with pain as a measurement is a not as reliable as MUO with pain and maximum assisted MUO. It is subjective to individual variations and might also vary within the same individual if the measurements are repeated.

5.3.4 Palpatory TMJ and muscle pain

In RDC/TMD, both the lateral and posterior parts of the TMJ are examined. Study I found a high degree of consistency in palpatory findings between the lateral and the posterior aspect of the TMJs. In 70% of the TMJs, the findings in the lateral and posterior part of the condyle coincided. Furthermore, palpatory pain was present in more than 50% of TMJs at baseline and 40% at the final examination. In Study I, no correlations were found between palpatory pain and TMJ deformities. However, in Study IV, the odds for having TMJ palpatory pain was 43% higher in children with TMJ deformities on CBCT versus children without TMJ deformities. It can be debated how much weight to attach to these findings regarding disease activity in the TMJ. The reliability of the RDC/TMD for the diagnose arthralgia (IIIa) is good in adults[200] but is, as previously mentioned, not validated for assessing TMJ arthritis or TMJ involvement in children with JIA. Furthermore, in a recent publication, the sensitivity and specificity of palpatory TMJ pain in healthy children (8–12 years) was shown to be unsatisfactory.[179]

Although joint pain is a cardinal symptom in most subtypes of JIA, myalgia is generally not described as a common symptom except in the orofacial area.[85,163,164] In the current study, half of the children showed signs of myalgia in the masseter muscle at all three examinations. However, palpatory pain in masticatory muscles was not related to TMJ changes over time nor were they associated with or predictive of finding TMJ deformities on CBCT.

The high frequency of masticatory muscle pain found is consistent with findings from a recently published Norwegian study that found that children with JIA had symptoms and clinical signs of muscular TMD twice as often as healthy children.[167] The study also found that approximately half of the children with JIA in their study suffered from TMD. Pain in masticatory muscles has also been reported to develop over time in children with JIA.[87,201] It is unclear whether masticatory muscle pain should be considered a symptom of or a consequence of JIA. However, the findings support that children with JIA should be regularly examined for signs of muscular TMD as well as for TMJ involvement in JIA and that differential diagnosis such as TMD always should be considered.

5.3.5 TMJ noise

The prevalence of TMJ noises found was high compared to expected prevalence numbers for the age group.[202] For TMJ clickings, there is a widespread in reported prevalence numbers for this age group and our result (6.4%–13.9%), although slightly on the high side, did not stand out as abnormal.[203] The prevalence of crepitations, however, was high and increased significantly over the study period. At the two-year follow-up, crepitations were present in almost 15% of the children. Crepitations are normally rare in younger children (prevalence ranging between 0.2 and 1.0%).[203] Crepitations are explained by changes in TMJ morphology and associated with disease such as TMJ osteoarthritis.[107] In adults, crepitations correlate with degenerative changes in TMJ morphology.[204-206] To our knowledge, there are no publications on children/adolescents that correlate or assess the diagnostic validity of crepitations to alterations in TMJ morphology found on CBCT. However, underlying morphological factors for crepitation are most likely the same in children as in adults. Assessment of joint noises should be included in a clinical evaluation and warrant a radiologic examination.

5.4 Radiological findings

Information from both clinical and radiological examinations are often needed to arrive at a diagnosis of joint disease. In children with JIA, imaging is important since the

sometimes-silent nature of TMJ arthritis and involvement makes it difficult to uncover.[80]

5.4.1 Radiological findings–*Studies I* and *IV*

Reported frequency of TMJ deformities differ between Studies I and IV, the primary explanation being that the radiological material has been reviewed twice. This is described in methods and discussed in detail under 5.4.3 Erratum. In Study I, data from a radiological review done in 2018 are presented and data in Study IV are based on a radiological review done in 2021.

In Study I, radiological data from 59 baseline CBCTs were presented. TMJ deformities were found in 38 (64%) of the children (24 unilateral and 14 bilateral). This is a high frequency compared to previous studies using conventional CT[93] and CBCT[105] and even higher than studies using PAN.[74] At that time, the high frequency of TMJ deformities were contributed to differences in in radiological techniques used, as CBCT is considered superior to PAN and conventional CT.[96] Another explanation was that the children with TMJ deformities had been diagnosed with JIA for a significantly longer time than the children without TMJ deformities (4.8 and 3.0 years, respectively).

In Study IV, the data were collected from radiological examinations of 197 matching pairs of PAN and CBCT examinations from 54 children. The frequency of children with TMJ deformities reported in Study IV, 38.8% at baseline and 42.5% at the two-year follow-up, is consistent with previous studies.[78,80,207]

The initial aim of the project was to identify variables that could predict presence of TMJ deformities as well as development of TMJ deformities. Study IV reports that number of years with disease and a smaller MUO without pain were predictive of having TMJ deformities on CBCT at baseline. No other predictive variables were identified. Furthermore, CBCT findings on improvement or deterioration in TMJ morphology did not correlate with clinical findings. A possible explanation for these results may be the small number of joints that show change over time (n = 13). Another explanation could be the timing of the examinations: the three “snapshots” of clinical variables in this study were not enough to detect flareups in disease activity. When assessing TMJ deformities in children, other explanations than JIA should also be

considered. TMJ injuries such as permanent disk displacement can lead to condylar deformity, simulating changes due to JIA[97,208] and the same can be said for growth disturbances.[208] The prevalence of TMJ deformities in healthy children are not known, and few reports are published.[209]

There are some strengths and some limitations to consider in Studies I and IV. Although representative for children with JIA in Sweden, the number of children included were limited. Second, the RDC/TMD examination protocol was not optimal for this cohort of children. Finally, the observational nature of the study design leaves open the possibility of unknown confounding factors.

5.4.2 Reliability of panoramic imaging compared to CBCT–Study III

There is an ongoing debate as to which imaging modality is preferable or superior for TMJ evaluation in children with JIA. Today, MRIs are considered the gold standard for detection of active TMJ arthritis,[42,113] but CBCT is the choice for assessing bony TMJ components.[96,118,210] PAN, on the other hand, has been questioned. There are many studies on adults comparing the diagnostic value of PAN and CBCT[118–120,211,212] that clearly demonstrate the inferiority of PAN. However, there seems to be no studies that confirm the inferiority of PAN for evaluation of TMJs in children.

It is important to remember that children have more radiosensitive tissues than adults. Consequently, all radiographic examinations should be performed on strict indication and with a radiation dose as low as diagnostically acceptable.[116] For a long time, PAN, a low-dose method, has been used in examinations of children with JIA.[98] PAN has also been shown to be reliable regarding the assessment of vertical dimensions.[213] At study start, although not supported by publications, the clinical experience in the research group was that PAN can more reliably identify TMJ deformities in children than in adults. To investigate this knowledge gap, a collaboration was established with maxillofacial radiologists at the University of Oslo.

Study III investigated the reliability of PAN for distinguishing between normal and abnormal TMJ morphology in children with JIA using a classification system for grading TMJ deformities and with CBCT as the gold standard. The main observation was that joints with normal morphology were identified equally often with PAN as with CBCT.

For PANs, 27.6% of the joints were graded as abnormal; for CBCTs, 28.1% of the joints were graded as abnormal. This result supports the idea that PAN is a valuable tool in the initial assessment of whether the TMJ is morphologically abnormal in children with JIA. If a PAN does not show any TMJ abnormalities, there is no indication for further radiological examinations unless there are symptoms suggestive of TMJ arthritis that need to be confirmed. If this is the case, MRI is the imaging modality of choice. However, the result also shows that CBCT was superior for assessing the severity of the TMJ abnormalities and for identifying additional diagnostic information in the examinations, such as erosions. That is, when assessing possible deterioration (or improvement) in TMJ morphology over time, CBCT is a better method than PAN. Furthermore, presence of erosions seen on CBCT might suggest active arthritis in the joint.

An explanation for why PAN to such a large extent correctly could distinguish between normal and abnormal TMJ morphology in this study can be found in anatomical differences between children and adults and in the impact JIA has on growth. In adults, the condyle resembles a roll or a spindle,[68,69] whereas in children the condyle has a more rounded shape.[67] The adult condyle is also angulated in the horizontal plan and the angulation shows considerable variation between individuals. How the condyle is angulated strongly influences how the shape of the condyle appears in a PAN.

As mentioned, JIA can have an impact on the growth of the TMJ. TMJ deformities found showed remodeling with various degrees of flattening (reduced condylar height) and simultaneous enlargement of the antero-posterior dimension. This pattern of bone-destruction and bone-production are characteristic for TMJ involvement in JIA and could be considered a form of growth disturbance due to arthritis within the growing joint (see Larheim et al.).[98] The study result shows that this pattern of morphological abnormalities can be identified on PANs.

The reliability of the study was good as intra-reader and inter-reader agreement was high to excellent despite no precognition of clinical findings or type of JIA among the readers. Intra-reader agreement for PAN and CBCT was high and excellent, respectively, although earlier studies on adults show a substantially higher agreement for CBCT.[118,212] The inter-reader agreement was high for the distinction normal or abnormal joint for both PAN and CBCT whereas other studies describe inter-reader

agreement for morphological abnormalities of the TMJ as fair to moderate for PAN[211] and good for CBCT.[214]

Explanations for the overall high intra-reader and inter-reader agreement might be the ongoing development of technical equipment in both the area of panoramic and of CBCT technology but also that all included radiologic examinations were exposed under supposedly optimal conditions.

There are some limitations that need to be considered. One weakness is that the diagnostic information obtained by PAN is limited to the morphology of the mandibular condyle while the temporal part of the TMJ as well as inflammatory activity in the TMJ cannot be assessed. In addition, the three maxillofacial radiologists evaluating the examinations in the study were highly experienced and their level of expertise could be hard to match in general practice.

5.4.3 Erratum

While conducting Study III, it became obvious that the frequency of observed TMJ deformity in this material was not in accordance with the result published in Study I. In Study I, 71% of the children with JIA showed signs of TMJ deformities on CBCT at baseline. When applying data from the radiological review for Study III to individual level, type of image, and time of examination, there was an evident discrepancy from the results presented in Study I. According to the radiological evaluation for Study III, 38.9% of the children showed TMJ deformities on CBCT at baseline (Table 22).

Table 22. TMJ deformities on individual level according to radiological findings from the 2021 evaluation.

	PAN Baseline	PAN Two-year examination	CBCT Baseline	CBCT Two-year examination
TMJ deformities	34.7%	40.8%	38.9%	41.5%

TMJ: temporomandibular joint; PAN: panoramic imaging; CBCT: cone beam computed tomography

While reviewing the original protocols from the radiological evaluation from 2018, we found a mistake. During the identification process of the anonymized reading protocols, data for baseline CBCT examinations for one of the readers were not

assigned to the correct participants. Consequently, the result in Study I regarding prevalence of TMJ deformities became overestimated and faulty.

When the correct data from the radiological evaluation in 2018 was used, 64.4% of the children with JIA examined showed signs of TMJ deformities at baseline CBCTs. This is a reduction of seven percentage units compared to the initial discovery. This, however, does not cover the discrepancy when comparing the findings in Study III. To further investigate the differences between the radiographic evaluations of 2018 and 2021, a calculation of intra-reader agreement was made (Table 18).

During the evaluation of radiographic examinations in 2018, readers 1 and 3 graded TMJs as abnormal to a higher degree than they did at the reading in 2021. When the majority decision was made based on 2018 gradings on TMJ abnormality, the result leaned more heavily towards abnormality in comparison with the consensus grading of 2021.

There are several possible explanations for the discrepancies between the two readings of PANs and CBCTs. First, the reading in 2018 was not performed with the same timetable. After a calibration meeting in Stockholm in December 2017, the readings were done over an extended period during 2018. Second, even though criteria for grading TMJ abnormalities were discussed at calibration meetings, no reference images were produced for the first reading. Third, at the first evaluation, PANs and CBCTs were graded at the same time and in random order. Taken together, these factors may have led to the readers having difficulties in maintaining coherence to written criteria.

After statistical re-analyses of data for Study I, an Erratum was written and sent to the publisher.

5.5 Saliva

In Study II, collection of whole saliva was done in a standardized fashion. Stimulated whole saliva was chosen as it was deemed the easiest technique to instruct and implement in children 7–14 years old and because it gives an adequate picture of the saliva content.[135] The chosen saliva sampling technique worked well in the age group. However, the younger children had some difficulties with the both the chewing

technique and the paraffin gum. They found the paraffin gum hard to chew, and they did not like the taste. For children younger than 7 years, it would be wise to consider other saliva samplings techniques than the one used in this study.

5.5.1 Saliva flow rate

The most surprising result was that a significant correlation was found between a reduced salivary flow rate and presence of orofacial pain, assessed by 3Q/TMD (Q1), regardless of the child having JIA or being in the control group. To our knowledge, this is the first study to show this effect of orofacial pain on saliva flow rate in children. The result supports the idea that the reduction in salivary flow is due to pain in the orofacial region rather than childhood JIA. This result is in accordance with previous studies that demonstrate a reduction in salivary flow in adults suffering from painful TMD.[132,215] One underlying reason may be that masticatory efficacy is affected by orofacial pain. However, masticatory performance is affected by several factors including number of missing teeth,[216] and, in our study, mixed dentition was common.

No differences were found in saliva flow rate between the children with JIA and the control group. This confirms the findings from a Swedish study that found no differences in either stimulated nor unstimulated salivary flow rate between children with JIA and health controls.[130] However, the findings are contrary to previous studies that show a reduction in unstimulated and stimulated saliva flow rate in children with JIA.[131,217,218] A recent publication also showed that reduced salivary flow rate was associated with early disease onset in children with oligoarthritis.[219] These inconsistences between studies may be due to study design, the selection of participants, JIA diagnostic criteria, saliva sampling technique, as well as where the studies are conducted. When evaluating saliva flow rate, many factors are important: age (at time of sampling), disease activity over time, pharmacological treatment, number of teeth and dental status, and, as observed in our study, presence of orofacial pain. It is also important to include an age-matched control group to validate the results.

5.5.2 Biomarkers

Several reports have shown that immunological markers in saliva in adults can be identified and measured.[141,143,144] However, very little was found in the literature on salivary biomarkers in children with JIA.[131,145] A literature review resulted in a target list of 21 immunological active proteins of interest: TNF-alpha, TNFRII/TNFRSF1B, MMP-1, MMP-2, MMP-3, MMP-13, IL-1 alpha, IL1-beta, IL-1 RII, IL-2, IL-6, IL-6R alpha, IL-8, IL-10, IL-12, CCL2,CCL3, CCL11, CCL22, CXCL9, and S100A8.[40,42-53,145,149,150,220-231]

The Luminex system was chosen for the analysis since it is a feasible and cost-effective technology for assay development and our analysis required a custom-built kit. However, the Luminex assays are validated for cell culture supernatants, serum, and plasma but not for saliva. Therefore, presence of and concentration of biomarkers were investigated in two steps: a pilot test was used to validate the technique, and this was then followed by the main analyses. As described, the pilot test evaluated linearity and detectability of preselected proteins. Proteins that showed matrix effects were excluded to minimize the risk of false positives. This approach was recommended by the manufacturer and the analysis was performed in collaboration with SciLifeLab, Karolinska Institutet, KTH Royal Institute of Technology, Stockholm University, and Uppsala University.

The two main findings were that two-thirds of the preselected biomarkers were detectable in saliva in both children with JIA and the control group and further, that there were no differences in levels of pro- and anti-inflammatory salivary markers between the groups.

The main analyses showed no association between protein profile and age, sex, or pharmacological treatment. There was, however, a trend towards an association between the concentration of IL-8 and a diagnosis of JIA. IL-8 is a proinflammatory chemokine, produced by activated monocytes and macrophages. Its main function is to activate and recruit neutrophils from blood vessels and promote cell migration to the area of inflammation.[39,48] The expression of IL-8 is different in monocytes and neutrophils in JIA compared to other autoimmune diseases,[220,221] and this change in neutrophil action is an example of auto-inflammation. Further investigations are needed to determine whether levels of IL-8 in saliva correlate with a diagnosis of JIA.

Our data also showed that a high concentration of TNFII-TNFRSF1B, a soluble receptor that acts as an inflammatory inhibitor in JIA,[49] was associated with a diagnosis of juvenile psoriatic arthritis. This result was based on one individual and no conclusions can therefore be drawn. However, previous studies indicate that there are differences in cytokine profile between subtypes of JIA,[48,54] and a larger sample size for each subtype of JIA in study II might have exposed differences in protein profiles in saliva.

The overall result of the study was not a surprise since previous studies show deviating results for saliva regarding coherence to other biofluids as well as differences in both detectability as well as levels of inflammatory biomarkers.[48,140-142] One possible explanation for the lack of difference in salivary biomarkers between healthy children and children with JIA could be the degree of disease control in the JIA group.

This study has several strengths, including its use of a representative group of children with JIA regarding distributions of sex, JIA diagnosis, and medication, a matched-control group, a standardized saliva collecting technique, and a validation of the immunoassay. To ensure that the children with JIA had an active disease, recent joint symptoms was added to the inclusion criteria.

There are some limitations to consider. The small sample size might lead to a type II error especially when looking at the JIA subtypes. The statistical analyses were hampered by several of the biomarker having extreme outliers and the data not being normally distributed. Another limitation could be how saliva samples were processed. That is, potentially interesting proteins could have been removed or damaged. Nevertheless, if this were the case, both groups would have been equally affected.

Today, a lot of research on biological markers in saliva are done in the field of proteomics. This allows for studies of all proteins expressed in a sample without a predetermined target list. Techniques like gel-based electrophoresis separates the proteins, which then can be identified with mass spectrometry.[232] A Swedish study (2020) used this technique and investigated total protein concentration and the concentration of inflammatory biomarkers in unstimulated parotid saliva from healthy children. They concluded that it was possible to analyze various inflammatory biomarkers in saliva.[218] However, a review from 2011 on salivary biomarkers detected by mass spectrometry showed inconsistencies in findings[233] and, in recent years, only a

handful of studies have been published on this subject. One can only speculate on what the result might have been if this technique had been chosen for the current study.

5.5.3 Protein concentration analyses

Reflecting over the results in Study II and reading methodological studies, a question was raised: Did total protein concentration in the samples affect the outcome of the analysis? To investigate this, a post-publication measurement of total protein concentration in the saliva samples was made with NanoDrop (Thesis). For spectrophotometer-based analyses such as NanoDrop, a reference substance with consistent properties is needed. In our case, we used sterile vatter for the blanking routine. After compensating for the total protein concentration in a statistical analysis, the association between JIA diagnosis and IL-8 became significant (from $p = 0.063$ to $p = 0.041$), but otherwise the result was not affected. This difference was too small to be important even though it changes the outcome given the chosen significance level of $p < 0.05$.

5.6 General discussion and clinical implications

This project started with a wish to scientifically contribute to improvements in the Swedish program for orofacial health in children with JIA and consequently enable clinicians to effectively perform care for children with JIA. The four studies of the thesis encompass clinical and radiographic examination techniques and an exploratory study on the value of saliva as a carrier of disease markers.

An increasing amount of evidence emphasizes that pain assessment is important in routine care of children with JIA.[85,234,235] A recent study from the Nordic JIA cohort shows that early self-reported, disease-related pain is common and seems to predict development of persistent pain and an unfavorable long-term disease outcome.[15] In addition, orofacial pain, especially in girls, is associated with having other pain conditions and is predictive of developing long-term pain conditions.[168,236]

With this in mind and adding that self-reported orofacial pain was associated with TMJ abnormalities in Study I and a high degree of self-report orofacial pain in the children

with JIA found in Studies I, II, and IV, the importance of regular assessment and treatment of orofacial pain is obvious. However, the fact that children with JIA have higher prevalence of TMD compared to healthy children[85,167] makes the assessment of whether the child suffers from JIA related TMJ arthritis or TMD difficult. To make this distinction, regular patient visits with the possibility to observe change over time in self-reported pain and dysfunction are mandatory. Specific questions on present and previously experienced pain at rest and during function should be used and ideally questions should be reinforced with visual aid and pain location should be confirmed by the caregiver.

Regarding the clinical assessment of TMJ involvement and arthritis, there is still a lack of validated, age-appropriate clinical examination protocols for children with joint disease. It is desirable to establish cut-off values for variables like MUO for when to suspect TMJ involvement and deformities. However, the results from Study IV show mostly stable measurements for mandibular range of motion over time. MUO was slightly smaller than expected compared to healthy children but within range of what is considered normal (>40 mm). The inter-individual variation in MUO is large, both among healthy children and children with JIA, making fixed cut-off values for MUO irrelevant. In addition, the cut-off value 40 mm used in RDC/TMD[107] is not a relevant benchmark for TMJ involvement in JIA. The only way for MUO to predict TMJ involvement is when there are repeated measurements available and an individual change over time can be observed. In Studies I and IV, variables such as palpatory TMJ pain, crepitations, and Angle Class II malocclusion were common in children with TMJ deformities. Although not unique,[167,237] these findings are important and an indication for when to launch additional examinations such as imaging and when to consider treatment options.[124,162] At this time, the best strategy for uncovering TMJ arthritis and involvement in JIA is the same as for self-reported pain, i.e., conduct regular examinations and on individual level observe change over time. Progression, improvement, or no change regarding TMJ involvement or TMJ deformities in children with JIA are consequences of overall disease activity, subtype of JIA, as well as pharmacological treatment (and response to treatment) and can most likely not be predicted by local variables as those investigated in Studies I and IV.

When considering which image modality is best suited for examining children with JIA, the first question should be whether the TMJ is the only structure of interest. PANs not

only provide information on TMJ morphology but also give an overview of teeth (erupted and unerupted), jaws, and surrounding structures, whereas CBCTs of the TMJ focus on that specific area. If the TMJ is the only structure of interest, the second question should be whether it is the degree of inflammation or whether if it is the bony components of the joint that are to be assessed. If the purpose of TMJ imaging is to evaluate the mandibular condyle and to exclude TMJ deformities, the results from Study III support the use of PAN as a first-line imaging modality in children with JIA. However, CBCT is a better option for evaluating the temporal component of the joint, the degree of morphological abnormality, erosions, and change over time.[96,118,210] Nevertheless, there is no reason to repeatedly perform radiographic examinations unless there is a clear suspicion of TMJ abnormalities that need confirmation. Furthermore, when radiographic confirmation is needed, the technique that can provide a diagnostically acceptable image at lowest radiation dose should always be used.[116]

That evaluation of TMJ deformities on both PAN and CBCT is a challenge and that explicit written criteria as well as reference images are crucial to achieve a high level of intra- and inter-reader is demonstrated in *study III*. This was also demonstrated by the differences in results between on one hand *study I*, and on the other hand *study III* and *IV*. The written criteria and reference images published in *study III* can be used to make assessments both over time, and between observers more reliable.

Pertaining saliva as a carrier of inflammatory biomarkers, the exploratory study performed showed that most inflammatory biomarkers examined were detectable in saliva and that there were no differences between children with JIA and healthy children. There was a trend toward an association between concentration of IL-8 and a diagnosis of JIA; however, this finding was not significant. Other findings from the study were that a diagnosis of JIA did not influence saliva flow rate and an interesting secondary finding was an association between lower saliva flow rate and orofacial pain (Q1) for both children with JIA and healthy children. To conclude, at present, the scientific support for using saliva to screen for disease activity in JIA is not sufficient.

As previously discussed, there are strengths and limitations of the studies to consider. First, the results relate to a specific cohort of children with JIA and cannot be transferred to other populations without careful considerations. The prospective and longitudinal design of the studies is a strength although the observational nature

leaves the possibility of there being unknown confounding factors. It is also a challenge to retain participants in a longitudinal study and some children were lost to follow-up. A strength is that the children recruited are representative for the Swedish population of children with JIA in age, sex, subtype of diagnosis, and pharmacological treatment. However, the relatively small sample size is a limitation and did not allow for comparison between subtypes of JIA. An inclusion criterium was active disease, but no objective measurement of overall level of disease activity was included. Regarding clinical examination, although not optimal for children with joint disease, the best protocol available at study start was used (RDC/TMD), and examinations were performed by dentists calibrated to reference standard. The radiological examinations in the studies were for the most part of good quality and were assessed by observers with a high level of expertise. This is a strength but also a limitation since this level of precision in performing and reading radiological examinations requires resources not always available in a clinical setting.

Taken together, this thesis offers the following recommendations for evaluation of TMJ involvement in JIA. Conduct regular and repeated clinical examinations focusing on change over time. For patient history, use targeted questions on TMJ pain and dysfunction at rest and during function (i.e., MUO and chewing). The clinical examination should encompass MUO without pain and MUO with pain, palpation and auscultation for TMJ noises (crepitations specifically), palpation of TMJs and masticatory muscles, as well as an assessment of occlusion and malocclusion including sagittal and vertical relations. Clinical variables should be registered in such a way that it allows for comprehensive evaluation of change over time. Radiological examinations and imaging such as PAN, CBCT, or MRI should be performed on individual indication. Moreover, PAN is the imagine modality of choice for a first-line exclusion of TMJ deformities in children with JIA.

6 Conclusions

In children with JIA, self-reported TMJ pain and dysfunction was common. In addition, a high degree of TMJ deformities were found, while clinical variables showed subtle variations from what is considered normal. No single clinical variable was identified to predict TMJ involvement in JIA in this patient material. The results suggest that clinical and radiological findings alone cannot predict disease activity. Thus, a clinical judgement of TMJ involvement in JIA should be based on a comprehensive assessment including self-reported pain and dysfunction, clinical and radiological findings, knowledge of overall disease activity, pharmacological treatment, facial morphology, and growth of the child.

The four studies in this thesis make the following observations.

Studies I & IV: At baseline, a higher proportion of TMJ deformities was found in children with self-reported TMJ pain and dysfunction. However, self-reported pain was not predictive of change in TMJ status. Predictive of TMJ deformities were disease duration and a smaller MUO.

Studies I & IV: TMJ deformities were associated with a smaller MUO, with the largest impact for bilateral TMJ involvement. TMJ deformities were also associated with palpatory TMJ pain and crepitations on mandibular movement. Palpatory muscle pain, although common, did not correlate with TMJ deformities.

Study II: Most of the preselected salivary biomarkers were detectable in a customized Luminex immunoassay. No significant differences were found in concentrations of cytokines and chemokines examined between children with JIA and healthy children.

Study II: No differences in salivary flow rate were found between children with JIA and healthy age-matched controls. However, there was an association between a reduced salivary flow rate and self-report of orofacial pain (Q1) regardless of a diagnosis of JIA or not.

Study III: High intra-reader and inter-reader reliability was found for the proposed classification system for grading TMJ morphology on PAN and CBCT in children with JIA.

Study III: When using the classification system for TMJ morphology, PAN and CBCT recognized presence of TMJ abnormality equally well. The reliability of PAN for distinguishing between normal and abnormal TMJ morphology was good, whereas CBCT was found to be superior for assessing the severity of TMJ abnormality. The technique that provides diagnostically acceptable information at the lowest radiation dose should be used in children.

7 Future perspective

This thesis includes studies on different methods for diagnostic assessment of TMJ involvement in JIA. Clinical implications have been discussed in terms of what variables to include in clinical examinations and what imaging techniques to use for monitoring orofacial health and TMJ deformities. Still, there are knowledge gaps to fill regarding how to assess and manage orofacial manifestations of JIA.

Considering how modern pharmacological treatment has improved overall outcome for children with JIA, new follow-up studies on TMJ involvement are needed. Improvement or deterioration in TMJ morphology are slow processes. Adding low disease activity leads to the conclusion that a two-year follow-up period as in Study IV was too short to be able to observe change over time in the post biological treatment era. A ten, or even fifteen-year follow-up of the cohort investigated in Studies I and IV could contribute valuable information on TMJ deformities and involvement over time in relation to the children being in remission on or off modern DMARDs or suffering from persistent disease.

What further is needed is a validated self- and/or parent-administrated instrument, such as the Child Health Assessment Questionnaire (CHAQ)[238] but for measuring masticatory and orofacial functional status in children with JIA. The eight-item Jaw Functional Limitation Scale (JFLS-8)[239] has potential but needs to be adapted and validated,[151] and cut-off values must be established for this specific subset of patients. However, questionnaires on orofacial pain and masticatory function in children with JIA must consider the children's young age, maturity, and ability for self-assessment as well as physical factors such as that the change from primary to permanent teeth also influence masticatory ability.

Saliva as a medium for assessment of inflammatory biomarkers was investigated in Study II and the current level of knowledge does not support the use of saliva for disease monitoring in clinical practice. However, considering the accumulating amount of knowledge in combination with the rapid development in technology, saliva still has considerable potential of becoming an important source of information. For example, cells obtained from saliva can be used to extract human DNA. The DNA extracted is considered to be of equal quality as DNA derived from blood.[240] However, one must remember that depending on sampling technique,[240] the DNA extracted from saliva can to different degrees be contaminated with DNA from the oral microbiome. In JIA. saliva could be used, for example, to map HLA alleles and non-HLA polymorphisms.

The fact that PAN identified normal joint morphology equally often as CBCT in children with JIA in Study III should be verified and validated in future studies using the classification system proposed. One way could be to examine the reliability of general

dental practitioners' ability to distingue between TMJs with and without deformities on PANs using material from Study III–i.e., PANs, CBCT consensus evaluation, reference images, and written descriptions of grades of abnormalities. This could also be integrated with a training program for TMJ assessment on PAN.

Novel techniques such as artificial intelligence (AI) and machine learning are being developed to help clinicians assess and diagnose diseases. Future research, preferably multicenter studies, combining clinical and radiological data form children with JIA might find correlations and help set cut-off values for when to suspect TMJ involvement. Furthermore, PANs from Study III could be compiled and used for machine learning with the CBCT consensus assessment done as the gold standard. In absence of an inhouse maxillofacial radiologist, it could be then used as a diagnostic guide in specialist clinics as well as in general dental practices.

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