Subjective symptoms and clinical signs and imaging features related to temporomandibular disorders in juvenile idiopathic arthritis

Johannes M. Fischer

Thesis for the degree of Philosophiae Doctor (PhD)
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Scientific environment

The research work presented in this thesis was carried out from 2018 to 2021 at the Department of Clinical Dentistry and Department of Oral and Maxillofacial Surgery, Haukeland University Hospital (HUS), as part of an affiliation with the Norwegian Juvenile Idiopathic Arthritis (NorJIA) Research Group.

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Professor Annika Rosén, Department of Clinical Dentistry, University of Bergen/ Department of Oral and Maxillofacial Surgery, Haukeland University Hospital, Bergen, Norway, is the main supervisor, while Professor emeritus Marit Slåttelid Skeie, Department of Clinical Dentistry, University of Bergen/ Center for Oral Health Services and Research, Mid-Norway (TkMidt), Trondheim, Norway; Professor Karen Rosendahl, Department of Radiology, University Hospital of North Norway (UNN)/the Arctic University of Norway, Tromsø; and Professor Xieqi Shi, Department of Clinical Dentistry, University of Bergen, Norway/Department of Oral and Maxillofacial Radiology, Faculty of Odontology, University of Malmö, Sweden, are co-supervisors.

The NorJIA research group is an interdisciplinary group (PI Professor Rosendahl) that includes dentists, pediatric dentists, maxillofacial surgeons, ophthalmologists, oral and maxillofacial radiologists, pediatricians, pediatric radiologists and pediatric rheumatologists from the children's hospitals of Haukeland University Hospital, Bergen, the University Hospital of North Norway, Tromsø, and St Olavs Hospital, Trondheim as well as the Public Dental Service Competence Centers (PDS) of North, West, and Middle Norway.

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Abstract

Introduction Temporomandibular disorder (TMD) is an umbrella term for orofacial muscle pain and temporomandibular joint (TMJ) conditions. Unfortunately, children and adolescents with juvenile idiopathic arthritis (JIA), who should be spared additional health problems, are frequently affected by TMD. As knowledge gaps in the literature covering TMD in young individuals with JIA have been identified, more research in this field is needed.

Aims The overall aim of this thesis was to gain knowledge of TMD in JIA. Subgoals were to investigate the prevalence of TMD in children and adolescents with JIA compared to their healthy peers and investigate potential associations between JIA and TMD; investigate the reliability of diagnostic imaging by examining the precision of imaging measures commonly used to assess mandibular morphology in children and adolescents with JIA; compare CBCT and MRI in the measurement of condylar height; and lastly, analyse whether there are associations between clinical signs of TMD pain and arthritis affected TMJ using CBCT as an imaging tool.

Methods This thesis has its origin in the Nordic JIA Study Group (NorJIA), a longitudinal multicentre study (2015-2020) addressing 228 children and adolescents (aged 4–16 years) diagnosed with JIA and recruited from three university hospitals in Norway. Among these, seven did not participate in TMD assessments and were excluded from studies I and II. The thesis comprised three studies based on baseline data originating from the 2015-2018 NorJIA study. Paper I was a matched comparative study with a cross-sectional design according to gender, age, and a centre site of 221 children and adolescents with JIA (mean age 12 years). The standardised TMD assessments were based on shortened protocols of the diagnostic tools "Axis I Clinical Examination for DC/TMD" and "TMJaw Recommendations for Clinical TMJ Assessment in Patients Diagnosed with JIA". In Paper II, the precision of three imaging techniques (MRI, CBCT and a lateral cephalometric radiograph (ceph) used for the assessment of mandibular morphology was examined. A subset of 90 children and adolescents with JIA underwent a MRI, CBCT of the TMJs and ceph. The agreement of continuous measurements was assessed with a 95% limit of agreement according to Bland-Altman and MDC at an individual level. Paper III was a cross-sectional study

that included 72 children and adolescents with JIA from the Bergen cohort. A newly devised and validated CBCT score for the overall impression of deformity (sound (no deformity), mild or moderate/severe deformity) was used to examine associations between clinical TMD signs/symptoms such as pain on palpation of the TMJs, pain on jaw movement, or a combination of the two.

Results In the first study, 26.7% of participants with JIA self-reported TMD jaw pain during the past 30 days vs. 5% of healthy controls. JIA participants revealed a lower vertical unassisted jaw movement than the controls, with a mean of 46.2 mm vs. 49.0 mm. Both painful masticatory muscles and TMJs on palpation were present in 50.2% of the JIA patients vs. 28.2% of the healthy controls. We examined three MRI, one CBCT and nine ceph-based measurements in the second study, of which the ceph-based SNA, SNB and RL3/ML3 (gonion angle) and the MRI-based total mandibular length had the highest test/retest reliability, with 95% limits of agreement (LOAs) within 15% of the sample means. In the third study, 29.2% of the subjects had palpatory pain at and around the lateral pole, and about 57% had TMJ pain upon jaw movement. Of 141 TMJs, 18.4% showed mild, and 14.2% moderate/severe, TMJ deformity on CBCT. No statistically significant associations were seen between pain on palpation and TMJ deformity on CBCT or between pain on jaw movement and CBCT findings.

Conclusions TMD was found in approximately half of the participants with JIA, as compared to about one-fourth of their healthy peers. The consistency of the tested imaging modalities used for the assessment of TMJ growth disturbances differed, highlighting the importance of applying the most precise imaging markers under the premise of acceptable diagnostic accuracy, both at a patient level and for clinical trials. This resulted in acceptable reproducibility for one MRI-based, one CBCT-based, and three ceph-based parameters. We found no associations between pain and TMJ deformity assessed by CBCT.

List of Publications

Paper I **Fischer J**, Skeie MS, Rosendahl K, Tylleskär K, Lie SA, Shi X-Q, Gil EG, Cetrelli L, Halbig J, von Wangenheim Marti L, Rygg M, Stoustrup P, Rosén A. Prevalence of Temporomandibular Disorder in Children and Adolescents with Juvenile Idiopathic Arthritis a Norwegian cross-sectional multicenter study. **BMC Oral Health (2020) 20:282 https://doi.org/10.1186/s12903-020-01234-z**

Paper II **Fischer J**, Halbig J, Augdal TA, Angenete O, Stoustrup P, Kristensen KD, Skeie MS, Tylleskär K, Rosén A, Shi X-Q and Rosendahl K. Observer agreement of imaging measurements used for evaluation of dentofacial deformity in juvenile idiopathic arthritis. Accepted: **Dentomaxillofacial Radiology DMFR (2022) 51 https://doi.org/10.1259/dmfr.20210478**

Paper III **Fischer J**, Augdal TA, Angenete O, Gil EG, Skeie MS, Åstrøm AN, Tylleskär K, Rosendahl K, Shi X-Q and Rosén A. In children and adolescents with temporomandibular disorder assembled with juvenile idiopathic arthritis - no association were found between pain and TMJ deformities using CBCT. **BMC Oral Health (2021) 21:581 https://doi.org/10.1186/S12903-021-01870-Z**

Abbreviations

AAOP	American Academy of Orofacial Pain
ACL	Acute closed lock
ACR	American College of Rheumatology
ADD	Anterior disk displacement
CBCT	Cone beam computed tomography
CBT	Cognitive behavioural therapy
CCL	Chronic closed lock
Ceph	Cephalometric radiograph
COAs	Considerations for evaluating clinical outcome assessments
CRF	Case Report Form
DC/TMD	Diagnostic criteria of temporomandibular disorder
DMARDs	Disease modifying antirheumatic drug
EULAR	European League Against Rheumatology
FOV	Field of view
GDP	Gross domestic product
GMMs	Geometric morphometrics
IACIs	Intraarticular corticosteroid injections
ICR	Idiopathic condylar resorption
IFN	Interferon
IL	Interleukin
ILAR	International League of Association for Rheumatology
IMMPACT	Initiative Methods Measurement Pain Assessment Clinical Trials
JIA	Juvenile Idiopathic Arthritis
LOA	Level of agreement
MDC	Minimal detectable changes
MIO	Maximal incisal opening
MPR	Multiplanar reconstruction
MR	Magnetic resonance tomography
MRI	Magnetic resonance imaging
MSCT	Multi-slice computed tomography

NASAIDS	Non-steroidal antirheumatic drugs
NorJIA	Norwegian Juvenile Idiopathic Arthritis Study
OMERACT	Outcome Measures in Rheumatology and Clinical Trials
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OPG	Orthopantomogram
RC	Reciprocal clicking
TMD	Temporomandibular Disorder
TMJ	Temporomandibular Joint
TMJaw	Temporomandibular Joint Juvenile Arthritis group
TNF	Tumor necrosis factor
T1-w	T1 weighted

Terminology

We have used a standardised terminology of orofacial conditions in JIA, which defines "TMJ arthritis" as active inflammation in the TMJ; "TMJ involvement" as clinical and/or radiological abnormalities, presumed to be the result of TMJ arthritis; "Dentofacial deformity" as abnormality in the growth, development, structure and/or alignment of the facial bones and dentition; and "TMJ deformity" as an abnormality in the growth, development or structure of the osseous and/or soft-tissue components of the TMJ **[1].**

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1. Introduction

1.1 Temporomandibular disorder

1.1.1 Definition, symptoms and signs

The term temporomandibular disorder (TMD), known as an umbrella or collective term, encompasses a heterogeneous group of pathologies. The precise aetiology of TMD has been debated in numerous epidemiological studies, with the result that TMD can be attributed to a multifactorial aetiology. Extensive prior research revealed that chronic headaches, fibromyalgia, sleep apnoea, and psychiatric disabilities are associated with TMD [2-5]. TMD`s general definition is related to various clinical signs and symptoms of musculoskeletal conditions, noted as disorders that involve the masticatory muscles or/and the TMJs [6, 7].

The most common symptoms in children and adolescents can be subdivided into myofascial pain, TMJ arthralgia, non-painful disorders associated with internal derangements and degenerative joint disease [8]. Their development in the adolescent lifespan revealed gender differences resulting that girls aged between 14 and 16 years revealing higher rates of TMD pain and jaw dysfunction compared to boys [2, 9]. The intensity, persistence, and psychological impact of TMD pain are all similar to back pain and implemented as a musculoskeletal dimension of TMDs [10]. Conditions as TMJ pain (arthralgia), masticatory muscle pain (myalgia) and non-painful TMD conditions as stiffness and cramping are the primary cause of non-odontogenic pain [11]. However, signs of bruxism i.e., tooth grinding or clenching revealed weak associations to jaw muscle signs/or symptoms [12]. Numerous studies have debated whether variations in dental occlusion may be one of the main contributing factors in myofascial pain [13]. Today, it has been shown that occlusal disorders are of minor importance regarding the aetiology of TMD which has a multifactorial background [11, 14]. And more, studies have excluded pain-free TMJ sounds from clinical screening, such as e.g., asymptomatic disc displacement (pain- free clicking) known as a prevalent physiological variant in 6% of 11-year-olds and 34% in 16- to 19-year-olds [15]. In a previous clinical approach, Lövgren and colleagues validated three pain screening

questions in relation to the diagnostic criteria of temporomandibular disorder DC/TMD [16]. They decided to exclude disc displacement with reduction and degenerative joint disease because both entities were primarily related to joint sounds and may not include functional limitations such as jaw locking or restricted movements. The third question detected more severe TMJ dysfunction and revealed that disc displacements without reduction and disc displacements with reduction and intermittent locking were more prevalent in the group that responded positive.

TMD is associated with neuralgic features like chronic lower back pain, chronic headache, migraine and fibromyalgia [17, 18]. Extracranial pain, like back pain associated with orofacial pain, can be explained by the confluence of the upper cervical nerves with trigeminal nerves and indicate comorbidity between pain conditions at different anatomical areas [19]. Additionally, the global burden of TMD also mirrors both the susceptibility to medication abuse and frequent treatment seeking [20-22].

1.1.2 Prevalence

Since the early 1970s, authors have reported signs and symptoms of TMD in children and adolescents [23, 24] with or without temporomandibular joint disorders, noting it as a common complaint in school-aged children [25]. At present, several classification systems most widely adopted in the literature are the 1) The Helkimo Index [26], 2) The American Academy of Orofacial Pain (AAOP) [27], 3) The Research Diagnostic Criteria for Temporomandibular disorders (RDC/TMD) [28], and their revised version 4) The Diagnostic Criteria for temporomandibular disorders (DC/TMD) [29]. To identify TMD symptoms at regular dental check-ups, screening questionnaires for both children and adolescents and adults are available. A self-reported questionnaire pertaining to painful TMD (TMD-P) tested by Nilson and colleagues [9] and three screening questions (3Q/TMD) for adults validated by Lövgren and colleagues are applicable [16]. Both questionnaires might identify patients with a further need for TMD examination. All of these are helpful in the search for etiologies of TMD. Among the classifications mentioned above, the RDC/TMD, established by Dworkin and colleagues, has hitherto been the most widely used protocol in TMD research groups of experts, also called the “Consortium Network” based on The International

Association of Dental Research and The International Association for the Study of Pain [28]. It was they who revised and renamed the RDC/TMD. The attempt was to differentiate subcategories of TMDs and improve a compact screening tool by dividing it into two axes. The first one contains clearly defined examination rules and a standardised questionnaire for common pain-related disorders. The second axis refers to the patients' psychosocial situation of experiencing chronic pain as well as pain-related disabilities. Renamed as DC/TMD, this has become a useful, reliable, and valid diagnostic tool for pain-related diagnosis and been shown to provide stepwise clinical decision-making for establishing the diagnosis of orofacial pain [29].

It seems challenging to reach an exact figure on the prevalence of TMD amongst children and adolescents in the normal population. This is documented by a wide range of reported prevalence, from 7% up to 35% [30, 31]. Examination protocols tailored for the adult population could be one reason for this confusion related to exact prevalence figures in the younger population. Furthermore, the DC/TMD is validated for individuals aged 18 years and above and not adapted for younger individuals. Hence, the global TMD prevalence depends on the studied population as well as the diagnostic system applied. A variety of inclusion criteria, e.g., bruxism or joint sounds and different examination methods, are responsible for this high variability [32, 33]. Moreover, the validity and reliability of internal derangements such as painful clicking and the chronic closed lock of the TMJ disk are not implemented in the DC/TMD diagnostic decision tree. Pain-free clicking is still judged as a TMD symptom, although it is a normal physiological variant in predominantly teenage girls during puberty [15, 34, 35]. Previous studies from Finland and Brazil have reported TMD prevalences of 35% and 34%, respectively [36, 37].

The burden of TMD in Scandinavia (Denmark, Norway, and Sweden) is a common pain condition experienced mainly by young female adolescent. In two studies from the Bergen municipality and Rogaland County, Western Norway [38, 39], the prevalence of painful TMD among otherwise healthy adolescents was reported to be around 7% based on self-reported pain screening questionnaires adopted by Nilsson and colleagues [9]. Graue and colleagues also conducted an examination based on the DC/TMD criteria, finding a TMD prevalence of 11.9%, with a peak at 16 years of age.

[38]. Multiple cross-sectional studies have revealed that the overall prevalence of TMD is significantly higher in the 20–40-year age group (reproductive period) compared to other age groups and that TMD seems to be far more prevalent in the female population [40]. A hypothesised reason for this is that TMD may be affected by reproductive hormones. Studies have shown that increased estrogen levels correlate with a higher prevalence of TMD [21].

1.2 TMD treatment

A therapeutic approach for a multifactorial condition such as TMD needs multidisciplinary investigation to obtain a suitable examination, diagnosis, and therapy. Dental specialist groups consisting of oral and maxillo-facial surgeons, orofacial pain specialists, pedodontists, prosthodontists, orthodontists, and radiologists can elucidate and analyse TMD conditions. The primary goal is to give the patient a better quality of life. Several treatment modalities have been described over the years. Conventional treatment techniques such as occlusal appliances, jaw exercises, and pharmacologic treatment or a combination of such can effectively alleviate TMD pain. A recent systematic review pointed out that catastrophic thinking in terms of rumination and exaggeration of an existing or foreseen painful act or stimuli has a significant impact on the intensity of TMD pain [41]. Therefore, interdisciplinary teamwork is a good option where also anaesthesiologists, psychologists, and physiotherapists add their knowledge. Cognitive-behavioural therapy (CBT), for example, could reduce catastrophising and pain in TMD patients, thereby improving treatment prognosis and outcome [42].

As mentioned above, the relationship between bruxism or jaw clenching and TMD has been much debated. Prolonged jaw clenching together with different occlusal features as, e.g., large overjet or anterior open bite, revealed more frequent signs and symptoms of TMD than bruxers without those occlusal features [43]. An overview of the available literature on this topic revealed that occlusal adjustments or equilibration in terms of TMD management is critical [11, 44]. In addition, controversial statements have been raised regarding associations between orthodontic treatment and TMD [45].

However, the treatment with orthodontic appliances, e.g., a tooth aligner, neither treats TMD nor causes TMDs [46, 47]. Features such as crossbite, deep bite, and asymmetric molar or canine Angle classes may not be associated with TMD [48].

Physical exercises and relaxing jaw muscles, maintaining dentition, and controlling headaches are therapeutic cornerstones in TMD treatment. The incorporation of a hard acryl stabilisation/repositioning splint both day and night impact the relaxation of masticatory muscle pain during parafunctions and relieves the joint, e.g., when affected by degenerative joint disease or painful clicking [49, 50]. Hyperactivity and habits in children and adolescents, e.g., nail biting, should also be managed by behavioural therapeutic measures and physiotherapeutic sessions instead of iatrogenic grinding of the dental occlusion [51]. However, psychosocial impairment is probably an essential predictor of treatment outcome [42].

Treatment of children and adolescents with TMD-related pain is a challenge and determines whether the origin of the pain is the masticatory muscles, the TMJs, or a combination of both. The current therapy concept of these comorbid pain conditions is pain-blocking as soon as possible to minimise the risk of persistent pain [52]. Analgesic treatment should be seen as part of the total care of TMD patients, i.e., non-pharmacological intervention, such as physical exercise and behavioural therapy, are the first choice. Successful pharmacological management of TMD pain depends on accurate pain analysis before medication of analgesics. Drugs such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) have been the mainstay of therapy and effectively relieve pain [53]. Suppose the pain management is unsatisfactory with masticatory muscle exercises, occlusal splint appliances or other non-surgical treatment, and additionally, that radiological examination reveals TMJ deformities; in such cases, surgical treatment could be an option. Minor invasive procedures such as injection with steroids like intraarticular corticosteroid injections (IACIs) or hyaluronic acid should be considered before arthrocentesis or arthroscopy with lysis and lavage, which are considered minimal invasive surgical treatments. Studies have shown that TMD cases of degenerative joint disease could be managed with minimally invasive surgical interventions [54, 55]. IACIs have been used to reduce active arthritis for most

TMJs, but their role is not completely clarified [56]. Features like mandibular growth retardation and metabolic alterations, such as intra-articular calcifications with a high risk of ankylosis, have led to a cautious choice of surgery in skeletally immature patients [57, 58].

2. Temporomandibular joint (TMJ)

The TMJ is a paired joint connecting the mandible to the skull. The temporal component consists of a shallow groove in the temporal bone, termed the glenoid- or condylar fossa, and the articular eminence of the temporal bone. The mandibular part is formed by the condyle (mandibular head) (Figure 1). The TMJ is a hinging-gliding joint (ginglymoarthrodial joint) surrounded by synovial tissue. However, the condyle and fossa do not articulate directly. The articular disc, an oval biconcave plate of fibrocartilage, separates the joint into superior and inferior compartments. The disk follows the joint movement and keeps rotational and translational motions smooth and soft [59]. The jaw apparatus is directly connected with the masticatory muscles and indirectly linked to the dental occlusion. Masseter muscle, medial and lateral pterygoid, and temporalis muscle are the main actors of mastication. The lateral pterygoid muscle performs protrusive and side movements of the jaw, whereas the other three muscles elevate the mandible and close the mouth. Due to its embryonic origin, the condyle with its growth site is beneath the articular disc and is covered with fibrocartilage, which differs from general hyaline [60-62]. There is an appositional growth in all directions, unlike a typical long bone. The condylar cartilage is a dynamic tissue and is exposed to endogenous and exogenous factors which may influence the multidimensional condylar growth course [60, 63]. Over time the cartilage is replaced by bone due to endochondral ossification. Compared to the other synovial joints in the body, these unique circumstances, i.e., the superficial positioned growth site, the magnitude and direction of condylar changes, and the slow cartilage maturation, make the TMJ unique and vulnerable [60, 64].

2.1 TMJ derangements

2.1.1 Anterior disk displacement (ADD)

Anterior disk displacement is one of the more common TMJ disorders [65, 66]. It occurs in all age groups, and often presents itself with clicking, pain, limited range of mouth opening and masticatory difficulty [67]. The diagnosis is based on history, clinical examination, and MRI of the TMJ, preferably a dynamic MRI to visualise the displacement, pathological movement and perforated articular disk, when present. It has been reported in around 63 % of JIA patients [68]. A critical comparison has been conducted in terms of condylar deformity between children and adolescents with ADD and an age-matched group of JIA [69].

2.1.2 Osteoarthritis

Osteoarthritis (OA) in general is often connected to the elderly, affecting movable joints, and is followed by anatomic and/or physiologic TMJ derangement. The main characteristics are demonstrated through cartilage degradation, bone remodelling, osteophyte formation, chronic/acute joint inflammation, and dysfunction. TMJ OA is listed as a subcategory of TMD [29] and is known as a low inflammatory disease. Other synonyms such as arthritis deformans, degenerative arthritis and arthrosis are in literature linked to TMJ OA. Crepitus sounds are often accompanied by OA, but TMJ OA can also be asymptomatic [70]. Patients in acute stages often report morning joint stiffness, joint pain both at rest and in action, reduced jaw opening, muscle pain, and difficulty in yawning, biting, and mastication. However, those conditions can decrease or disappear altogether. In addition, posterior malocclusion, premature contacts, and open bite on the contralateral or the affected side with TMJ OA have been observed [71, 72]. It is difficult to diagnose TMJ OA clinically since all the TMD conditions often share similar signs and symptoms. Therefore, clinical examination frequently underestimates the presence of TMJ disease. As mentioned before, there is a wide range of examination systems according to TMD. DC/TMD, for instance, requires the presence of joint crepitus registered by both examiner and patient, but the sensitivity for that is low. Therefore, anamnestic information and TMJ imaging are crucial for the detection of TMJ OA. In children and adolescent patients, severe TMJ OA may lead to

facial growth disturbances seen in reduced condylar width and height, which can negatively impact dental occlusion [73]. However, the regeneration capacity of the TMJ components in children and adolescents is unique compared to other joints.

Reciprocal clicking (RC), or a chronic closed lock (CCL) are two clinical TMD variants of disc derangements and the prevalence for each variant, increases with age [74]. Both disorders develop differently from each other, and in contrast to RC, CCL is a degenerative intraarticular joint disease often accompanied by TMJ OA. CCL is associated with morphological changes of the disk, the articular surface, and chronic synovitis; moreover, it is apparent under surgical interventions. Holmlund and colleagues termed RC with limited and painful jaw movement as closed lock (CL) syndrome, which may progress into acute closed lock (ACL) or CCL [75]. Furthermore, tissue-based clinical research has revealed that abnormal joint tissue metabolism in patients with CCL is more associated with macrophages and cytokines than patients with RC. Clicking or popping sounds without pain are also common findings and mainly perceived by female teenagers during puberty; these will mostly disappear [15].

2.2 Miscellaneous TMJ conditions

2.2.1 Idiopathic condylar resorption (ICR)

About six decades ago, Dr. Burke was the first to describe mandibular condylar hypoplasia [76]. The condition was later renamed idiopathic, or progressive, condylar resorption (ICR) by Arnett and colleagues. They suggested that ICR represented a “low-inflammatory arthritic” or degenerative temporomandibular joint disease, without inflammatory evidence on MRI [77-79]. Female adolescents are affected more often than boys, with a 9:1 female-to-male ratio. ICR seldom develops after the age of twenty years [80]. There is an overlap between JIA and ICR regarding the dysfunctional remodelling of condylar mass, and ICR`s aetiology is more nourished by empirical conviction and tradition than science [81]. The literature describes two types of idiopathic condylar resorption, both bilateral and symmetrical [82]. One theory is

that TMJ ICR is a type of juvenile TMJ OA, subsequently developing into osteoarthrosis over time. Others have suggested that ICR is due to improper mechanical loading in genetically predisposed individuals with hypoestrogenemia and hypermobility of the joints [79, 83]. It has been shown in one study that women with severe condylar resorption also had irregular menstrual cycles and used contraceptives [83]. Furthermore, Abubaker and colleagues found that low circulating estradiol led to increased regulation of estrogen receptors on the articular tissues of the TMJ [84]. Thought to be a local inflammatory disease, ICR may lead to growth disturbances similar to those seen in JIA. In sum, the pathogenesis and diagnostic criteria for ICR are not clearly defined.

2.2.2 Growth related changes of the TMJ

The majority of new bone formation occurs at the posterior margin of the ramus and mandibular condyle [85]. They are the two major sites for mandibular elongation. The growth of the mandibular condyle appears to be stimulated in part by mechanical loading of the joint, which grows as a secondary ossification centre, elongating the condylar neck as well as widening and lengthening the condyle [86]. The condylar cartilage of the TMJ is the greatest growth centre in the craniofacial complex and is located on top of the bony surface of the condyle [87]. In young children, the articular eminence and the glenoid fossa are flat. However, during growth, the fossa gets deeper, and both articular eminences and glenoid fossae gain a more sigmoid shape which is reached around puberty [88, 89]. Studies have also shown that on sagittal oblique scans, the condylar head is more frequently rounded with a straight condylar neck in children up to five years of age [90, 91]. In addition, the more anterior tilted condylar neck and angular-shaped condyle head are age-dependent characteristics together with flattened joint surfaces on coronal scans. High variability in condylar surface and volume is seen in individuals from the age of 15 up to 29 years (mean age 19.2 years) between genders and between the right and left sides of the mandible [92], whereas condylar flattening might represent normal variations, as previously shown [93, 94]. Peck and colleagues described condylar flattening as undetermined conditions of degenerative joint disease, which may represent normal variation [95].

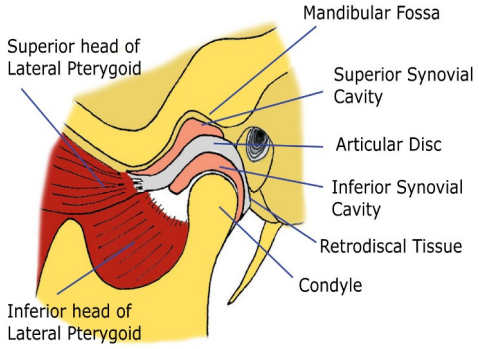

Figure 1 Illustration of the TMJ
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3. Juvenile idiopathic arthritis (JIA)

3.1 Definition, symptoms and clinical features, diagnosis

Definition. Paediatricians Sir Georg Frederic Still and Mayer Saul Diamantberger were the first to characterise chronic arthritis in children and its progressive destruction [96, 97]. Over the past 120 years, various definitions and abbreviations have been used, including Still`s disease, juvenile chronic polyarthritis (JCP), juvenile rheumatoid arthritis (JRA) and juvenile chronic arthritis (JCA). The International League of Associations for Rheumatology (ILAR) proposed the most recent classification criteria for juvenile idiopathic arthritis (JIA) by Petty and colleagues in 2004 [98]. According to the ILAR, JIA includes all heterogeneous arthritis in children and adolescents under the age of 16 years, with a disease duration of 6 weeks or more, after excluding other known conditions [99]. It is divided into seven subgroups based on the features present in the first six months of illness (Table 1).

Table 1. JIA subtypes (ILAR criteria 2011) and clinical features [55].

JIA subtype	Joints involved	Age at onset (years)	Gender (female: male)	Prevalence %
Oligo-JIA - Persistent - Extended	≤4 Asymmetric (e.g., knee and PIP) ≤4 for 6 months but then >4 Asymmetric	2-4 2-4	3-5:1 3:1	 27-56%
Poly-JIA - RF-negative - RF-positive	5 or more, asymmetric 5 or more, symmetric	2-4 teens	3:1 3:1	11-28% 2-7%
Systemic JIA	Variable, usually polyarticular	Throughout childhood	1:1	4-17%
Psoriatic	Usually ≤4 Asymmetric, dactylitis	3-11	1:1	2-11%
ERA	Usually ≤4, lower extremities, SI joints and LS spine	>6	1:7	3-11%
Undifferentiated	Peripheral and axial spine	Older children, adolescents	1:1	NA

Symptoms and clinical features. The cardinal feature of JIA is arthritis, defined as heat, swelling, pain on motion and/or limitation of motion [98]. Typical complaints are morning stiffness and limping. Based on the number and pattern of joint involvement, patients are placed in one of the seven main types (Table 1), of which oligoarticular JIA (involving four or fewer joints) is the most common in western countries [100]. The TMJ can be involved in all JIA subtypes.

Diagnosis. The diagnosis of JIA is based on the presence and persistence of arthritis and simultaneously a careful exclusion of any other disease through evaluation of medical history, physical examination, and laboratory tests. The diagnosis is moreover supported by imaging.

3.1.1 Epidemiology

Globally, the prevalence of JIA is reported at 50-100/100,000 [101-103] or 1 to 2 per 1,000 children [104], while the annual incidence varies between 1.3 to 22.6 per 100,000 children [105, 106]. In the Nordic countries, high incidence rates of 15 per 100,000 children per year have been reported [107, 108], with prevalence from 86 up to 164 per 100,000 children [102, 105, 109, 110]. A multicentre study from south eastern Norway

conducted between 2004 and 2005 found an annual incidence of 71 per 100,000 children [111]. Oligoarticular onset is more common in western countries or among people of European descent, while enthesitis-related arthritis (ERA) and systemic onset JIA categories are more common in Asian countries such as China and Japan [100, 112]. JIA prevalence is also higher in children and adolescents living in lower income countries than those living in wealthier areas [100] and is characterised by a short and long-term disability of function and pain. Except for ERA and systemic JIA, girls have an earlier peak in age distribution at onset than boys [113].

3.1.2 Aetiology

Despite research studies on potential predisposing mechanisms such as infection, trauma, psychological factors, heredity, familiar influences, and a host of immunologic phenomena, the aetiology of juvenile arthritis is largely unknown. It is thought to be an autoimmune disease resulting from a combination of genetic and environmental causes. Infections with borrelia burgdorferi are obvious in Lyme`s disease, vaccinations, early and repeated antibiotic use, and the human microbiome might be contributing factors to disease aetiology [114-117].

3.2 TMD and JIA

3.2.1 TMJ arthritis-related signs and symptoms

Children and adolescents with JIA may suffer pain from the temporomandibular joints (TMJs), either because of the inflammation and destructive changes themselves or secondary muscular tensions from the surrounding muscles. Common TMD signs and symptoms are reduced vertical jaw opening, pain during jaw movements, tiredness of the jaws, TMJ crepitus, chewing disabilities, TMJ morning stiffness, and pain upon palpation of the masticatory muscles and the TMJ [118]. The reported prevalence of TMD in JIA varies significantly, regardless of JIA subcategory. A recent study on individuals with JIA indicated that signs and symptoms of TMD can occur early, with an estimated median age of 6.6 years at the first presentation [119] and TMJ pain (25.1%), chewing limitation (20.5%), and TMJ sounds (14.2%) were the most prominent TMD symptoms. A retrospective chart review with a balanced gender ratio

of 2413 children and adolescents (mean age 9.5 ±4.5) revealed that clinical symptoms such as pain on palpation and pain while chewing had the strongest association to TMJ involvement upon inspection with an MRI [120]. Moreover, female children had a higher proportion of TMJ involvement during follow up examination as compared to males. However, there are no validated clinical criteria for identifying JIA's most common pain related TMD symptoms [121]. As mentioned before, the DC/TMD protocol is used in numerous studies but is still tailored for adolescents from the age of 18 years, and its TMJ sound analysis, in jaw movements, will define pain-free/asymptomatic TMJ clicking as a TMD symptom, although it is a normal thing [29]. In addition, a recent interdisciplinary debate suggested that chronic low-grade inflammation might facilitate TMJ destruction, despite the fact that those JIA patients were well-treated by medical treatment regime such as systemic disease modifying drug (sDMARDs) or biologic DMARDs (bDMARDs) [122, 123]. It is also noteworthy that long-term follow-up studies have shown that TMD is present in more than half of all JIA patients [124, 125].

3.3 TMJ arthritis and its consequences

3.3.1 Pathogenesis

The hallmark feature of JIA is chronic inflammation of the joint with preceding cardinal clinical signs of inflammation: "Swelling within a joint, or limitation in the range of joint movement with joint pain or tenderness" [98]. Furthermore, the disease can affect any joint. The first pathophysiologic changes show the hyperemic edematous synovium turning into a hypertrophied synovial membrane (hyperplasia) by infiltration of T cells, B cells, macrophages, dendritic cells, and plasma cells [126]. Those mononuclear cells perform pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF)-α, interleukin (IL)-1β, IL-6, interferon (IFN)-γ, and IL-17. This inflammatory process leads to the activation of pathogenic cells (like TH17) and osteoclasts in the joint with cartilage and bone deformation during autoimmune arthritis [127-129]. A well-coordinated immune response requires a suitable balance between pro-inflammatory and anti-inflammatory cytokines. Synovial inflammation results from an unregulated immune response between pro-inflammatory and anti-

inflammatory cytokines (IL-4 and IL-10, and IL-27) in JIA [130] with periods of progression as well as remission. The fluctuating episodes represent the dynamic and insidious character of JIA [131]. A previous study by Olsen-Bergem and colleagues focused on the concentration of cytokines and bone markers from synovial fluid [132]. Their results revealed negative correlations between TMJ pain to TNFα and osteoprotegrin in the synovial fluid.

3.3.2 Treatment JIA

There is increasing evidence that many, if not most, children and adolescents with JIA will have a chronic disease with ongoing activity into adulthood [133, 134]. However, disease activity is manageable with treatment and support, and children and adolescents can live full and active lives [135, 136]. Early aggressive intervention with disease-modifying anti-rheumatic drugs (DMARDs) is recommended in children and adolescents with high or moderate disease activity and/or features of poor prognosis [135]. Regardless of both concomitant therapy and JIA category, intra-articular corticosteroid joint injection (IAC) for active TMJ disease has been debated. Previous research revealed that IAC might be associated with inhibited mandibular growth and intraarticular calcifications in the TMJ [58, 137]. A recent prospective pilot study by Frid and colleagues preferred a more cautious use of IAC and suggested a single IAC after the peripubertal growth [138].

Other treatment options are nonsteroidal anti-inflammatory drugs, methotrexate and other DMARDs [135, 139]. In recent years biologic treatments interfering with key cytokines of inflammation have been developed, such as the TNF-blocking agents etanercept, infliximab and adalimumab [140, 141]. Since 2000, biologic agents have provided a major improvement in medical treatment for severe JIA.

4. TMJ – Imaging

The rationale for soft and hard tissue imaging in patients with JIA is two-fold, namely, evaluation of pathomorphological changes in TMJ components and assessment of dento-maxillofacial asymmetry secondary to growth disturbances. The most commonly used imaging modalities for assessment of JIA with TMJ involvement

include magnetic resonance imaging (MRI), panoramic radiography (OPG), cone beam computed (CBCT) and lateral cephalometric radiography (ceph). MRI plays a key role in detecting early synovial inflammation. In the following, I will focus on the imaging modalities used in the present works, i.e., MRI, OPG, CBCT and ceph.

4.1 MRI

MRI is a technique that uses non-ionising radiation, and currently, there are no known significant biological side effects [142]. The physics of magnetic resonance signals are generated by nuclei of hydrogen atoms within the human tissues. In a magnetic field, a radiofrequency coil located beside the body detects the changes in protons. This coil sends radiofrequency pulses to the body part under examination and registers and converts signals to images [143]. Since an MRI can provide contrasts between different soft tissues, it can be used to depict synovitis, bone marrow edema/inflammation, and cartilage damage. Currently, MRI is the method of choice for the diagnostics and interval monitoring of inflammatory changes of the TMJs in children with JIA [144-146]. MRI also displays the osseous structures of TMJ but not in detail in comparison with CBCT or CT [147]. However, recent developments applying ultra- and zero-short echo-time sequences have shown the potential to enable useful MRI-based bone imaging. In a recent study on adults comparing zero-short MRI and CBCT, the authors found substantial agreement between the two methods for assessing degenerative changes in TMJ bone structures [148]. Similar studies in children are lacking [149]. MRI is not believed to detect small erosions and subtle osseous changes in the absence of inflammation better than CT [150]. The abnormal position of the disc in relation to the condyle and temporal eminence is a very common intra-articular abnormality of the TMJ. However, CT scanning of the disc has never reached its expected diagnostic potential. MRI opened a new diagnostic and achieved excellent evaluation of the disc, especially in early disease [151-153].

Imaging markers of early disease are of particular interest, and it has been proposed that bone marrow edema represents a precursor of erosive change [154]. The rate of TMJ involvement in patients with JIA is reported at around 40% in a large series of consecutive patients [155]. More recently, the potential of MRI for the evaluation of

growth disturbances secondary to TMJ involvement has been addressed, using T1-weighted (T1-w) 3D sequences to construct oblique sections through the mandible on which measurements are based [156-158].

4.2 OPG

Panoramic imaging, also known as orthopantomography, is the most widely used x-ray examination among dentists. The x-ray source and image receptor rotate around the patient's head, and a curved focal trough of dentition and surrounding bones is created after exposure. Objects in front of or behind this focal trough are blurred and largely not seen [159]. Therefore, a proper diagnosis is dependent on the patient's positioning and head posture. Evaluation of TMJ deformity has traditionally been performed using OPG, based on its availability and simplicity in image acquisition. However, the condyles may only be sharply depicted on OPG when located in the focal trough. In addition, diagnostics of structural changes in the temporal part of the TMJ are challenging using OPG [160]. Although visualising condylar resorption, antegonal notching, shortened ramal height and anterior open bite, its sensitivity for detection of small bony lesions at the condylar head or temporal bone is low [161, 162]. Based on OPG, up to 67% of patients with JIA are reported to have TMJ involvement [163]. A panoramic study by Liukkonen and colleagues of 182 healthy children and adolescents at the ages of 7 (mean 7.5, range 6.4-8.5 years) and 16 years (mean 15.9, range 15.2-17.2 years) revealed that linear measurements have shown significant differences in growth of condyle and ramus heights on the right and left side [164]. However, standardised head posture is of importance to conduct vertical measurements [165, 166].

4.3 CBCT

CBCT has been tested and compared with other diagnostic modalities in evaluating TMJ in different patient categories [167]. The method provides accurate and reliable linear measurements regarding the spatial dimensions of TMJ and mandible, according to Hilgers et al. [168].

The advantages of CBCT over other imaging modalities are the easy image acquisition and remarkable 3D reconstruction with high spatial resolution. For TMJ diagnosis, CBCT is considered a cost- and dose-effective alternative to CT for investigating osseous TMJ abnormalities. CBCT has been applied to measure condylar volume or 3D asymmetry in JIA patients [169-171]. The radiation burden of a CBCT examination on TMJ was 30% lower than CT with better image quality [172]. A CBCT study among the non-JIA population revealed an association between TMJ arthralgia and a degree of condylar erosion [173]. A split-face study revealed an association between unilateral condylar abnormalities in terms of deformity or erosion and dentofacial asymmetries in children and adolescents with JIA [174]. The affected site was first associated with a shortened condyle, while reduced mandibular posterior height was associated with both deformity and erosion. Studies have shown that children and adolescents with JIA have microscopic erosions within the condylar cortex and complete deformations of the mandibular head. CBCT imaging may detect those signs early to prevent the possible manifestation of facial asymmetry due to growth disturbance of mandible [169, 171]. In summary, it can be said that CBCT imaging allows for a precise assessment of cortical and trabecular osseous structures involvement and evaluates disease extent and progression. However, comparative studies focused on TMJ pain, and CBCT findings are not widely explored in the literature and thus so far inconclusive.

CT and MRI scans in adults who had JIA during childhood and adolescence have shown that flawless cortical outlines of deformed TMJs may be the result of previous damage with consecutive regeneration [134]. Furthermore, CBCT studies debated an association between poor mechanical loaded TMJs and TMJ symptoms and signs resulting from JIA-induced TMJ deformity [94]. On the other hand, Mao and colleagues found that functional overloading of none JIA TMJ may influence the intra-articular condylar growth cartilage, resulting in morphological signs such as condylar flattening [63]. Hence, condylar flattening alone is not an indicator of JIA TMJ involvement since this was seen in healthy individuals. A more recent study underscores why CBCT is the diagnostic radiographic examination of choice for the assessment of osseous changes in the TMJ [175]. In their retrospective study of 88 JIA

participants (mean age 11.6 ± 4.3) and 45 healthy controls (average age 11.5 ± 4.4), JIA patients with unilateral TMJ-involvement presented a statistically significant lower condyle and ramus volume in the affected hemi-mandible than the unaffected side [175]. Moreover, the mandibular ramus volume played a key role in the development of mandibular asymmetry.

4.4 Ceph

This technique has been a standardised diagnostic method in orthodontic practice and research. However, the method is flawed due to magnification, difficulties in identifying some landmarks and inconsistent head posture between exposures [176-178]. In addition, Baumrind, Broch and colleagues argued that cephalometric landmark-based measurements such as edges are easier to localise [179, 180], whereas landmarks placed on curves showed a higher measurement error. A variety of ceph-studies have demonstrated that the use of 2D view in the analysis of 3D objects can cause landmark identification errors due to overlapped structures, which has in turn led to a search for new techniques. CT and CBCT imaging have come into use over the past decades and have been found to overcome the limitations associated with traditional ceph-analysis. Several studies have been conducted to assess the accuracy of ceph-measurements using 3D CT images [181-184]. However, studies examining the precision of imaging markers using a radiological approach, as described by Fryback and Thornsbury [185] are sparse.

4.5 Research questions

The literature described above covering TMD in children and adolescents with JIA but has also revealed research related insecurities. A systematic review and meta-analysis by our research team [186], focusing on oral health including TMD, included four articles reporting TMD related subjects as TMJ destruction features, joint inflammation or TMJ pain and facial symptoms [186]. These articles, covering the period up to November 2018 [187-190], consolidated the previous knowledge that TMD was more frequently found in children and adolescents with JIA than in healthy peers. Nevertheless, three of the articles were based on small sample sizes of 20 to 41

individuals and 10-41 controls. While the mean age of individuals with – and without – JIA were to some extent comparable, it might be questioned whether the low sample sizes could give a reliable estimate of TMD prevalence. Also in comparative cross-sectional studies, priority should be set for obtaining well matched controls. This issue has not been given high priority.

Regarding exact TMD prevalence figures, calibration and recalibration sessions of the diagnostic tool used might be imperative to gain high interexaminer measurement reliability [191]. Part of our research team has also focused on this issue [192]. Due to all these publications with low sample sizes, insufficient matching of controls and calibration, there are questions regarding the reliability of the existing prevalence TMD figures.

The accuracy of imaging measures and the reliability of landmark identification commonly used to assess mandibular morphology in children and adolescents with JIA are also of vital importance [185]. To our knowledge, this issue is not widely explored in the literature and has not been conclusive so far. Kellenberger and colleagues addressed the precision of MRI-based TMJ measurements by applying the Bland-Altman mean-difference plots in children and adolescents with JIA as a target group [69]. Also, imaging diagnosis is crucial in JIA with non-symptomatic TMJ involvement. We do not yet know whether there exists an association between clinical TMD signs/symptoms and CBCT findings of TMJ structural deformities in this group of children and adolescents with JIA.

5. Aims and hypotheses

Due to the above shortcomings and the knowledge gap in current literature restricted to children and adolescents with JIA, the overall aim of this thesis was to gain knowledge of TMD in JIA. Subgoals were to investigate the prevalence of TMD in children and adolescents with JIA compared to their healthy peers and also investigate potential associations between JIA and TMD; investigate the reliability of CBCT, MR and ceph in terms of the precision of linear and angle measures commonly used to assess mandibular morphology in children and adolescents with JIA; and analyse

whether there are associations between clinical signs of TMD pain and arthritis affected TMJ using CBCT as a imaging tool.

5.1 Hypotheses

Paper 1 Children and adolescents with JIA have a higher prevalence of TMD compared to their healthy peers.

Paper 2 There are reliable measurements with ceph, CBCT and MRI-based scans for assessing mandibular morphology in children and adolescents with JIA.

Paper 3 There is no association between TMD pain and CBCT imaging features of the TMJ in patients with JIA.

6. MATERIAL AND METHODS

6.1 Ethical considerations

The research project was approved by the Norwegian Regional Committee for Medical and Health Research Ethics West (2012/542/REK West). The study was conducted in accordance with the Declaration of Helsinki [193]. Written informed consent was obtained from all the participants or their caregivers, as appropriate (Appendix IV). During the recruiting process, our senior paediatric rheumatologists underlined that withdrawal from the study was possible at any stage, without any negative consequences for the future patient-doctor relationship. Moreover, the study nurses at each of the participating centres followed the child/caregiver for the whole day and were open to any questions and concerns that might arise.

6.2 Study design and cohorts

The work presented in this thesis is based on baseline data from the Norwegian Juvenile Idiopathic Arthritis Study (NorJIA), a multicentre, prospective cohort study, including 228 patients (93 males) aged 4-16 years with a diagnosis of JIA according to the International League of Associations for Rheumatology (ILAR) criteria. Amongst these, 221 participated in TMD assessments. Children and adolescents were matched

(1:1) with healthy controls according to gender-, centre site- and age. Exclusion criterion was the lack of written informed consent. There were no participants with major medical comorbidities such as congenital facial anomalies, skeletal dysplasia, or malignancies in the study group.

The present work is based on baseline cross-sectional data. Paper I: Data from the whole JIA cohort and a matched control group (each group of 221 children and adolescents) examining the prevalence of TMD and potential associations between JIA and TMD (Paper I); Paper II: A subset of 90 patients who had undergone an examination of MRI, CBCT of the TMJs and a lateral ceph of the head taken between March 2015 and May 2018; and Paper III: a subset of 72 children and adolescents residing in Bergen and surrounding regions in Hordaland to examine for associations between CBCT and TMD-findings (Paper III).

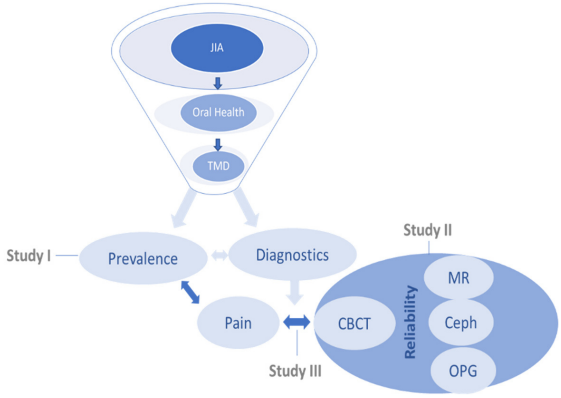

Figure 2. Flowchart of Study design

6.3 Examination of TMD

6.3.1 Case Report Form of clinical examination and questionnaire

The Case Report Form (CRF) (shown in Appendix I) contains assessment procedures, which were standardised and based on two shortened versions of diagnostic tools: the "Axis I Clinical Examination for DC/TMD" [29] and "The Euro^{TM}Joint Recommendations for Clinical TMJ Assessment in Patients Diagnosed With JIA" (shown in Appendix II) currently termed the Temporomandibular Joint Juvenile Arthritis (TMJAW) group. A self-assessment questionnaire on pain-related oralfacial

issues was filled in by the participant, his/her carer or in consensus while the participant was seated in the waiting area (shown in Appendix III). The latter was used to enhance the operational specification of DC/TMD due to the fact that the DC/TMD tool alone is reported to show a weak validity for TMJ assessment, *e.g.,* disc displacement diagnosis (low sensitivity) and degenerative joint disease diagnosis (low sensitivity and specificity) [29]. One of the main concerns of the former Euro^{TM}Joint group was to create a standardized short examination protocol for patients who are under treatment for an ongoing TMJ arthritis or JIA patients getting a routine orofacial evaluation. Established on current knowledge and consensus based recommendations of TMJ arthritis in children and adolescents with JIA [194], the Euro^{TM}Joint examination protocol generates information about TMJ symptoms, TMJ dysfunction and dentofacial deformity. The examination takes less than 3 minutes to complete and should be applicable to all practitioners without dental training.

Regarding the CRF protocol, prior to and during the study period, calibration sessions for the five participating examiners were performed, including four calibration exercises according to procedures previously described by our research team [192]. Further details on the calibration results and procedures are presented in Paper I, supplementary Tables S1 and S2, and in the Statistic section.

6.3.2 Examination procedures of CRF

- Stage 1a/b: Location of pain within the last 30 days

On the day of the TMD examination, the eligible children and adolescents were asked whether they had experienced any TMD-related pain and headache during the last 30 days by indicating this location themselves.

- Stage 2A/C: Vertical range of motion

Subsequent measurements of the vertical range of motion were registered in mm as pain free opening, maximal unassisted mouth opening and maximal assisted mouth opening (Figure 3B).

- Stage 3: Mandibular deviation at maximal mouth opening endpoint

The mandibular position was assessed at the maximal mouth opening endpoint.

- Stage 4: TMD pain during jaw movements

Evoked TMD pain during vertical, lateral and protrusive jaw movements were registered and asked if those were familiar or not and familiar to headaches or not.

- Stage 5/6: Joint noises as clicking and crepitation during opening and closing movements and lateral and protrusive movements were registered.
- Stage 7: Jaw locking was noted during mouth opening and maximal mouth opening.
- Stage 8: Pain upon palpation of the masticatory muscles and at the lateral and around lateral pole

Evoked pain upon masticatory muscle palpation and palpation both at lateral pole and around lateral pole was registered and asked if pain were familiar or not and familiar to headaches or not (Figure 3A).

- Stage 9: Registration of TMJ pain on palpation with open mouth and/or closed mouth.
- Stage 10 is linked to the self-assessment questionnaire and summarises pain frequency and pain intensity.
- Stage 12/13: Frontal asymmetry/ Facial profile
- Stage 14: Swelling of the TMJ

Registration of a swollen TMJ was present or not.

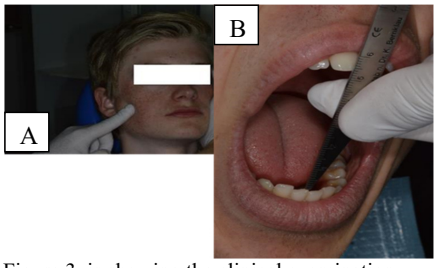

Figure 3, is showing the clinical examination,
including A) masticatory muscle palpation and
B) measurement of vertical jaw movement.
Follow up images 2017, NorJIA Study REK: 2012/542

6.3.3 Variable and outcomes

Subjective symptom outcomes were TMD pain within the last 30 days (n, %) reported by the participants or the parents and pain during vertical, lateral and protrusive jaw movements. Clinical outcomes were derived from maximal unassisted vertical mouth opening and lateral jaw movements (mm), pain upon palpation of the masticatory muscles and the TMJ area. Outcome variables which have been excluded from the results are summarised under statistical analysis 7.1.

6.4 Imaging

6.4.1 MRI

All MRI examinations were performed on a 3 Tesla system (Skyra, Siemens Healthcare, Erlangen, Germany), using a 64-channel head coil (or a 32-channel in 30 patients, StOlavs). In Paper II, a sagittal T1-w MPRAGE (ultrafast gradient-echo 3D) sequence (TR/TE/FA/SL =2000/2.26/8/1) was used. The images were assessed independently by two consultant paediatric radiologists using a high-resolution PACS-screen for assessment of intra- and interobserver variation. The following three measurements were made a) total mandibular base length Co-Gn, b) posterior mandibular length (Go-Co) and c) condylar height Co-In (Figures 5A-B).

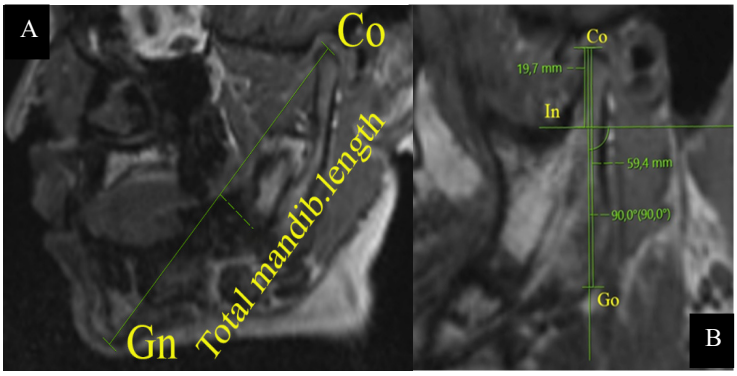

Figure 5. a) Total mandibular base length measured between the most cranial point of the condyle (Co) and the most anterior/inferior border of the chin in the mandibular midline (Gn) and b) Posterior mandibular ramus length measured between the most cranial point of the condyle and gonion (Co-Go). Images A and B, NorJIA Study REK: 2012/542

6.4.2 CBCT

The CBCT examinations were performed on one of three CBCT machines, with kVp / mAs / field of view (FOV) (diameter * height in mm) / voxel dimension (isotropic, mm) settings: 3D Accuitomo 170 (Morita Mfg Corp, Kyoto, Japan) 85 / 175 / 40*40/ 0.125; Promax 3D (Planmeca Oy, Helsinki, Finland) 90 / 13.6 / 200*60 / 0.40; or Scanora 3D (Soredex, Tuusula, Finland) 90 / 45 / 60*60 / 0.13. The exposure parameters in terms of exposure time and kVp were adjusted individually according to the patient's size and age. The participants were positioned with the Frankfort plane horizontal and their teeth in maximal intercuspal position. The images were exported together with the accompanied image viewers included in the three respective CBCT systems and assessed independently by two consultant radiologists, twice (at an interval >4 weeks) by TAA and once by OWA (both with 13 years of experience in musculoskeletal imaging).

Condylar height was measured in the same manner as for MRI; however, due to the limited field of view, we approximated the ramus corrected sagittal view to include the coronoid process and the ramus tangent along the posterior border at the lowermost point of the condyle or ramus included in the field of view (Figure 6).

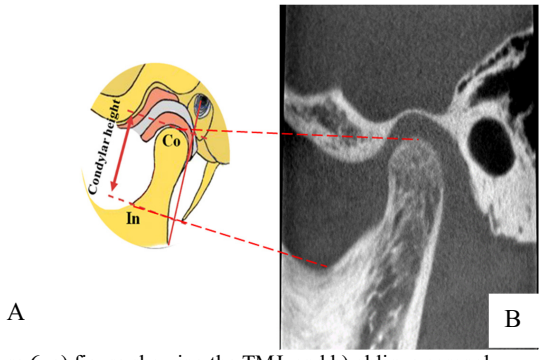

Figure 6. a) figure showing the TMJ, and b) oblique coronal CBCT view of the TMJ. Image A modified from: https://www.physio-pedia.com, image B: NorJIA Study REK: 2012/542.

6.4.3 Ceph

Lateral cephalometric radiographs were performed using one of three different pan/ceph systems: Orthophos xg 5 (Sirona Dental Systems, Bensheim, Germany), with the settings 73 kVp, 15 mA, exposure times 9.7 and 9.4 seconds for adolescents and children, respectively, and a magnification factor of 1.1 with a 16-bit pixel depth for all images; Promax Type Version 3.8.1.0; Planmeca, (Helsinki Finland) with the settings kVp 62 – 70, mAs: 7 – 10 mA 6,7 sec; and Soredex Cranex D (Helsinki, Finland) with settings 70 kVp, 10 mA, exposure time 5.8 seconds. The radiographs were taken under standardised conditions with a natural head position (Frankfort horizontal (FH)-line parallel to the ground) and teeth in maximal intercuspation (Figure 7).

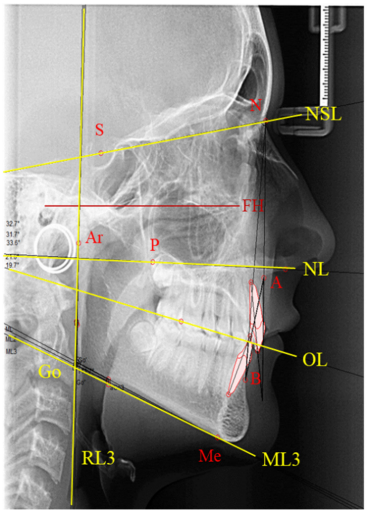

Figure 7: A: Point A; ANS: Anterior Nasal Spine; Ar: Articulare; B: Point B; Me: Menton; N: Nasion; OLp: Occlusal line, posterior point; pGo_{1+2}: Posterior gonion (posterior point on ramus); PNS: Posterior Nasal Spine. S: Sella; aGo_{1+2}: Anterior gonion (lower border of mandible). Ii: Tip of the crown of the left/right first inferior incisor. Iia: Apex of the left/ right first inferior incisor. Is: Tip of the crown of the left /right first superior incisor. Isa: Apex of the left/right first superior incisor. ML3: Mandibular line; RL3: Ramus line; Go: Gonion angle.

7. Statistic

7.1 Statistical analysis

Statistical analyses for all three papers were carried out using the IBM Statistical Package for the Social Sciences (SPSS) statistics version 25 or 26 (IBM Corp, Armonk NY), and a p-value <0.05 was considered statistically significant. Descriptive statistics are reported as means, medians with 95% CIs and SDs for continuous data, and as

frequencies and percentages for categorical data. Further details on the statistical methods used are described in each of the three papers.

Due to very low variation between the examiners pain-free opening, and maximum assisted opening (stage 2), mandibular opening pattern (stage 3) were excluded from the results. The proportion of participants who gave response to the following stages was sparse: TMJ crepitation during jaw movement (stages 5, 6), joint locking (stage 7). Familiar pain symptoms, the calculation of pain frequency/intensity (stage 10), the analyses of frontal asymmetry (stage 12) and profile of the face (stage 13) and finally swelling of the TMJ (stage14) exhibited low values and have been excluded from statistics.

7.2 The Bland-Altman approach

Bland-Altman plots are used for the estimation of the agreement between two continuous measurements made by the same observer using the same method (repeatability) for the estimation of agreement between two continuous measurements made by different observers but with same method (reproducibility), and for estimation of the agreement between two different methods. The plots show the difference between the two measurements on the y-axis against the mean of both measurements on the x-axis, giving the difference against the mean. One sample t-test is used to assess if the mean difference between the two measurements differs significantly from zero, indicating the presence of a systematic bias. We report the 95% limits of agreement (LOA), which is the mean difference ± 1.96 SD of the difference, indicating where 95% of the differences are located. The mean difference and the upper and lower 95% LOA are often shown as horizontal lines on the plot. The 95% LOA enables from one observed measurement an estimate of what the value of a measurement on the same person at the same time by either the same observer, a different observer, or different method might be, as a range of possible values. If the 95% LOA is sufficiently narrow, one can conclude that the observers or methods agree sufficiently to be used interchangeably.

For the purpose of this study, a sufficiently narrow 95% LOA was set a priory at 15% of the mean value measured, assuming this to be of sufficient precision for clinical use.

Our analysis found no dependency on the measurement variation on the mean measured lengths, and the differences (d) between measurements, either by observers or methods, were therefore expressed in mm or degrees (mm; °). The mean of (d) is used as a measure of systematic bias, and the standard deviation (SD) of d, denoted as S_d, and twice this value indicates the variability of these differences.

7.3 Minimal detectable change

The MDC is a concept that is tightly connected to measurement error. The standard error of measurement (SEM) provides a value for measurement error in the same units as the measurement itself, i.e., it indicates absolute reliability. This type of reliability is more clinically applicable daily, rather than a relative reliability co-efficient value, such as an ICC, which is more difficult to interpret for clinical decision-making. The SEM also allows for the calculation of the MDC, which is an estimate of the smallest change in score that can be detected objectively for a client, i.e., the amount by which a patient's score needs to change to be sure the difference is greater than measurement error. Thus, for interpreting the change scores, measuring measurement error based on a test-retest parameter is required. So, a change in scores within the limits of agreement or smaller than the MDC can be attributed to measurement error. Only outside the limits of agreement can we be confident that these are statistically significant changes.

7.4 Intraclass correlation coefficients

Intraclass correlation coefficients (ICC) is a reliability index in test-retest reliability analysis [195]. In Paper I, we used two-way mixed effects to calculate ICC and percent agreement for palpation measurements, i.e., measurements (level 1) performed by several different examiners (level 2), or repeatedly by the same examiner, are compared with each other. It is assumed that the difference between raters is a fixed parameter, while the difference between patients is random (fixed + random = mixed). Calibration measurements were pain-free jaw opening, maximal assisted, and unassisted, jaw opening and lateral movements at both sites, as well as protrusive movements (mm). Test 1 (2015 January) showed ICC values between "a reference" and the examiner who

examined the first participants included in the study. Test 2 (2015 Sept), Test 3 (2017 February), and Test 4 (2017 Nov) are all based on ICC values between "a reference" and other examiners. The ICC values reported are average measurements. A rating within and outside accepted limits was performed for pain-free, maximal unassisted, and assisted incisal mouth opening and lateral and protrusive jaw movements.

7.5 Sample size and power calculation

The sample size estimate was based on a Swedish study, reporting a TMD prevalence of 26% in children with JIA [196]. Using the program https://select-statistics.co.uk/calculators/sample-size-calculator-two-proportions, and the assumption that healthy children have a TMD-prevalence of 13% [26,176], a sample size of 235 would have 95% power to detect a difference at a 95% confidence level.

8. SUMMARY OF RESULTS

Paper I: Prevalence of Temporomandibular Disorder in Children and Adolescents with Juvenile Idiopathic Arthritis – a Norwegian cross-sectional multicentre study.

Study I estimated the prevalence of TMD in a relatively large group of children and adolescents, with JIA (n=221) and in healthy peers (controls: n=221). Among the JIA participants, the results showed that the prevalence of subjective symptoms or clinical signs were 56.1% or 50.2%, respectively. Due to the combination of both subjective symptoms and clinical signs, the prevalence of TMD was 39.8% (Figure 8). Moreover, the JIA-group had significantly more pain on palpation of the masticatory muscles and of the TMJs than their healthy peers ($p<0.001$) (Figure 8). As the control group was matched, there was not statistically difference in mean age between the two groups ($p = 0.98$).

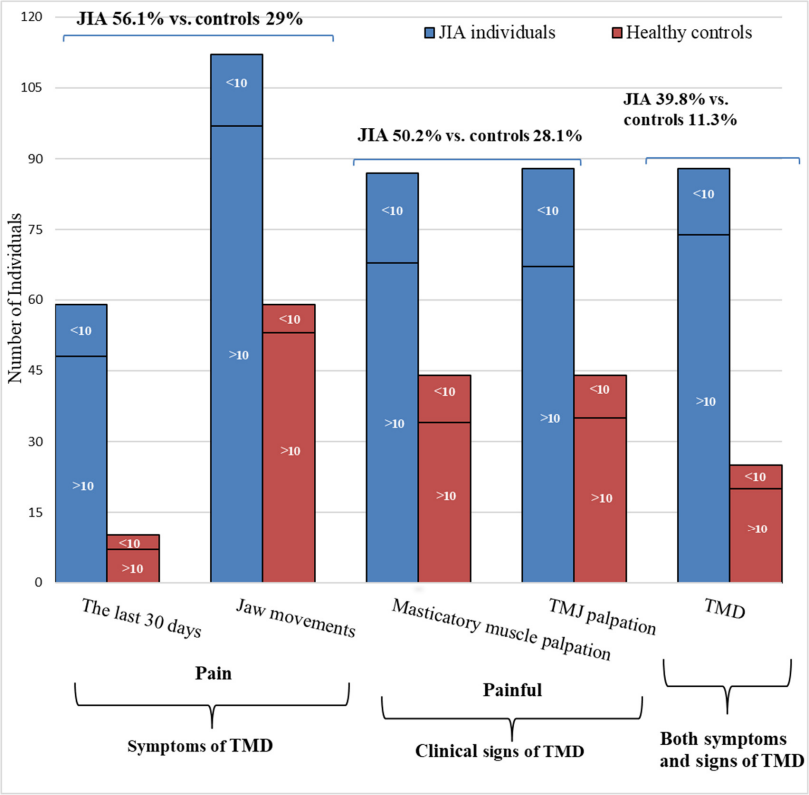

Figure 8. Prevalence of TMD in children and adolescents with JIA vs. healthy peers, >10 years and <10 years of age, 1) subjective symptoms: pain the last 30 days and pain at jaw movements; 2) clinical signs: pain at palpation of masticatory muscles and TMJ and 3) a combination of subjective symptoms (1) and clinical signs (2).

Paper II. Observer agreement of imaging measurements used for evaluation of dentofacial deformity in juvenile idiopathic arthritis.

Study II, this was a methodological study, aimed at identifying precise measurements for assessing mandibular morphology based on MRI, ceph and CBCT in children and adolescents with JIA, and additionally, at comparing CBCT and MRI in the measurement of condylar height. Since the main project focused on the TMJ joint itself, using a small field of view CBCT, only condylar height could be assessed for CBCT. The MRI 3D volume allowed for the assessment of three different measurements, while all the commonly used ceph measurements were tested. Ninety patients with JIA, mean

age 12.8 years (2.9 SD), were included. A 95% limits of agreement (LOA) within 15% of the sample mean was considered acceptable. Three MRI, one CBCT and nine ceph measurements were examined, of which the ceph-based SNA, SNB and RL3/ML3 (Figure 9) one MRI-based, total mandibular length and one CBCT-based, condylar height had the highest test/retest reliability. However, the clinical use of condylar height was not appropriate based on his inaccuracy because its MRI-measurement was higher than that registered by CBCT. Minimal detectable changes (MDC) within and between observers have been calculated at an individual level for a series of measurements.

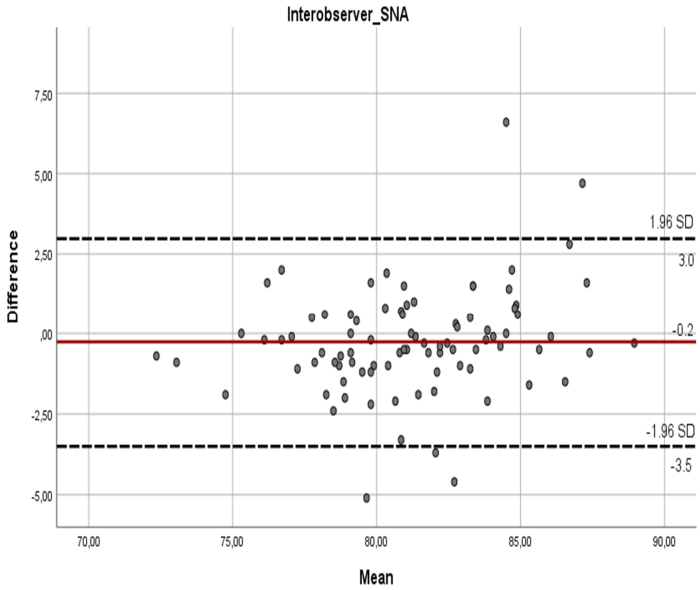

Figure 9. Bland-Altman plot interobserver SNA: Single red bold line = mean difference; black bold dashed lines = 95% limits of agreement lower and upper bounds of 95% confidence. Differences and means given in millimetres.

Paper III: In children and adolescents with temporomandibular disorder assembled with juvenile idiopathic arthritis, no associations were found between pain and TMJ deformity using CBCT.

This cross-sectional design of Study III addressed potential associations between TMD and findings on CBCT. Seventy-two children and adolescents with JIA, restricted to the municipality of Bergen, were included in the study. No statistically significant associations were seen between pain on palpation and TMJ deformity on CBCT (p=0.96 right side and p=0.38 left side, respectively) (Figure 10) or between pain on jaw movement and CBCT findings (p=0.45 right side and p=0.84 left side) (Figure 11).

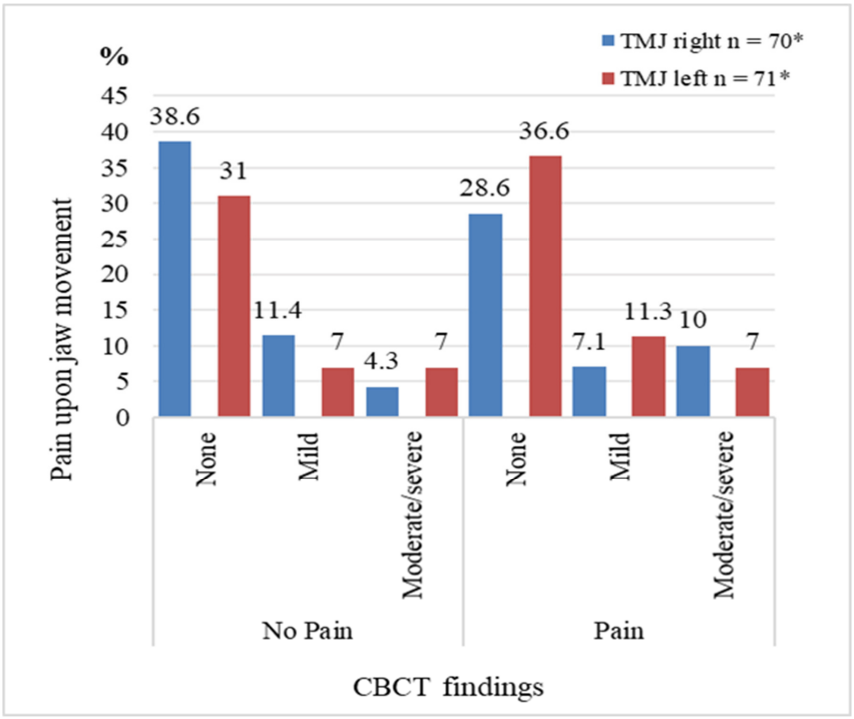

Figure 10. Painful TMJ palpation at- or around the lateral pole by TMJ deformity on CBCT in 72 children and adolescents with JIA, for right and left TMJ separately. * 3 CBCT scans are not available for these analyses as the field of view (FOV) did not cover the relevant structures.

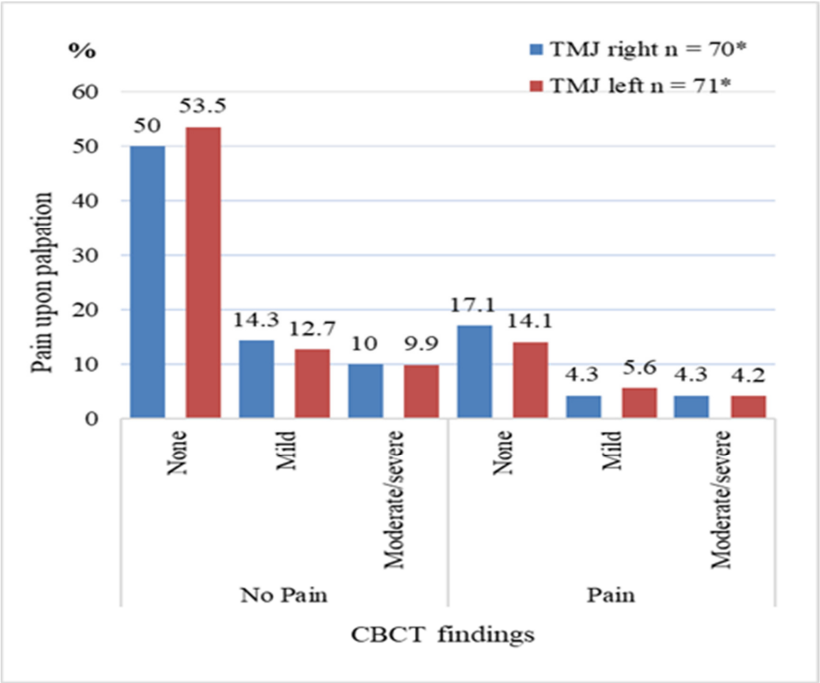

Figure 11. Pain upon jaw movements and TMJ deformity on CBCT. * 3 CBCT scans are not available for these analyses as the field of view (FOV) did not cover the relevant structures.

9. Discussion

9.1 Discussion of the main findings

The work presented in Paper I revealed that 56.1% of children and adolescents with JIA had self-reported TMD symptoms and 50.2% had clinical signs of palpatory pain on masticatory muscles and/or the TMJ. TMD prevalence according to the current literature, orofacial symptoms and signs are present in all JIA subcategories [119, 120, 124]. However, in our study, we show that orofacial symptoms and such as muscle pain, may not be caused by JIA disease itself but rather by more regular TMD, which is a quite prevalent condition in teenagers [37-39]. Numerous studies on the prevalence of TMD in children and adolescence have been carried out using RDC/TMD or the revised DC/TMD examination protocol [40, 197]; however, both criteria have been validated from the age of 18 years. One large study from Sweden used the pain screener

questions and found that the overall weekly prevalence of subjective symptoms in terms of self-reported pain related to TMD was 2.0 percent for boys and 2.7 percent for girls at the age of 12 years [9]. These findings partly corroborate our results, where 5% of healthy controls self-reported jaw pain within the last 30 days. Another study from southern Europe assessed 567 children and adolescents (aged 11-19 years) and revealed that the occurrence of myalgia was higher in females than in males [198]. This outcome is not directly comparable to our results because 39 girls of 62 controls had painful masticatory muscles and TMJ on palpation.

JIA and other comorbidities can complicate the diagnostic process, but the detection of orofacial signs and symptoms in patients with JIA may have the same clinical appearance but diverse etiologies [199]. In children and adolescents with JIA, the clinical figures of TMJ arthritis are substantially high, ranging between 39% and 87% [119, 200, 201]. A cross-sectional study by Koss and colleagues pointed out that myofascial pain on palpation seems to be more prevalent in patients with JIA compared to controls with a mean age of 13.3 years [202]. A recent chart review pointed out that about one-third of children and adolescents with JIA may reveal MRI-confirmed TMJ involvement in the first years of disease [120]. Herein, clinical signs such as pain upon palpation and subjective symptoms such as pain during laterotrusion, were the leading conditions. A comparative study by Collin and colleagues reported that out of 59 patients with JIA, 37% of children and adolescents (aged 7-14 years) reported TMJ symptoms at examination (self-reported), and 42% had previous self-perceived symptoms from the TMJ area during jaw movements [203]. However, in their child pain memories study of 51 children and adolescents (aged 8–16 years) [204], Wauters and colleagues focused on those higher amounts of self-reported symptoms in paediatric pain studies. They pointed out that self-reported symptoms in children and adolescents should be analysed carefully based on intersections between child pain-related attention and parental pain/non-pain attending conversations.

Paper II addresses the precision of lateral ceph, CBCT, and MRI-based measurements for the assessment of mandibular morphology, using the Bland-Altman mean-difference plots and MDC at an individual level. As previously mentioned, reporting

agreement using Bland-Altman plots enables the detection of any systematic bias, which is impossible with correlation analysis [205]. This study showed little or no constant bias, but varying agreement both within and between observers. Based on MRI, measurements of total mandibular length, right side, showed that intra- and interobserver 95% limits of agreement (reliability and reproducibility) were relatively narrow, at 9.6% of the sample mean, which was well within the a priori set value of ±15% considered acceptable for clinical use. This cut-off value was a clinical decision rather than one based on statistics. Others have reported on moderate interobserver agreement for an MRI-based measurement of the total mandibular body length using ICC (0.74), while CBCT performed better with an ICC of 0.95 [148]. MRI, in particular, holds the potential to add valuable information on growth disturbances by adding a 3D T1-w series to the routine arthritis protocol, thus replacing ceph. A recent repeatability study from the NorJIA research group devised a scoring system and identified 11 relevant markers of 25 imaging features on MRI, which used to describe anatomy, structural deformity and inflammation of the TMJ in a large cohort of children and adolescents with JIA [206]. However, there are no studies reporting on absolute reliability, such as the limits of agreement or MDC; thus, direct comparisons with our results are not possible. For condylar height, the variation within and between observers was higher for MRI (55.4% and 34.8%) than for CBCT (16.0% and 29.5%). This was comparable to an earlier study by Markic et al., where the 95% LOA for the CBCT-based condylar height can be estimated at 10% of the sample mean compared to 22% for MRI if the mean condylar height is around 18 mm (similar to our measurement). However, our study's MRI measurements for condylar height were generally higher than those obtained via CBCT, making them not directly comparable. Further, the agreement ranges were generally smaller for condylar height than posterior mandibular length, similar to Markic and colleagues. For ceph measurements, it is well known that landmark identification depends on observer experience [207, 208]. SNA, SNB, and gonion angle revealed high precision and low MDCs comparable to findings obtained from multiplanar images (MPRs) derived from volumetric CBCT scans of adult patients by Maspero and colleagues [157]. Furthermore, there were high levels of agreement between the measurements on CBCT and corresponding measurements on

3T-MRI, with no statistically significant difference between them.

The work presented in Paper III examined the association between TMD and CBCT-findings in terms of the overall impression of TMJ deformity in children with JIA. No statistically significant associations between TMD and CBCT based TMJ deformity were found, reflecting the complexity of the disease, the asymptomatic course, and the fact that CBCT cannot visualise inflammation. However, CBCT imaging has proven to be the gold standard in the assessment of osseous TMJ deformity after an ongoing TMJ arthritis and is the appropriate method to represent long-term consequences as TMJ OA [167]. For evaluation of active TMJ arthritis and TMJ in remission, MRI is found to be capable of diagnosing ongoing soft tissue inflammation, which is closely related to pain and structural deformity [118]. Moreover, our study revealed that 26.4% of patients without pain on palpation at and around the lateral pole had mild and moderate/severe TMJ deformity. On jaw movement, around one third without pain showed moderate/severe TMJ deformity. A recent retrospective chart review with a balanced gender ratio of 2413 children and adolescents with JIA (aged 4-17 years) revealed a statistically significant association between TMJ involvement on MRI and pain on palpation and pain while chewing [120]. Then again, a recent CBCT study discussed changes in the condyle-fossa relationship and the amount of resorption in 34 children and adolescents with JIA (mean age 14 years) and their healthy peers (mean age 16 years). The mandibular-fossa depth, anterior joint space, axial angles, and the resorption index showed statistically significant differences between the JIA and matched participants [209]. A most recent study used the RDC/TMD Axis I and screened 59 JIA patients aged 7 and 14 years [203]. They confirmed our findings that a proportion of children and adolescents with JIA rarely report TMJ pain even though TMJ deformities are visible. Moreover, they noticed that palpatory pain was not associated with TMJ deformity, which corroborates our findings.

9.2 Methodological considerations

9.2.1 Study designs

The methodologic design in Study I has its limitations, including differentiating between cause and effect of events. Recruitment of patients was performed by

experienced paediatric rheumatologists at three study centres in Bergen, Trondheim and Tromsø, respectively. The overall response rate was 63.3%, which is acceptable; nevertheless, it might have influenced the results since the group not participating, on average, was slightly younger and comprised a lower proportion of girls. The degree of JIA involvement in these children was not assessed, hindering speculations concerning the likely direction of bias, e.g., over or underreporting of TMD-prevalence.

Although we did not register the parental education level as a marker of socioeconomic status, it is reasonable to believe that the cases and controls were drawn from populations that did not differ significantly from each other, thus reducing the risk of potential *selection bias*. Our assumption lends support from a survey from 2016, demonstrating that living conditions in the municipality of Bergen were overall very similar to the rest of the Norwegian population with respect to its socioeconomic status [210]. The JIA cohort revealed no participants with major medical comorbidities such as congenital facial anomalies, skeletal dysplasia, or malignancies in the study group. A questionnaire on pain-related oral issues was filled in by the participant, his/her carer or in consensus while the participant was seated in the waiting area. Potential bias was *recall bias* (e.g., the subject did not remember TMD). We included children from four years of age onwards since children younger than this requires sedation for the MRI examination. However, the youngest patient was aged four years; thus, our results are valid for the age group 4-16 years of age. All but two were Caucasians.

9.2.2 Assessment of TMD

Every TMD assessment is dependent on factors such as time available for each patient, profession, and educational background of the examiner. Repeated calibration sessions have been shown to improve the reliability of clinical TMD assessments [192]. Appendix I demonstrates the TMD Case report protocol, which includes fourteen examination stages. Due to very low variation between the examiners, variables as: TMJ creptation during jaw movements (stages 5, 6), and joint locking (stage 7) were excluded. Furthermore, the proportion of participants who gave responses to these stages was sparse. Another aspect is that familiar pain symptoms exhibited low values and have been excluded from statistics. A previous diagnostic accuracy study of the

DC/TMD criteria in 282 children and adolescents (aged 8-12 years) argued that the ability to understand the concept of familiar pain could be a possible problem including children's unreliable pain memory [197].

The dentists underwent theoretical courses in how to use the CRF-version for TMD assessments. However, a recent study has debated the examination of mandibular range of motion in children and adolescents with JIA and clinical established TMJ involvement [211]. Herein, the authors compared active, passive maximum interincisal opening, protrusion and laterotrusion in 298 children and adolescents with JIA (aged 6-18 years) and 196 healthy peers. Their results of active maximum interincisal opening are in concordance with our result which was lower for JIA participants than for controls (Paper I); furthermore, the authors elucidated the differences of mandibular range of motion in JIA participants with and without clinical TMJ involvement. Such distinction could have been a comparative design in Paper III. A limitation of the TMD assessment method was the use of a diagnostic procedure that was designed for adults and subsequently adapted for children and adolescents instead of constructing an entirely new diagnostic tool.

9.2.3 Imaging

For the test-retest studies presented in Paper II, lateral ceph, MRI and CBCT from 90 children and adolescents with JIA were analysed and scored/measured. For the ceph measurements, 9 measurements based on 16 anatomical landmarks were used, while the direct measurements used for CBCT (condylar height) and MRI (total mandibular length and heights of the ramus and condyle) were devised by team members for the purpose of this study.

The precision of measurements is dependent on the image quality/resolution and identification/determination of measurement points, as well as on the examiners' previous experience in identifying the anatomical landmarks using the images mentioned above. For an assessment of ceph images, two examiners (JF and JH) underwent training sessions under the supervision of an experienced orthodontist, followed by piloting and discussions on measurement points used. Three out of 9 measurements, namely the SNA, SNB and RL/ML3, performed better than the

remainder. The poor precision of ANB can be explained by the small value of around 2 - 3 degrees and the more complex position of point A. This result is in line with the orthodontic literature, describing angular measurements of ANB as being sensitive to small changes in Nasion and Sella Turcica landmarks, the length of the anterior skull base, and the vertical growth pattern [212]. Further, dental landmarks are prone to have poorer validity than skeletal landmarks [213, 214].

When comparing MR with CBCT in the measurement of condyle height, the higher observer agreement in MR is somehow unexpected. For MRI, all the measurements were performed on multiplanar reconstructed T1-w images as described in Paper II. The field of view (FOV) was 25 x 25 cm with a matrix of 256 x 256 and slice thickness of 1mm, yielding nearly isotropic voxels of 1mm. The physical spatial resolution of CBCT imaging is known to be superior to MR with a possible voxel size down to 0.08mm. However, in this multicentre study, default examination protocols at each centre were applied. Since there were no national or international guidelines for the JIA examination using CBCT, the variations in CBCT devices and the applied exposure protocols made it difficult to standardise the resulting image quality.

For both MR and CBCT, having to reorient the volume and choose the most representative cross-sectional view, define the measurement points and set the cursors for each of the measurements may, to some extent, explain the observer variation, although only a small systematic bias was seen. Using specific software allowing measurements directly on a 3D rendering model might have improved the precision. There are other methods (NOT programs) that overcome some of the inherent problems of conventional (linear and angular) methods like geometric morphometrics (GMMs). GMMs use a least-square criterion: the forms are superimposed so that the sums of the squared distances between corresponding landmarks are minimised [215].

The system for assessment of TMJ pathology, on the other hand, showed substantial to almost perfect agreement between and within observers for an assessment of the overall impression of damage on a 0-2 scale (Augdal TA et al., manuscript submitted 2022).

9.3 Statistical considerations

Previous studies on the actual topic have mainly examined the correlation between repeat examinations or between methods [157]. However, both Pearson's correlation coefficient and intra-class correlation (ICC) measure the strength of an association only, and ICC is affected by the range of values across the population [216]. Furthermore, correlations ignore any systematic bias between two observers or methods; consequently, even a highly significant correlation between two methods does not guarantee clinically acceptable agreement [205]. We, therefore, found the Bland-Altman approach to be the appropriate use of statistics for this purpose. Bland-Altman plots graphically display the difference on a y-Axis between the measurements against their mean value on an x-Axis.

Similar to the MDC, smallest detectable changes, real minimal change or actual change, it assesses differences rather than correlations. The MDC was defined as a change that falls outside the limits of agreement of the Bland-Altman method, i.e., limits of agreement give information about MDC [217]. Difference in scores within the limits of agreement or smaller than the MDC can be ascribed to measurement error and outside the limits of agreement. Those values are statistically significant or true changes [217].

9.4 Clinical implications

Paper I showed that TMD is a common disorder in children and adolescents with JIA, when based on the current protocols. The clinical assessment of TMD pain symptoms in children and adolescents might be biased by indirect input from their parents, and by their intellectual, social, and emotional development. Since children and adolescents with JIA and/or their caregiver(s) may ignore TMD signs and symptoms, dentists and rheumatologists are at the front line for targeting the patients at risk of TMD among JIA patients. On the other hand, the risk of over-diagnosing TMD based on standardised questions should be kept in mind. In sum, an individual TMD assessment plan taking the child's age and development stage into consideration should be established.

In Paper II, the reliability of the three image modalities was investigated. Our results revealed that five imaging markers had the capacity to give the exact measurements between and within operators on repeated application. Due to the lack of a gold standard in the current clinical study, these methods' validity (accuracy) could not be verified. The accuracy of anatomical landmarks recognition and distance/angle measurements should be investigated before clinical implementation. Provided an acceptable validity, the high precision of the MR-based total mandibular length is promising, particularly since TMJ-involvement is routinely followed with MRI. By adding a 3D T1-w sequence to the standard protocol, a measurement to evaluate potential growth disturbances is gained. A caveat is a need for sedation in children under five.

Furthermore, to gain a robust and validated scoring system, similar technical and environmental conditions and a systemised calibration of the raters/readers are needed. Studies addressing the precision of lateral ceph, CBCT and MRI-based TMJ measurements applying the Bland-Altman mean-difference plots in children and adolescents are desirable. Others based their results on consensus among readers but did not assess agreement or discuss agreement or precision at all [202, 218, 219].

Paper III supports the understanding that clinical assessment alone is insufficient to detect TMJ deformities. The system for assessment of TMJ pathology, on the other hand, showed substantial to almost perfect agreement between and within observers for assessment of the overall impression of damage on a 0-2 scale (Augdal TA et al., manuscript submitted 2022). However, CBCT examination gives a much higher radiation dose than conventional radiographic examinations, such as panoramic radiography. The reported effective dose ranged greatly from 20 to 500 μSv depending on the applied CBCT device, field of view and applied exposure parameters [220]. Thus, clinical criteria on when CBCT is beneficial for the diagnostics and treatment for this patient group is in urgent need.

9.5 Conclusions

This project highlighted the prevalence of TMD pain among a population of children and adolescents with JIA and the necessity of diagnostic imaging tools.

Based on the results, the conclusions can be summarised as follows:

Paper I: Compared to their healthy peers, the prevalence of subjective symptoms and clinical signs was 56.1% and 50.2%, respectively, and 39.8% had TMD pain.

Paper II: One MRI-based (total mandibular length), one CBCT-based (condylar height), and three ceph-based measurements were reliable image markers in terms of repeatability and reproducibility. The MRI-based measurement of condylar height was higher than that obtained by CBCT and determined the MDC for a set of measurements.

Paper III: There are no associations between TMD pain and CBCT-based pathology in children with JIA, which means that clinical symptoms and signs of TMD pain cannot predict TMJ deformity and vice versa.

10. Future perspectives

Future research to reduce and prevent chronic childhood pain is a crucial priority area. The burden of chronic pain comprises reduced quality of life for children and adolescents, redundancy of productivity, and immense costs to parents/caregivers [221, 222]. Studies have shown that children and adolescents with chronic pain may develop or continue physical symptoms with psychiatric complaints into adulthood. Sharpened diagnostic tools are key for investigating the best treatment available. Adequate validated protocols and effective treatment of children and adolescents with chronic pain may hinder the social impact of adult chronic pain. There is still a need for a systematic review of the current standardised protocols and a short TMD screening protocol validated for children and adolescents with JIA. Future protocols should consider the following categories: Differentiation between ordinary TMDs and symptoms and signs resulting from JIA disease activity and a method to detect memory bias by young children and adolescents. It will be a unique aspect to involve the parents and or caregivers in clinical examination because their influence might impact their children`s adjustment to pain/chronic pain coping [204, 223-225]. An essential method item is the calibration of the observers, i.e., to train and correlate the clinicians to investigate in the same way. The role of imaging in TMD/JIA diagnosis needs future in-depth investigation. All three imaging tools have their advantage and disadvantage. The diagnostic accuracy in structure recognition and JIA pathology must be tested.

Further studies are needed to test how accurate our method measures are to gain valid results. MRI, in particular, holds the potential to add valuable information on growth disturbances by adding a 3D T1-w series to the routine arthritis protocol, thus replacing ceph. A recent repeatability study from the NorJIA research group can be used which introduced a scorings system on MRI, describing anatomy, structural deformity and inflammation of the TMJ [206].

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12. Original Papers

I

Paper I

Prevalence of temporomandibular disorder in children and adolescents with juvenile idiopathic arthritis – a Norwegian cross- sectional multicentre study

J. Fischer, M S. Skeie, K. Rosendahl, K. Tylleskär, S. Lie, X-Q. Shi, E. Grut Gil, L. Cetrelli, J. Halbig, L. von Wangenheim Marti, M. Rygg, P. Frid, P. Stoustrup and Annika Rosén

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RESEARCH ARTICLE Open Access

Prevalence of temporomandibular disorder in children and adolescents with juvenile idiopathic arthritis – a Norwegian cross-sectional multicentre study

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Abstract

Background: Children and adolescents with juvenile idiopathic arthritis (JIA) may suffer pain from temporomandibular disorder (TMD). Still, routines for the assessment of temporomandibular joint (TMJ) pain in health and dental care are lacking. The aims of this study were to examine the prevalence of TMD in children and adolescents with JIA compared to their healthy peers and to investigate potential associations between JIA and TMD.

Methods: This comparative cross-sectional study is part of a longitudinal multicentre study performed during 2015–2020, including 228 children and adolescents aged 4–16 years with a diagnosis of JIA according to the ILAR criteria. This particular substudy draws on a subset of data from the first study visit, including assessments of TMD as part of a broader oral health examination. Children and adolescents with JIA were matched with healthy controls according to gender, age, and centre site. Five calibrated examiners performed the clinical oral examinations according to a standardised protocol, including shortened versions of the diagnostic criteria for TMD (DC/TMD) and the TMJaw Recommendations for Clinical TMJ Assessment in Patients Diagnosed with JIA. Symptoms were recorded and followed by a clinical examination assessing the masticatory muscles and TMJs.

Results: In our cohort of 221 participants with JIA and 221 healthy controls, 88 (39.8%) participants with JIA and 25 (11.3%) healthy controls presented with TMD based on symptoms and clinical signs. Painful TMD during the last 30 days was reported in 59 (26.7%) participants with JIA vs. 10 (5.0%) of the healthy controls ($p < 0.001$). Vertical unassisted jaw movement was lower in participants with JIA than in controls, with means of 46.2 mm vs. 49.0 mm, respectively ($p < 0.001$). Among participants with JIA, a higher proportion of those using synthetic disease-modifying antirheumatic-drugs and biologic disease-modifying antirheumatic-drugs presented with painful masticatory muscles and TMJs at palpation.

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Conclusion: Symptoms and clinical signs of TMD were seen in approximately half of the JIA patients compared to about one fourth of their healthy peers. Painful palpation to masticatory muscles and decreased vertical unassisted jaw movement were more frequent in participants with JIA than among healthy controls and should be part of both medical and dental routine examinations in patients with JIA.

Keywords: Juvenile idiopathic arthritis, Temporomandibular joint arthritis, Temporomandibular disorder, Temporomandibular joint disease, Children and adolescents

Background

Juvenile idiopathic arthritis (JIA) is currently the most common chronic rheumatic disease in children and adolescents [1, 2]. The International League of Associations of Rheumatology (ILAR) defines JIA as arthritis of unknown aetiology, starting before the age of 16 years with a duration of at least 6 weeks [3]. It encompasses seven categories, including systemic arthritis, oligoarthritis (persistent or extended), rheumatoid factor negative polyarthritis, rheumatoid factor positive polyarthritis, psoriatic arthritis, and enthesitis-related arthritis with different, though overlapping, characteristics. Cases that fit none or more than one of these categories are defined as undifferentiated arthritis. The burden of JIA is characterised by short and long-term functional disability and pain. Common features at presentation are morning stiffness, swelling of one or more joints, functional disturbances, and sometimes pain. The reported prevalence is around 1–2 cases per 1000 children, with girls more frequently affected than boys [1, 2].

Temporomandibular disorder (TMD), known as an umbrella or collective term for muscle pain and jaw dysfunction, covers a heterogeneous group of conditions [4]. TMD is associated with various clinical signs and symptoms involving the masticatory muscles, teeth, tongue, temporomandibular joint (TMJ), and/or their supportive tissues [5–7]. Changes in motor behaviour caused by musculoskeletal pain and pain-related movement disorders reflect sustained pain perception. In two recent studies from Western Norway [8, 9], the prevalence of painful TMD among otherwise healthy adolescents was reported to be around 7% based on self-reported pain screening questionnaires adopted by Nilsson and colleagues [10]. In the study by Graue and colleagues [9], the prevalence of TMD was 11.9% when using the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD). In all three studies, females were more frequently affected than males.

In children and adolescents with JIA, the reported figures are substantially higher. Previous studies of children and adolescents with JIA reported a broad spectrum of TMD prevalence ranging between 39 and 87% [11–13], depending on the study designs and the sample size. Therefore, it is a need to reinforce the evidence with a relatively high number of samples and give insights to the effects of medication in JIA participants when they are examined by palpation of masticatory muscles and TMJ.

Previous studies revealed that children and adolescents, irrespective of their JIA category, are prone to develop TMJ arthritis [11, 14]. Also, younger children with JIA might suffer pain from TMJs caused by inflammation and/or destructive changes, by muscular tensions from the surrounding muscles as a component of TMD, or by a combination of the two [12]. Symptoms indicating TMJ arthritis include decreased mouth opening and/or ear ache and pain during eating, chewing, or yawning [15–17]. At present, there are no precise clinical or imaging markers for active TMJ arthritis [18, 19]. As for TMJ involvement, several studies have shown that even significant deformities may be undiagnosed due to a lack of symptoms or clinical findings [16, 20–22]. In younger children, the clinical assessment of painful TMD symptoms might be biased by indirect input from their parents.

The aims of the present study were to examine the prevalence of TMD in children and adolescents with JIA compared to their healthy peers and to investigate potential associations between JIA and TMD.

Methods

Study design and participants

This cross-sectional study was part of a longitudinal multicentre study, the NorJIA study, performed during 2015–2020 and including 228 children and adolescents. Inclusion criteria were a diagnosis of JIA according to the ILAR [3] and age 4–16 years. In the exclusion criteria, absent of written informed consent or major medical comorbidities such as congenital facial anomalies, skeletal dysplasia or malignancies were excluded.

This particular substudy (2015–2018), using a matched comparative cross-sectional design, drew on a subset of data from the first study visit, including assessments of TMD as part of a broader oral health examination. Children and adolescents were matched (1:1) with healthy controls according to gender, age, and centre site. The healthy controls were recruited from seven different Public Dental Service clinics representing both rural and urban areas in the western, middle, and northern parts

of Norway. The sample size estimate was based on a Swedish study reporting a TMD prevalence of 26% in children with JIA [23], and a sample size of 296 was required for a precision of 5% with a 95% confidence interval.

Data collection

At the study visits, children and adolescents with JIA were examined by experienced paediatric rheumatologists at Haukeland University Hospital in Bergen, University Hospital of North Norway in Tromsø, and St. Olavs University Hospital in Trondheim. Registered data included background characteristics in terms of age at disease onset, disease category, disease status on the day of the examination, a thorough joint examination, blood tests, and validated measures for patient-reported disability, general body pain, and health assessments. Furthermore, the applied dose was according to the international recommendations, while duration varied significantly, with or without combination with other medication. However, detailed drug history concerning duration and doses was not available in the study database. Both children and adolescents with JIA and controls underwent a thorough clinical oral examination performed by experienced dentists, including a TMD assessment.

TMD screening and assessment

The assessment procedures were standardised and were based on two shortened versions of the diagnostic tools "Axis I Clinical Examination for DC/TMD" [20] and the self-assessment questionnaire "TMJaw Recommendations for Clinical TMJ Assessment in Patients Diagnosed with JIA" [21]. The latter was used to enhance the operational specification of DC/TMD due to the fact that the DC/TMD tool alone is reported to show weak validity for TMJ assessment, e.g. disc displacement diagnosis (low sensitivity) and degenerative joint disease diagnosis (low sensitivity and specificity) [20].

Prior to and during the study period, calibration sessions for the five participating oral examiners were performed, including four calibration exercises according to procedures previously described by our research team [22]. Further details on the calibration results are presented in Supplementary Tables S1 and S2.

Variables and outcomes

The demographic variables were age, gender, JIA categories, and medication status. The subjective symptom outcomes were TMD pain in the last 30 days (n, %) reported by the participants or the parents. The examining dentists also registered how many of the individuals expressed pain during jaw movement in the clinical examination (n, %). The clinical outcomes included vertical and lateral unassisted jaw movements (mm), pain upon palpation of the masticatory muscles and the TMJ (n), and if the TMJ disc was clicking in a painful manner (n).

Statistical methods

Two-way mixed intraclass correlation coefficient (ICC) and percent agreement were used for calibration measurements. Differences between groups were tested using Chi-square statistics or a two-sample t-test as appropriate. All statistical tests were performed using SPSS version 25 (IBM, Chicago, IL). The level of statistical significance was set at 5% ($p \leq 0.05$).

Ethical considerations

The study was approved by the regional ethics committee (2012/542/REK vest). Written informed consents were obtained from all parents and/or participants as appropriate. The study was registered at ClinicalTrials.gov (No: NCT03904459).

Results

A total of 360 children and adolescents with JIA were eligible for the main study, of whom 228 accepted the invitation to participate, yielding a response rate of 63.3%. The acceptance rate for healthy controls was 224/294 (76.2%). The mean age for participants with JIA and healthy controls was 12.0 years (SD 3.17 and 3.21, respectively) ($p = 0.98$), and the mean age of the 228 participants with JIA was higher than for the 132 eligible patients that did not participate at 12.0 years vs. 10.5 years (SD 3.16 and 3.5, respectively) ($p < 0.001$). The proportion of girls with JIA was also higher than among the 132 patients not participating (59.2% vs. 58.3%, $p = 0.027$). Among the 228 participating children with JIA, 224 underwent an oral examination and 221 underwent the TMD assessment and were thus included in the present substudy (Fig. 1).

Of the 221 children with JIA, 132 were girls (59.7%), the median age at disease onset was 6.1 years (IQR 8.1, 2.3–10.4), the median age at the study visit by paediatric rheumatologists at the hospital was 12.7 years (IQR (5.3, 9.4–14.7), and the median disease duration was 4.6 years (IQR 5.7, 2.6–8.3) (Table 1). Oligoarticular JIA was the most common category and was seen in 98 of 221 patients (44.3%) with 77 having persistent oligoarticular disease and 21 having extended disease. In total, 146 of the 221 patients (66.1%) had on-going medication with synthetic disease-modifying antirheumatic-drugs (sDMARDs) and/or biologic disease-modifying antirheumatic-drugs (bDMARDs).

Clinical oral examination

Taking into consideration that self-reported pain is a combination of parent-reported and participant-reported

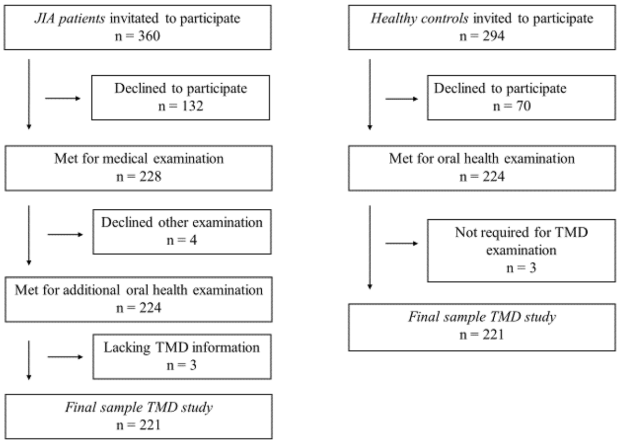

Fig. 1 Flow chart of patients and healthy individuals included in the study

pain outcome, self-reported pain in the jaws during the last 30 days was reported in 59 (26.7%, 44 girls) participants with JIA vs. 10 (5%, 8 girls) in healthy controls ($p < 0.001$). Pain during jaw movements at the clinical examination was reported in 112 (51%, 67 girls) participants with JIA vs. 59 (26.8%, 34 girls) in healthy controls ($p < 0.001$) (Fig. 2), ranging from 28.6 to 50% in the different JIA categories (Table 1). No statistically significant differences in the presence of TMD according to JIA categories were found ($p = 0.848$) (results not shown).

Table 1 Clinical characteristics of participants with Juvenile idiopathic arthritis (JIA) in relation to temporomandibular disorder (TMD)

	Total cohort	TMD	No TMD
	n = 221	*n* = 88	*n* = 133
	Value	Value	Value
Girls, n (%)	132 (59.7)	61 (69.3)	71 (53.4)
Age at onset, median (IQR)	6.1 (8.1, 2.3–10.4)	6.8 (8.4, 0.7–14.2)	5.2 (7.2, 0.9–14.7)
Age at visit by paediatric rheumatologists at the hospital, median (IQR)	12.7 (5.3, 9.4–14.7)	13.1 (3.3, 5.2–16.1)	11.7 (6.5, 4.8–16.5)
Disease duration, median (IQR)	4.6 (5.7, 2.6–8.3)	4.6 (6.0, 0.2–14.2)	4.6 (5.5, 0.2–14.7)
JIA categories, n (%)			
Oligoarthritis persistent	77 (34.8)	27 (30.7)	50 (37.6)
Oligoarthritis extended	21 (9.5)	11 (12.5)	10 (7.5)
Systemic arthritis	7 (3.2)	2 (2.3)	5 (3.8)
RF negative polyarthritis	49 (22.2)	17 (19.3)	32 (24.1)
RF positive polyarthritis	4 (1.8)	2 (2.3)	2 (1.5)
Psoriatic arthritis	9 (4.1)	6 (6.8)	3 (2.3)
Enthesitis-related arthritis	23 (10.4)	9 (10.2)	14 (10.5)
Undifferentiated JIA	31 (14.0)	14 (15.9)	17 (12.8)
Ongoing medication, n (%)			
No DMARDs	75 (33.9)	26 (11.8)	49 (22.2)
sDMARDs*	60 (27.1)	23 (10.4)	37 (16.7)
bDMARDs**	86 (38.9)	39 (17.6)	47 (21.3)

JIA Juvenile idiopathic arthritis, *TMD* Temporomandibular disorder
*sDMARDs = Synthetic disease-modifying antirheumatic- drugs; methotrexate, mykofenolatmofetil, **bDMARDs = Biologic disease-modifying antirheumatic-drugs; etanercept, infliximab, adalimumab, tocilizumab, abatacept, certolizumab, golimumab

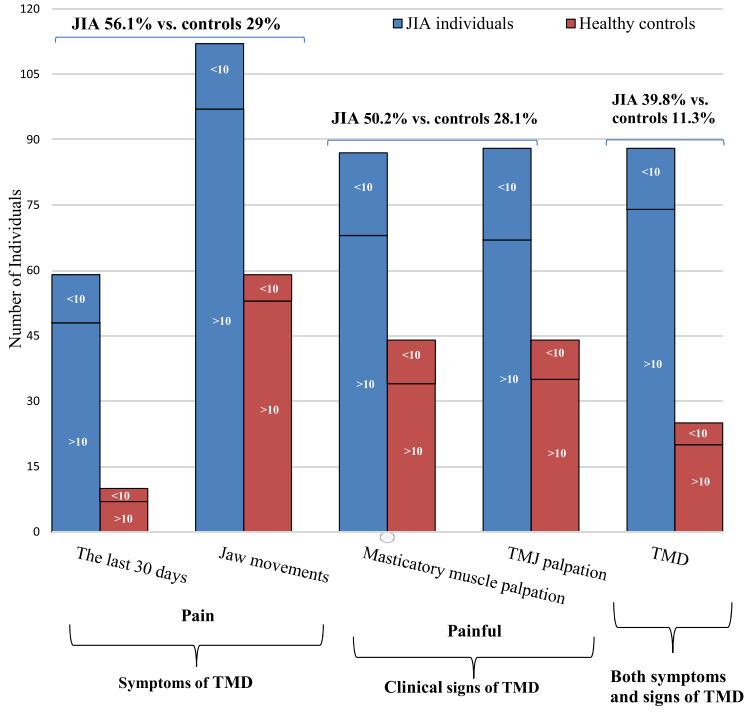

Fig. 2 Prevalence of TMD in children and adolescents with JIA vs. healthy peers, ≥ 10 years and < 10 years of age, 1) symptoms: pain the last 30 days and pain with jaw movements; 2) clinical signs: pain upon palpation of the masticatory muscles and TMJ, and 3) a combination of symptoms (1) and clinical signs (2)

The clinical examination revealed that the mean vertical unassisted jaw movement was lower for participants with JIA than for controls, 46.2 mm vs. 49.0 mm, respectively ($p < 0.001$) (Table 2). A total of 88 (39.8%, 61 girls) participants with JIA and 25 (11.3%, 17 girls) healthy controls had both symptoms and clinical signs of TMD (Fig. 2). When assessing the jaw muscles and TMJ, 111 (50.2%, 75 girls) participants with JIA had both painful masticatory muscles and TMJs on palpation vs. 62 (28.2%, 39 girls) of the healthy controls ($p < 0.001$) (Table 3). A higher proportion of participants on current sDMARDs and/or bDMARDs treatment presented with painful masticatory muscles and TMJ at palpation compared to participants with no biologic treatment (Table 4).

Among participants with JIA, there were no significant differences in vertical unassisted jaw movement according to medication, with a mean of 46.4 mm (SD 7.1) in the JIA group and 45.8 mm (SD 7.1) among those not using DMARDs ($p = 0.986$) (results not shown). However, in both groups, more than half of the participants had a vertical unassisted jaw movement of more than 40 mm. The proportion without this medication treatment was slightly higher (82.7%) compared to those on current sDMARDs and/or bDMARDs (77.4%).

Table 2 Jaw movement in 221 participants with JIA compared to controls

Jaw movement	n	JIA mm mean (SD)	n	Healthy controls mm mean (SD)	*p*-value*
Vertical unassisted	221	46.2 (7.1)	221	49.0 (6.7)	< 0.001
Lateral to the right side	215	9.7 (2.2)	220	9.8 (2.1)	0.408
Lateral to the left side	211	9.7 (2.4)	219	10.1 (2.0)	0.077

JIA Juvenile idiopathic arthritis, *SD* Standard deviation. *Student's t-test

Table 3 Pain on palpation and painful clicking in participants with JIA and controls

Clinical signs	n	JIA, n (%)	n	Healthy controls n (%)	*p*-value*
Painful palpation in masticatory muscles & TMJ	220	111 (50.5)	220	62 (28.2)	< 0.001
Painful palpation in masticatory muscle	217	87 (40.1)	218	44 (20.2)	< 0.001
Painful palpation at the TMJ lateral pole	220	64 (29.1)	219	29 (13.2)	< 0.001
Painful palpation around TMJ lateral pole	220	75 (34.1)	219	33 (15.1)	< 0.001
Painful clicking	221	13 (5.9)	221	2 (0.9)	0.0041

JIA Juvenile idiopathic arthritis, *TMJ* Temporomandibular joints. *Chi-square test

Discussion

We have shown using a comparative cross-sectional multicentre design that around one third of the participants with JIA in this cohort had TMD. Half of children and adolescents with JIA reported pain during jaw movements and pain on palpation of the masticatory muscles and TMJs as compared to one fourth of their healthy peers, palpatory pain was associated with sDMARDs and bDMARDs treatment, and children and adolescents with JIA had a significantly lower mean vertical unassisted jaw movement. Moreover, TMJ-related clinical signs and vertical unassisted jaw movement ≤40 mm had the highest association in the JIA group.

The reported prevalence of TMD in children with JIA varies between 38 and 83% according to the definitions and methods of ascertainment used, to the cohort examined, and to differences in populations [15, 24–27]. Ferraz and colleagues, in their study of 15 children with JIA ranging in age from 6 to 28 years (mean age 16.3 years), reported a high prevalence of 83%. Still, they did not describe the method of ascertainment, i.e., whether the figures were based on self-reporting or on clinical examination [28]. A previous study from Rongo and colleagues based on 50 participants with JIA aged 9–16 years found a prevalence of TMJ damage from 100 joints to be 74% as assessed by MRI [25]. Others have reported a prevalence of 55% based on a questionnaire [29] and of 72% based on clinical signs [24]. However, none of those studies were based on the research diagnostic criteria RDC/TMD, and the children were older than those in our study. In contrast, a longitudinal study by Zwir et al., including 75 children (mean age 12.4 years), revealed a prevalence of 38% based on symptoms and 47% based on clinical examination [30]. Their results are in line with ours.

In our study, the prevalence of TMD, either based on symptoms or clinical signs, in the healthy peers, were quite high at 28 and 29%, respectively. This was higher than in earlier studies among adolescents reported by Graue and colleagues (7 and 12%, respectively) and Østensjø and colleagues (7%) [8, 9]. Studies from Finland and Brazil confirm our results with a high prevalence of TMD in the normal population. Vierola et al. [26] reported a TMD prevalence of 35% (mean age 7.9 years) and de Paiva Bertoli reported a TMD prevalence of 34% (mean age 11.0 years) [27]. The difference in TMD prevalence in the normal population of children and adolescents is probably due to the use of different diagnostic tools, different numbers of participants, different ages of the studied populations, different countries, and different study designs. In studies from Norway, Graue and colleagues [9] used two screening questions for pain related to TMD [10] and DC/TMD [20] for symptoms and clinical signs in a population of 210 children and adolescents aged 12–19 years. Østensjø et al. [8] used the same two screening questions of TMD symptoms [10] for screening a population of 560 adolescents aged 13–19 years. Then a modified RDC/TMD examination [31] was used for those who answered yes to 1) having pain in the temples, face, TMJ, or jaws once a week or more and 2) having pain once a week or more when opening the mouth wide or chewing. The Finnish group [26] used the RDC/TMD [31] for clinical signs in 483 children aged 6–8 years, and the Brazilian group [27] used

Table 4 Clinical signs and pain at palpation according to DMARDs in 221 participants with JIA

	Current sDMARDs and/or bDMARDs		No current sDMARDs and/or bDMARDs		*p*-value*
	n	n (%)	n	n (%)	
Vertical unassisted jaw movement (> 40 mm)	146	113 (77.4)	75	62 (82.7)	0.361
Painful palpation to masticatory muscles & TMJ	145	80 (72.1)	75	31 (41.3)	0.052
Painful palpation to masticatory muscles	143	62 (43.4)	74	25 (33.8)	0.173
Painful palpation at the TMJ lateral pole	145	49 (33.8)	75	15 (20.0)	0.033
Painful palpation at the TMJ around lateral pole	145	56 (38.6)	75	19 (25.3)	0.049

sDMARDs Synthetic disease-modifying antirheumatic-drugs; methotrexate, mykofenolatmofetil, *bDMARDs* Biologic disease-modifying antirheumatic- drugs; etanercept, infliximab, adalimumab, tocilizumab, abatacept, certolizumab, golimumab, *TMJ* temporomandibular joint, * Chi-square test

the American Academy of Orofacial Pain [32] form for screening and the RDC/TMD [31] for clinical examination in a population of 934 individuals aged 10–14 years. Thus it is clear that it can be challenging to get an exact figure on the prevalence of TMD in the normal population. A previous meta-analysis conducted by da Silva and colleagues showed the overall prevalence of intra-articular joint disorder to be 16% [33].

In our study, approximately half of the JIA subjects had clinical findings consistent with TMD, with no differences according to JIA category. Because the numbers for three of the categories – systemic arthritis, rheumatoid factor positive polyarthritis, and psoriatic arthritis – were relatively low, these results should be interpreted with caution.

The sensitivity and specificity of the clinical orofacial examination in relation to TMJ has been debated because displacement of the disc, although eliciting a clicking sound, might be asymptomatic [34–36]. Based on the DC/TMD criteria, asymptomatic TMJ clicking is still defined as TMD. However, several studies have shown that pain-free clicking represents a normal variant, typically seen in girls during puberty [15]. Recently, a clinical examination protocol for JIA was developed by the Temporomandibular Joint Juvenile Arthritis Working Group (TMJaw). This examination protocol focuses on three general items, namely TMJ symptoms, TMJ dysfunction, and dentofacial deformity in JIA, and it shows acceptable reliability and validity [7].

We found, in accordance with other studies, that the TMJ area and the masseter muscle region were common locations for pain in JIA [29]. However, a recent study from Koos and colleagues reported a lower frequency of masticatory pain on palpation [15], and Kristensen and colleagues stated that masticatory pain complaints could develop over time [37]. In the present study, more than half of the participants with JIA showed clinical signs in the TMJ region and the masseter region, and more than one-fourth of the participants with JIA had TMD. A longitudinal multicentre approach might elucidate the development of masticatory muscle pain, as Kristensen and colleagues have suggested [37].

The vertical unassisted jaw movement has been widely used as a valid marker for TMJ arthritis [38]. We showed that participants with JIA had lower vertical unassisted movements compared to their healthy peers, but the differences were relatively small, thus questioning its clinical significance. Viewed differently, for children and adolescents aged < 11 years, the cut-off value of 40 mm was within the range of normal vertical jaw movement [39]. Further, our findings suggest that lateral movement did not differ significantly between the two groups, which is in line with the results of Twilt and colleagues [40] and Küseler and colleagues [19]. In the latter study of 15 children with JIA with a mean age of 12 years, the recorded decreased lateral movements were ≤ 5 mm with no significant relevance [19].

We found no statistically significant differences in the presence of TMD according to JIA categories. However, we found a significantly higher occurrence of clinical signs in participants with JIA currently on DMARDs medication (whether synthetic or biologic) compared to those not taking such medication. A high risk of developing clinical signs of TMD was associated with a severe disease course, as indicated by the use of DMARDs.

The strengths of this study are the relatively large number of participants, in which the study groups were well matched, and the meticulous standardisation of the clinical TMJ assessment performed prior to and during the study period. However, the large number of participants should not hide the fact that we are dealing with an underpowered sample size that was lacking 75 participants. An additional limitation is that the overall response rate of 63%, although considered acceptable, might have influenced the results because the group that did not participate was, on average, slightly younger and had a somewhat lower proportion of girls. Also, the shortened version of the DC/TMD used in this study is not directly comparable with studies having used the full DC/TMD score. In the present study, children and adolescents with JIA with TMD involvement were defined based on clinical examination, and both self-reported and parent-reported pain. Further studies will focus on the role of imaging on the diagnosis of TMJ arthritis in children and adolescents with JIA. Clinical orofacial examination may not be reliable for diagnosing disc displacement without reduction [5]. Imaging diagnosis is particularly important in JIA with non-symptomatic TMJ involvement because hard tissue loss in the condyle might hinder the growth of the mandible and subsequently affect chewing function and cause aesthetic problems [15].

Conclusion

Symptoms or clinical signs of TMD were seen in approximately half of the participants with JIA compared to about one fourth of their healthy peers. Painful palpation of masticatory muscles and decreased vertical unassisted jaw movement are more frequent in children with JIA than in healthy controls and should be part of both medical and dental routine examinations in the follow-up of JIA.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12903-020-01234-z.

Additional file 1 Table S1. Reliability tests (using intraclass correlation coefficients) between "a reference" and the examiners.

Additional file 2 Table S2. Percent agreement values between "a reference" and the examiners.

Abbreviations

DC/TMD: Diagnostic criteria for temporomandibular disorder; bDMARDs: Biological disease-modifying antirheumatic drugs; DMARDs: Disease-modifying antirheumatic drugs; sDMARDs: Synthetic disease-modifying antirheumatic drugs; ILAR: International League of Associations of Rheumatology; JIA: Juvenile idiopathic arthritis; RDC/TMD: Research diagnostic criteria for TMD; TMD: Temporomandibular disorder; TMJ: Temporomandibular joint

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Authors' contributions

JF: contributed to the conception and design of the study, agreed to be accountable for all aspects of the work and ensure questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved, was involved in writing the manuscript, and approved the final version to be published. MSS, KR, XQS, MR, PS, AR: contributed to the conception and design of the study and analysis/ interpretation of the data, were involved in drafting the manuscript and revising it critically for important intellectual content, and approved the final version to be published. SL: performed biostatistics. KT, EGG, LC, JH, LvWM, PF: contributed to data collection and provided valuable comments. All authors have read and approved the final manuscript.

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Availability of data and materials

The datasets used and analysed in the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the regional ethics committee (2012/542/REK vest). Written informed consents were obtained from the parents/legal representatives and the adolescents. The study was registered at ClinicalTrials.gov (No: NCT03904459).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

Paper II

Observer agreement of imaging measurements used for evaluation of dentofacial deformity in juvenile idiopathic arthritis.

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RESEARCH ARTICLE

Observer agreement of imaging measurements used for evaluation of dentofacial deformity in juvenile idiopathic arthritis

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Objectives: To examine the precision of imaging measures commonly used to assess mandibular morphology in children and adolescents with juvenile idiopathic arthritis (JIA). Secondly, to compare cone-beam computed tomography (CBCT) and magnetic resonance imaging (MRI) in the measurement of condylar height.
Methods: Those included were children diagnosed with JIA during 2015–18 who had had an MRI, a CBCT of the temporomandibular joints (TMJs) and a lateral cephalogram (ceph) of the head within one month of each other. Agreement within and between observers and methods was examined using Bland-Altman mean-difference plots and 95% limits of agreement (LOA). A 95% LOA within 15% of the sample mean was considered acceptable. Minimal detectable change (MDC) within and between observers was estimated.
Results: 90 patients (33 males) were included, with a mean age of 12.8 years. For MRI, intra- and interobserver 95% LOA were relatively narrow for total mandibular length: 9.6% of the sample mean. For CBCT, condylar height, both intra- and interobserver 95% LOA were wide: 16.0 and 28.4% of the sample mean, respectively. For ceph, both intra- and interobserver 95% LOA were narrow for the SNA-angle and gonion angle: 5.9 and 8% of the sample mean, and 6.2 and 6.8%, respectively.
Conclusions: We have identified a set of precise measurements for facial morphology assessments in JIA, including one MRI-based (total mandibular length), one CBCT-based (condylar height), and three ceph-based. Condylar height was higher for MRI than for CBCT; however, the measurement was too imprecise for clinical use. MDC was also determined for a series of measurements.
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Keywords: Observer agreement; Temporomandibular joint; Magnetic resonance imaging; Cone-beam computed tomography; Cephalometry

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Introduction

Juvenile idiopathic arthritis (JIA) is an autoimmune, heterogeneous condition that includes different forms of chronic arthritis of unknown origin and affects around 1–2 in 1000 under the age of 16 years.[1,2] The disease is characterised by synovial inflammation, with a potential risk of developing progressive joint destruction and severe functional disability.[1] The temporo-mandibular joint (TMJ) is more frequently involved than previously believed (in up to 78% of cases), of which a high proportion appears to be clinically silent.[3–6] TMJ arthritis is associated with all JIA subtypes, and active inflammation is often difficult to detect clinically.[7,8] Moreover, around one-third of JIA patients with TMJ arthritis with JIA onset during growth will develop mandibular growth disturbances before skeletal maturity.[9]

Monitoring mandibular growth during childhood and puberty in children with JIA and TMJ arthritis has traditionally been performed using cephalometric tracings (cephs) and their superimpositions.[10] However, evaluation of growth using two-dimensional radiographs is flawed by distortion and overlapping of 3D structures, varying magnification and issues with positioning. Thus, over the past 20 years, the method has been replaced by cone-beam CT (CBCT) in many centres, at the cost of higher radiation doses.[11] A recent paper by Maspero and colleagues comparing measurements of mandibular body length and growth by CBCT and reconstructed lateral cephalograms, the authors found that although the direct measurements differed between the two methods, mandibular growth assessment was almost identical. They concluded that two-dimensional radiographs remain the preferred method in evaluating mandibular body growth.[12] However, knowledge on the precision or accuracy of cephs or CBCT using Fryback and Thornbury's widely cited principles for radiological research is lacking.[13] They suggest a hierarchical model, where level one addresses technical image quality, level two addresses diagnostic accuracy, sensitivity, and specificity, and so on until level six, which addresses the examination's impact on social costs and benefits. The demonstration of efficacy at each lower level in this hierarchy is logically necessary but not sufficient to assure efficacy at higher levels.[13] Their statements have fuelled our efforts to examine the precision of imaging markers used in children.[14] For CBCT, validation of the measurements has mainly been performed on specimens using small datasets.[15,16] Systematic reviews on accuracy of measurements and reliability of landmark identification with CT techniques in the maxillofacial area concluded, that there is just a limited number of studies and that most studies had methodological limitations and were of moderate quality.[17,18] According to recently published guidelines for imaging of TMJs in patients with JIA, magnetic resonance imaging (MRI) of the TMJs is advised for the assessment of inflammatory change.[19,20] The potential of MRI for the evaluation of growth disturbances secondary to TMJ involvement has been addressed, using T1W 3D sequences to construct oblique sections through the mandible on which measurements are based.[21,22] By adding a T1W 3D sequence of the whole head to the TMJ protocol, we aimed to examine the precision of three MRI-derived measurements for mandibular morphology. Moreover, we examined the precision of one measurement derived from CBCT (small field of view) and commonly used ceph-measurements in a large cohort of children and adolescents with JIA. Finally, a comparison between CBCT and MRI for the measurement of condylar height was performed. The overall aim was to identify the most precise measurements for the assessment of mandibular morphology, for further use in the monitoring of mandibular growth.

Methods and materials

The present study is part of a longitudinal multicentre study addressing children and adolescents diagnosed with JIA, which was performed during 2015–2020 (NCT03904459 in www.clinicaltrials.gov).[1] The study was approved by the Regional Ethics Committee (REK number 2012/542), and written informed consent was obtained from each participant and/or a caregiver according to the national guidelines. This particular study includes a subset of 90 patients who had undergone an examination of MRI, a CBCT of the TMJs and a lateral cephalogram of the head, taken within one month of each other between March 2015 and May 2018. The patients were identified on the basis of clinical, demographic information to reflect the whole range of disease duration, JIA subgroup and severity, in order to robustly test the variables in question.

Magnetic Resonance Imaging (MRI)

All MRI examinations were performed on a 3 Tesla system (Skyra, Siemens Healthcare, Erlangen, Germany), using a 64-channel head coil (or a 32-channel in 30 patients). For the present study, a sagittal T1W magnetisation prepared rapid gradient echo (ultra-fast gradient-echo 3D) sequence (TR/TE/FA/SL = 2000/2.26/8/1) was used. Following several calibration-meetings and discussions, the images were assessed independently by two consultant radiologists using a high-resolution PACS-screen, twice (at an interval of 4 weeks) by KR and once by TAA (30 and 14 years of experience in paediatric imaging, respectively), without any other information available. The following three measurements were made: a) posterior mandibular length (Go-Co) and condylar height Co-In, b) total mandibular length Co-Gn (Figure 1).

To measure the total mandibular length, gnathion was used as origo when the multiplanar reconstruction

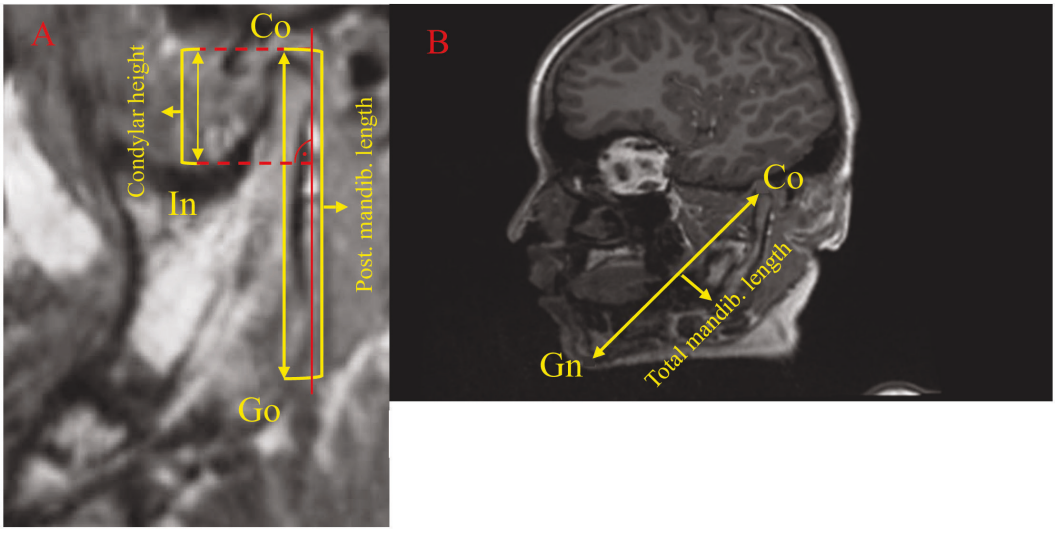

Figure 1 Constructions and both linear measurements of posterior mandibular length measured from the gonion to the top of condyle (Co-Go) and condylar height measured from the most caudal point of incisura mandibulae to the top of the condyle (Co-In). Figure 1B: Construction of total mandibular base length measured between the gnathion and the top of the condyle (Co-Gn). Co: Condyle; Go: Gonion; Gn: Gnathion; In: Incisura; Post: Posterior; Mandib: Mandibular.

(MPR) volume was reoriented to include the top of the condyle. Co-Gn was measured, and the reorientation was repeated for the contralateral side. The method for measuring the posterior mandibular length and condyle height included reorienting the volume to a ramus-corrected oblique sagittal view, and determining the ramus tangent, gonion, top of the condyle and the lowest (caudal) point of the incisura mandibulae, to then measure the Co-Gn and Co-In (Figure 1).

Cone-beam computed tomography (CBCT)
The CBCT examinations were performed on one of three CBCT machines, with kVp / mAs / field of view (mm) / voxel dimension (isotropic, mm) settings: 3D Accuitomo 170 (Morita Mfg Corp, Kyoto, Japan) 85/175/40*40*40/0.08; Promax 3D (Planmeca Oy, Helsinki, Finland) 90/13.6/200*200*60/0.40; or Scanora 3D (Soredex, Tuusula, Finland) 90/45/60*60*60/0.13. The participants were positioned in the Frankfort horizontal plane, with their teeth in maximal intercuspal position.

The images were exported together with the accompanying image viewers included in the three respective CBCT systems – Planmeca Romexis Viewer (Planmeca Oy, Helsinki, Finland); OnDemand3DApp Project Viewer Limited (version 1.0.10.4304, CyberMed, Daejeon, Republic of Korea); and iDixel One Volume Viewer (J. Morita MFG. Corp., Kyoto, Japan) – and were assessed independently by two consultant radiologists, twice (at an interval>4 weeks) by TAA and once by OWA (both with 13 years of experience). Prior to scoring, meticulous calibration was performed. Condylar height was measured in the same manner as for MRI; however, due to the limited field of view, we approximated the ramus corrected sagittal view to include the coronoid process and the ramus tangent along the posterior border at the lowermost point of the condyle or ramus included in the field of view (Figure 2).

Cephalogram (ceph)
Lateral cephs were performed using one of three different pan/ceph systems: Orthophos xg 5 (Sirona Dental Systems, Bensheim, Germany), with the following settings: 73 kVp, 15 mA, exposure times 9.7 and 9.4 sec for adolescents and children, respectively, and a magnification factor of 1.1 with a 16-bit pixel depth for all images; Promax Type Version 3.8.1.0 (Planmeca, Helsinki, Finland), kV: 62–70, mAs: 7–10 mA, 6.7 sec; and Soredex Cranex D (Helsinki, Finland) 70 kV, 10 mA, exposure time 5.8 sec. The radiographs were taken under standardised conditions with a natural head position (Frankfort horizontal line parallel to the floor) and teeth in maximal intercuspation.

Calibration of ceph-measurements
Two observers (JH and JF) underwent four calibration exercises (two on five cases and two on 30 cases – not included in the study) under the guidance of an expert (KDK), where nine measurements based on 16 anatomical landmarks were calculated (Supplementary Material S1) and (Figure 3). At the completion of the

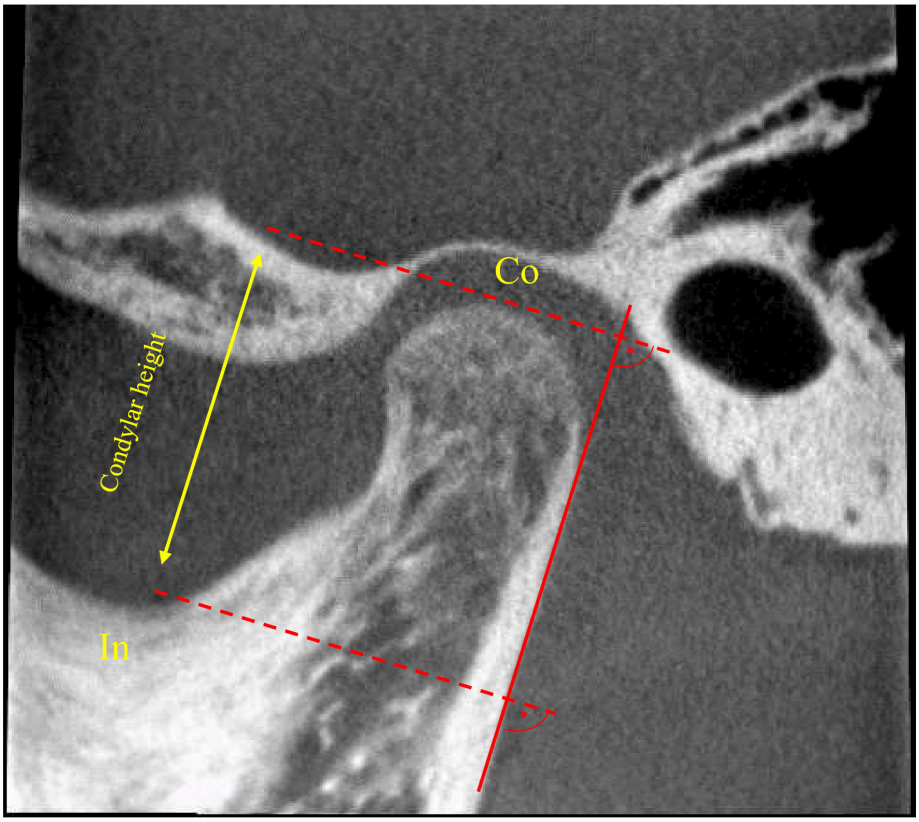

Figure 2 CBCT measurement of condylar height (Co-In). Condyle; In: Incisura

calibration phase, the bias level between observers was acceptable (Supplementary Material S2).

Statistical analysis

The normality of the data was confirmed using Q-Q plots and the Shapiro Wilks test. Agreement within and between observers and methods was analysed using Bland-Altman mean-difference plots.[23,24] The mean difference was reported as a measure of constant bias, whilst the 95% limits of agreement (95% LOA = mean difference±1.96 x standard deviation) of the differences (SD_{diff}) was reported as a measure of intra- and interobserver variation. 95% LOA was expressed in the actual units of the measurements and as a percentage relative to the mean measurement, since there was a clear dependency of the measurement variation on the mean values. The limit for clinically acceptable agreement was informally set at a 95% LOA of 15%.[25,26]

Absolute reliability was also determined by standard error of measurement (SEM) and minimal detectable change at a 95% confidence interval (MDC_{95}).[27,28] A one-way between-groups analysis of variance was conducted to explore the impact of CBCT machine type on the intraobserver variation of measurements of condylar length, right side.

All statistical analysis was performed using IBM SPSS version 26 (IBM, Chicago, IL). The level of statistical significance was set at 5% ($p \leq .05$).

The NorJIA study was approved by the Regional Ethics Committee; REK nr 2012/542. Informed consents were given by the children if ≥16 years, and by the parents if the child were <16 years. Data were collected and stored according to the General Data Protection Regulation (GDPR).

Results

90 JIA patients (33 boys and 57 girls) were included, with a mean age of 12.8 years (range 4.9–16.3 years). Among the 90 cases, 39 (43.3%) were oligoarticular, 26 (28.9%) were polyarticular, 10 (11.1%) were enthesitis-related, 3

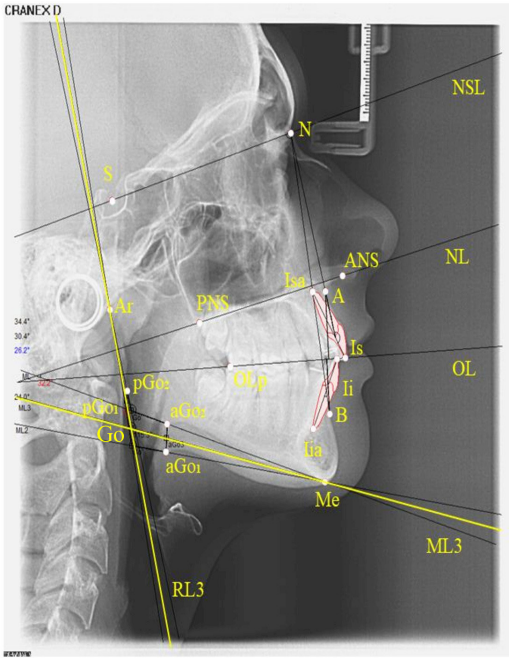

Figure 3 Geometrical redesigning of Go: Go was defined as the intersection of RL3 and ML3. RL3 was the average of two lines drawn from the point Ar to the posterior border of the left and right ramus (pGo_1 and pGo_2, respectively). Similarly, ML3 was the average of two lines drawn from the point Me to the lower border of the left and right mandible (aGo_1 and aGo_2, respectively). Point A; ANS: Anterior Nasal Spine; Ar: Articulare; B: Point B; Me: Menton; N: Nasion; OLp: Occlusal line, posterior point; pGo1+2: Posterior gonion (posterior point on ramus); PNS: Posterior Nasal Spine. S: Sella; aGo1+2: Anterior gonion (lower border of mandible). Ii: Tip of the crown of the left/right first inferior incisor. Iia: Apex of the left/ right first inferior incisor. Is: Tip of the crown of the left /right first superior incisor. Isa: Apex of the left/right first superior incisor. ML3: Mandibular line; RL3: Ramus line; Go: Gonion angle.

(3.3%) were systemic, 3 (3.3%) were psoriasis-related, and 9 (10%) were undifferentiated types of JIA. The median duration of the disease was 5.0 years (IQR 6.2, 0.4–14.4). Two JIA patients had a poor head posture and/or a lack of maximal intercuspidation at the image acquisition.

MRI measurements

The intra- and interobserver 95% limits of agreement (LOA) were relatively narrow for total mandibular length (9.6% of the sample mean, right side) (Table 1 and Supplementary Material S3). For the posterior mandibular height, both intra- and interobserver 95% LOA were wide: 17.2 and 17.3% of the sample mean, respectively. The variation within and between observers was even higher for the condylar height, with 95% LOA of 55.4 and 34.8%, respectively. The intra- and interobserver mean differences (bias) were low, ranging from 0.1 to 0.9 mm (2.0 and 18.4%) (Table 1). For individual subjects, a change in overall distance of at least 5.4 mm for mandibular length, 4.8 mm for posterior mandibular height and 5.4 mm for condylar height right side would have to be observed to confirm that a true change, beyond measurement error, has occurred (Table 1).

CBCT measurements

For the condylar height, both intra- and interobserver 95% LOA were wide: 16.0% and 28.4% of the sample mean, right side, respectively (Table 2). The intraobserver mean difference (bias) was zero (Supplementary Material S4), whilst the interobserver mean difference was 0.1 mm and 0.4 mm for right and left condyle, respectively (Table 3). MDC varied between 1.4 mm and 3.1 mm (Table 2).

Ceph measurements

For the SNA angle, both intra- and interobserver 95% LOA were narrow: 5.9 and 8% of the sample mean, respectively (Supplementary Material S5). The variation within and between observers was even lower for the SNB angle, with 95% LOA of 4.5 and 6%, respectively. The variation within and between observers was narrow for the gonion angle (RL3/ML3) (Supplementary Material S5), with 95% LOA of 6.2 and 6.8%, respectively. For the mandibular plane angle demonstrated by ML3/NSL, only the intraobserver 95% LOA was narrow with 13.4% (Supplementary Material S5). The remaining ceph-based measurements showed wide limits of agreement. The MDC varied between 1.4 ° and 7.0 ° (Table 3).

Condylar height; comparison between CBCT and MRI

Mean condylar height as measured by CBCT was 17.3 mm (SD 3.6), as compared to 19.3 mm (SD 3.6) by MRI (95% LOA = −1.3 to 5.3, right TMJ) in 52 patients who had both CBCT and MRI examinations at either baseline or at two years follow-up (Table 4).

A one-way between-groups analysis showed that the mean difference between observer one's first and second measurement was 0.01 mm for the CBCT machine in Bergen, *vs* 0.001 mm for Trondheim and 0.09 for Tromsø (p = 0.875), implying that the 95% limits of agreement did not differ significantly across different CBCTs.

Discussion

In their hierarchal model of efficacy in diagnostic imaging, Fryback and Thornbury pointed out that each level of efficacy is necessary but not sufficient to assure efficacy at higher levels such as diagnostic thinking.[13] Our study addresses the lower end of this hierarchy, namely the precision of measurements for mandibular morphology. We found little or no constant bias, but varying agreement within and between observers for

Table 1 Intra- and interobserver agreement and MDC_{95} of MRI-based measurements (mm) of total mandibular length, posterior mandibular length and condylar height in 78* children and adolescents with JIA

	OBS1 (Intraobserver) *(first* vs *second measurements)*						***OBS2 (Interobserver)*** *(OBS one* vs *OBS 2)*				
	first mean (SD)	second mean (SD)	Mean diff. (SD)	*95% LOA*	first LOA %	MDC_{95} individ.	Mean (SD)	Mean diff. (SD)	*95% LOA*	LOA %	MDC_{95} individ.
Total mandibular length Rt	112.6 (8.4)	111.7 (9.0)	0.9 (2.7)	−4.5–6.3	9.6	5.4	112.6 (7.6)	−0.2 (2.7)	−4.9–5.4	9.6	5.4
Total mandibular length Lt	112.9 (7.9)	112.4 (8.8)	0.5 (3.5)	−6.5–7.5	12.4	7.0	112.3 (7.8)	0.6 (2.9)	−5.6–6.0	10.3	5.8
Posterior mandibular length Rt	55.3 (7.0)	55.8 (6.9)	0.5 (2.4)	−4.3–5.2	17.2	4.8	55.4 (6.3)	−0.1 (2.4)	−4.3–5.3	17.3	4.8
Posterior mandibular length Lt	55.4 (6.4)	54.8 (6.5)	0.6 (2.3)	−4.0–5.2	16.6	4.6	55.4 (6.1)	0.0 (2.9)	−5.6–6.0	20.9	5.8
Condylar height Rt	19.5 (3.5)	19.0 (3.4)	0.5 (2.7)	−4.9–5.9	55.4	5.4	19.8 (3.4)	−0.3 (1.7)	−2.8–4.0	34.3	3.4
Condylar height Lt	19.0 (3.4)	19.1 (3.2)	−0.1 (2.4)	−4.6–5.0	50.5	4.8	19.8 (3.4)	−0.8 (2.2)	−3.5–5.3	44.4	4.4

Diff: Difference. LOA: Limit of agreement. Lt: Left side. MDC_{95}individ: Individual minimal detectable change. MRI: Magnetic resonance imaging. OBS: Observer. Rt: Right side. SD: Standard deviation.
* 78* 78 of the 90 children and adolescents included had MRIs available for these analyses.

a set of MRI, CBCT and ceph-based measurements commonly used for the assessment of mandibular morphology in JIA. The measurements with the highest test/retest agreement, were the ceph-based SNA, SNB and RL3/ML3, and the MRI-based total mandibular length, with LOA within 15% of the sample means.

Using SEM data, we were able to calculate the MDC at an individual level, providing a more clinically useful means of interpreting agreement. The MDC indicates the lower boundary for detectable change, whilst the MDC around the mean difference provides the LOA.[29] Thus, based on MDC from this study, we are 95% confident that differences lower than 4.6to 7 mm for the MRI-measurements of both total mandibular and posterior mandibular lengths are attributable to measurement error. In the evaluating of an intervention, one might argue that these MDC values, lying within 11% of the measured means but within 17% of the 95% LOA, are acceptable. This may well be the case, illustrating the difference between MDC and minimally clinically important differences. Thus, the a priori set limit for clinically acceptable agreement, *e.g.,* an LOA of 15%, is adjustable and obviously depends on different clinical scenarios.

Measurement of the condylar height by CBCT had a suboptimal interobserver agreement, but acceptable intraobserver agreement and MDC, whilst the MRI-based measurement was too imprecise for clinical use,

Table 2 Intra- and interobserver agreement and MDC_{95} of CBCT-based measurements (mm) of condylar height in 73* children and adolescents with JIA

	OBS1 (Intraobserver) *(first* vs *second measurements)*						***OBS2 (Interobserver)*** *(*OBS one vs OBS 2*)*				
	first mean (SD)	second mean (SD)	Mean diff. (SD)	*95% LOA*	first LOA %	MDC_{95} individ.	Mean (SD)	Mean diff. (SD)	*95% LOA*	LOA %	MDC_{95} individ.
Condylar height Rt	17.5 (3.6)	17.5 (3.4)	0.0 (0.7)	−1.4–1.4	16.0	1.4	17.6 (3.7)	−0.1 (1.3)	−2.4–2.6	28.4	2.8
Condylar height Lt	18.1 (4.1)	17.9 (3.8)	0.2 (1.1)	−2.0–2.4	24.3	2.2	18.2 (3.7)	−0.4 (1.6)	−2.7–3.5	34.1	3.0

CBCT: Cone-beam computed tomography.Diff: Difference.LOA: 95% Level of agreement. Lt, Left side ; MDC_{95}individ, Individual minimal detectable change; OBS: Observer.Rt: Right side.SD: Standard deviation.
* 73 of the 90 children and adolescents with JIA had CBCT examinations available for these analyses because the field of view (FOV) did not cover the structure of incisura mandibulae in 17 participants.

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Table 3 Intra- and interobserver agreement and MDC_{95} of cephalometric measurements in 88* children and adolescents with JIA

	OBS1 (Intraobserver) *(first* vs *second measurements)*						***OBS2 (Interobserver measures)*** *(*OBS one vs OBS 2*)*				
Angle (°), distance (mm)	first mean (SD)	second mean (SD)	Mean diff. (SD)	*95% LOA*	first LOA %	MDC_{95} individ.	Mean (SD)	Mean diff. (SD)	*95% LOA*	LOA %	MDC_{95} individ.
SNA °	81.1 (3.6)	81.5 (3.7)	−0.4 (1.2)	−2.8–2.0	5.9	2.2	81.3 (3.2)	−0.2 (1.7)	−3.5–3.0	8	3.3
SNB °	78.2 (3.4)	78.6 (3.6)	−0.4 (0.9)	−2.2–1.3	4.5	1.4	78.2 (3.1)	0 (1.2)	−2.4–2.3	6	2.2
ANB °	2.9 (2.6)	2.8 (2.7)	0.1 (1.0)	−1.8–1.9	127.6	1.9	3.1 (2.4)	−0.2 (1.0)	−2.3–1.7	125.8	1.9
ML3-NSL °	32 (6.3)	31.4 (6.3)	0.6 (1.1)	−1.6–2.7	13.4	2.2	32.3 (6.3)	−0.3 (1.3)	−3.0–2.2	16.1	2.5
ML3-NL °	24.3 (5.6)	24.5 (5.8)	−0.2 (1.3)	−2.8–2.5	21.8	2.5	24.5 (5.9)	−0.2 (1.9)	−3.9–3.7	31.0	3.6
Wits-appraisal (mm)	−2.1 (3.1)	−2.3 (3.0)	0.2 (1.2)	−2.1–2.5	−219	2.2	−1.8 (3.2)	−0.3 (1.4)	−3.0–2.4	−300	2.8
ILsNA°	23.0 (6.8)	22.5 (7.3)	0.5 (2.1)	−3.6–4.6	35.7	4.2	21.5 (6.7)	1.5 (3.5)	−5.3–8.3	63.3	7.0
ILiNB°	26.5 (7.1)	26.8 (7.3)	−0.3 (1.9)	−4.0–3.4	27.9	3.6	26.9 (7.4)	−0.4 (2.7)	−5.8–5.0	40.1	5.4
RL3ML3°	123.4 (6.8)	123.1 (6.9)	0.3 (2.0)	−3.5–4.1	6.2	3.9	124 (6.7)	−0.6 (2.2)	−4.9–3.7	6.8	4.4

ANB, Nasion-AB; Diff, Difference; ILiNB, Inclination inferior incisors to NB line ; ILsNA, Inclination superior incisors to NA line; LOA, Level of agreement; MDC95individ, Individual minimal detectable change; ML3-NL, Angle of mandibular line and palatal plane; ML3/NSL, Angle between mandibular line and cranial base; OBS, Observer; RL3ML3, Angle between posterior mandibular ramus line and the mandibular line; SD, Standard deviation; SNA, Sella-Nasion-A angle; SNB, Sella-Nasion-B angle.
[a]of the 90 children had cephalometric examinations available for these analyses. two had poor head posture and/or a lack of maximal intercuspidation at the image acquisition.

with wide variation, both for the same and between observers. Of note is that the MRI-measurement of condylar height was higher than that obtained by CBCT, which is the opposite of what was reported in a study of eight cadaver skulls, comparing MRI, CBCT and radiographs.[21] This may in part be due to slightly different planes, measurement points and image qualities, such as slice thickness. For example, Markic et al used a temporomandibular surface coil, which provided higher resolution images than the head coil used in our 3T MRI scanner.[21] Further, Markic et al reported that measurements of condylar height with MRI were comparable to those of CBCT in terms of intra- and interobserver agreement.[21] However, their 95% LOA were around 2 mm for CBCT and 4 mm for MRI for the same observer. Given a mean condylar height of around 18 mm similar to a recent study, the 95% LOA for the CBCT-based condylar height can be estimated at 10% of the sample mean, as compared to 22% for MRI, suggesting that CBCT, but not MRI, has an acceptable precision for clinical use.[21] This compares well with our results, although our 95% LOA for MRI was even higher,

Table 4 Comparison of mean condylar height (Co-In) between MRI and CBCT

	OBS1 (Intraobserver) *(first* vs *second measurements)*						***OBS2 (Interobserver)*** *(*OBS 2 MRI vs OBS 2 CBCT*)*		
	MRI n = *52*	*CBCT* n = *52*		*MRI* n = *49*	*CBCT* n = *49*		*MRI* n = *45*	*CBCT* n = *45*	
Condylar height	*first Mean (SD)*		Mean difference (95% LOA)	*second Mean (SD)*		Mean difference (95% LOA)	*Mean (SD)*	*Mean (SD)*	Mean difference (95% LOA)
Co–In Right (mm)	19.3 (3.6)	17.3 (3.6)	2.0 (-1.3–5.3)	18.9 (3.4)	17.3 (3.5)	1.6 (-7.4–10.6)	19.6 (3.6)	17.5 (3.8)	2.1 (-6.3–10.5)
	MRI *n* = 47	CBCT *n* = 47		MRI *n* = 47	CBCT *n* = 47		MRI *n* = 44	CBCT *n* = 44	
Co–In Left (mm)	19.2 (3.3)	17.8 (3.6)	1.4 (-6.0–8.8)	19.2 (3.0)	17.5 (3.7)	1.7 (-5.7–9.1)	19.9 (3.6)	18.3 (4.1)	1.6 (-7.8–11.0)

CBCT: Cone-beam computed tomography. LOA: Level of agreement. MDC_{95}individ: Individual minimal detectable change. MRI: Magnetic resonance imaging. OBS: Observer. SD: Standard deviation.

up to 55%. In another comparative study including 18 adults, with a mean age of 37.8 years, CBCT performed better than MRI with regard to intra- and interobserver variation for a set of direct measurements and angles, using the Mimics Research program.[22] The interobserver intraclass correlation (ICC) for mandibular body length was excellent (ICC = 0.95) for CBCT and only moderate (ICC = 0.74) for MRI. However, there was no information on the absolute reliability, such as the limits of agreement or MDC, thus, preventing a direct comparison with our results.[22]

High interobserver variations were found for condylar height based on both CBCT and MRI, and for MRI-measurements of posterior mandibular length and condylar height. The wide variation might be explained by the fact that we oriented the CBCT and MR volumes to reconstruct the multiplanar views prior to all measurements – *i.e.,* we identified the landmarks during each of the reading sessions. Previous 2D and 3D analyses have shown that condylar height represents one of the most critical measurements in assessing dentofacial growth deviation.[30] In their radiographic study, Kjellberg and colleagues found significantly shorter relative condylar height in 35 children and adolescents with JIA (aged 7–16 years) compared to their healthy peers; however, their results were based on condylar ratio and not on linear measurements.[31] In their reliability and validity study of 23 3D measurements, Stoustrup and colleagues identified, and highly recommended seven measures for the study of dentofacial growth in JIA.[32] In addition, they recommended several additional measures, including condylar height.

Studies have shown that identifying landmarks introduces errors that contribute to measurement inaccuracy.[33] Our results contrast with those of Ludlow et al in a study of 20 patients, which show that landmark identification with CBCT- MPR was accomplished with less variability than conventional ceph, implying that MPR-based measurements are more precise than measurements based on cephalograms.[34]

Similarly, some authors suggest that measuring directly on the 3D surface-rendered CBCT images introduces higher variability of certain landmarks – *e.g.,* in the mediolateral direction, probably related to the inadequate definition of the landmarks in the third dimension.[35] Baumrind, Broch and colleagues argued that cephalometric landmarks-based measurements such as edges are easier to localise, whereas landmarks placed on curves showed a higher measurement error.[36,37] Taken together, the body of studies published on the reliability of both ceph and CBCT is heterogeneous with respect to design and statistical analysis used; thus, the results are difficult to compare (Supplementary Material S6).

Several of the measurements obtained from conventional cephalograms, *i.e.,* the SNA, SNB, gonion angle (RL3/ML3), showed high precision and small MDC, which is a finding that has also been reported for these measurements obtained from MPRs derived from volumetric CBCT scans.[22,38] Conversely, poor precision was found for the remainder of the measurements – for example, an intraobserver LOA as high as 127.6% of the measured mean for the ANB angle. The poor precision of ANB can, in part, be explained by its small value, but more crucial; point A is more challenging to locate than point B.[39,40] Moreover, numerous studies have shown that dental landmarks tend to have poorer validity than skeletal landmarks.[41,42] Kamoen et al addressed the high variability of landmark identification, and the cumulative effect of errors in a study of 50 cephs.[43] In our study, the clinical acceptance of the Wits appraisal is insufficient. This measurement is determined by perpendiculars from points A and B to the occlusal plane, and any change in the occlusal plane enhances the measurement error.[44] The clinical implication and the use of these variables to detect actual treatment effects can be questioned, but the literature reveals that the clinical significance is usually regarded as a difference of less than one or two measuring units.[45] Clinical relevance becomes more evident using the Bland-Altman approach when reporting on differences between observers and methods, rather than on relative reliability, such as the ICC or paired t-test.[42,46] Hitherto, few cephalometric studies and TMJ-imaging studies have tested the precision of CBCT and MRI-measurements applying the Bland-Altman mean-difference plots and 95% LOA (Supplementary Material S6). Thus, further studies addressing the accuracy of commonly used measures for morphological assessment of the mandibular complex in children and adolescents with JIA.

Our study has several limitations. Firstly, there is the subjective nature of identifying the landmarks with inherent biases in the reader's past experiences and understanding of the images. We endeavoured to overcome this by hosting several calibration sessions between all readers prior to scoring and analysis. Our study does not address the clinical validity of the measurements; however, this was not our intention, which was instead to primarily examine whether adding a 3D anatomical sequence to the routine MRI protocol for TMJ-imaging might provide precise measurements of dentofacial deformity, with the view to then assessing these for clinical validity.[13] Similarly, we intended to test the precision of one CBCT-based measurement derived from a routine examination with a small field of view, as well as commonly used cephalometric-based measurements. The strengths of this study include the reasonably high numbers, the thorough calibration process, and the multireader aspect of our data analysis.

Conclusion

We have identified a set of precise radiological measurements for the assessment of dentofacial deformity in JIA. The measurements include one MRI-based, one CBCT-based and three ceph-based, in the hope that these can be helpful for studies that assess clinical

validity and long-term patient outcomes. MRI-based measurement of condylar height was higher than that obtained by CBCT; however, the measurement was too imprecise for clinical use. Moreover, we have determined the MDC for a set of measurements.

Acknowledgment

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S1. Definitions of craniofacial degrees, planes and distances.

	Morphometric measures	Definition	Landmarks*
MRI	Total mandibular length	Measured between the most cranial point of the condyle (Co) and the most anterior/inferior border of the chin in the mandibular midline (Gn)	Co-Gn
	Posterior mandibular length	Measured between the most cranial point of the condyle (Co) and the intersection point with the lower border of the ramus (Go)	Co-Go
	Condylar height	Measured between the most cranial point of the condyle (Co) and the most caudal point of the incisura mandibulae (In)	Co-In
CBCT	Condylar height	Measured between the most cranial point of the condyle (Co) and the most caudal point of the incisura mandibulae (In)	Co-In
CEPH	Sella-Nasion-A angle	The angle between Nasion-Sella and the Nasion-A lines	SNA
	Sella-Nasion-B angle	The angle between Nasion-Sella and the Nasion-B lines	SNB
	Nasion-AB	The angle between point A-Nasion and point B	ANB
	Mandibular plane angle	The angle between the mandibular line and the cranial base	ML3/NSL
	Interbasal angle	The angle between the mandibular line and the palatal plane	ML3/NL
	Wits appraisal	Distance between A-point and molar coronal construction plane (minus) distance B-point to molar coronal construction plane	AO-BO
	ILsNA	Inclination of the upper incisors in relation to NA line	ILsNA
	ILiNB	Inclination of the lower incisors in relation to NB line	ILiNB
	Gonion angle	The angle between the posterior ramus line Ar-pGo (RL) and the mandibular line Me-aGo (ML)	RL3ML3

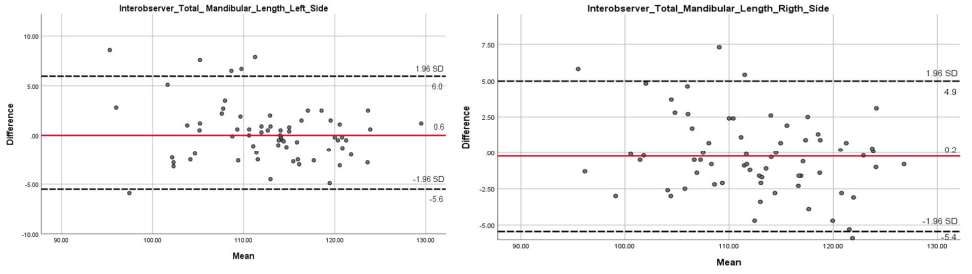
** The Landmarks are abbreviated in Figure 3*

S2. Level of bias interobserver-calibration

	SNA	SNB	ANB	ML3/NSL	ML3/NL	RL3/ML3	Wits	ILs/NA	ILi/NB
Bias	0,376667	0,433333	-0,05667	-0,19333	-0,17	-0,12667	0,296667	1,133,333	-0,95667
stan dev	2,910,209	3,689,902	2,652,104	5,500,646	4,546,971	6,078,946	2,770,537	8,802,102	5,349,621
Lower LOA	-532,734	-679,888	-525,479	-109,746	-908,206	-120,414	-513,359	-161,188	-114,419
Upper LOA	6,080,677	7,665,542	5,141,458	9,528,591	9,528,591	9,528,591	9,528,591	9,528,591	9,528,591

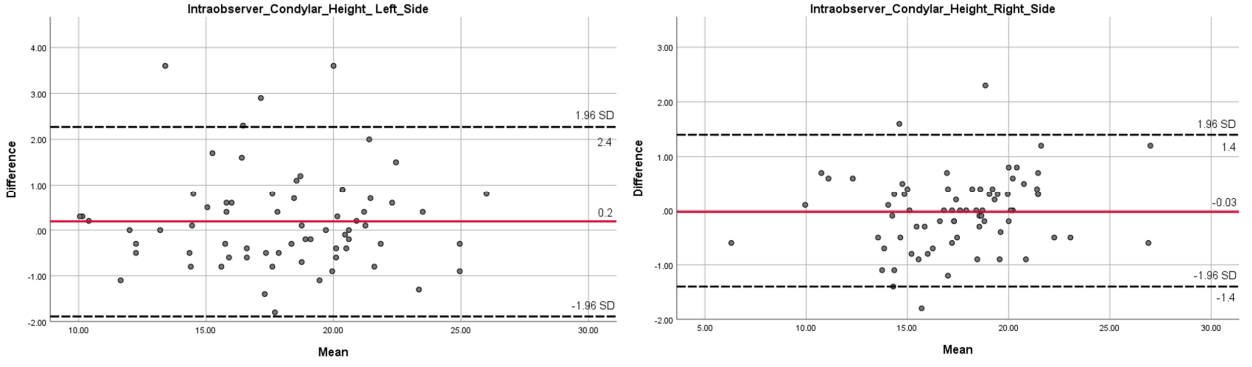
30 children and adolescents with JIA included had Ceph`s available for these analyses
Stan dev: Standard deviation. LOA: Level of agreement.

S3 Bland-Altman plot of MRI-measurements.



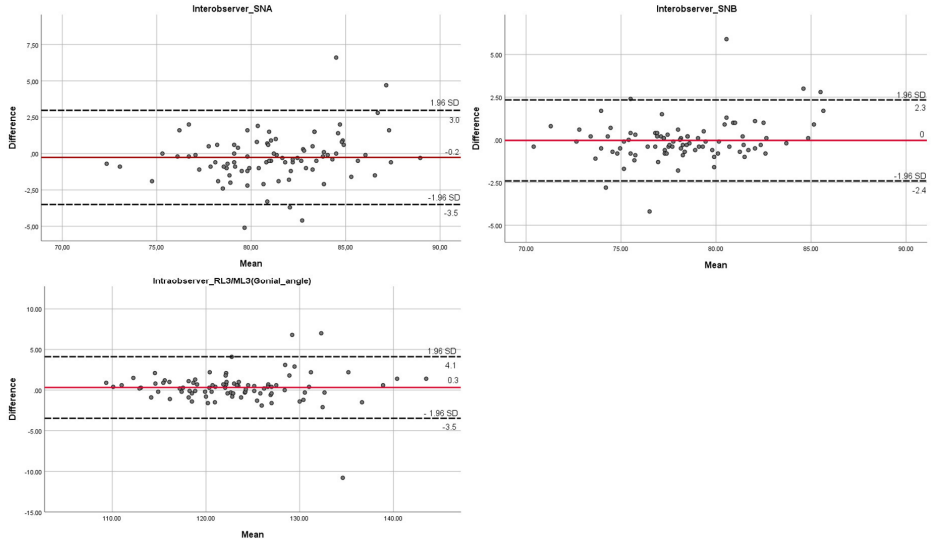
S2. Bland–Altman plots of agreement between left and right side. Differences and means given in millimetres. Single red bold line = mean difference; paired black bold dashed lines = 95% limits of agreement lower and upper bounds of 95% confidence. MRI: Magnetic resonance imaging.

S4 Bland-Altman plot of CBCT-measurements. Differences and means given in millimetres.



S3 Single red bold line = mean difference; black bold dashed lines = 95% limits of agreement lower and upper bounds of 95% confidence. Differences and means given in millimetres. CBCT: Cone-beam computed tomography.

S5 Bland-Altman plot of ceph-measurements.



S4 Single red bold line = mean difference; black bold dashed lines = 95% limits of agreement lower and upper bounds of 95% confidence. Differences and means given in millimetres.
Ceph: Cephalometric.

S6 Overview of intra- and interobserver articles using Bland-Altman mean plot and 95% (LOA) in children and adolescents

Author	Number of participants	Mean age years (range)	Design and images used	Outcome	Statistics	Results 95% LOA
Angenete O. 2021	86	n/a (4-16)	Selected participants from a prospective, longitudinal observational study	Precision of 25 measurements	Cohen`s Kappa, 95% LOA, Bland Altman	11 precise out of 25 measurements for scoring system. Most precise MRI marker interobserver Kappa value (95% CI) Loss of condylar volume: 0.78 (0.62-0.94) Joint fluid: 0.71 (0.48-0.95) Synovial enhancement: 0.54 (0.4-0.69) Bone marrow oedema: 0.54 (0.28-0.80)
Maspero C. 2020	25	♂12.3 ♀ 8.9 (n/a)	Retrospective Comparing CBCT-MPR and reconstructed. CEPH (RCL)	Precision CBCT and RCL	Coeff. var ICC Bland-Altman	15.1 - 7.9 right side 15.3 - 8.5 15.9 - 7.4 left side 15.5 - 8.2
Juerchott A. 2020	12	26.1 (17 - 40)	Comparing MRI-MPR and CBCT-MPR in 3D ceph	Precision of 35 measurements	ICC Bland-Altman	Intermodal agreement Angular measures (-1.4, 1.5) Linear measures (-1.4, 1.4)
Kellenberger C. 2019	18	15.1 ♀ (11.9- 19.2)	Retrospective comparative assessment of contrast enhanced TMJ MRI	To compare morphology and inflammation between 36 TMJs with ADD and 36 TMJs with JIA	Bland-Altman t-test, Chi^2 -test	−1.3 to 1.4 mm −5.9° to 8.9°
Heil A. 2017	21	13.9 (8 - 26)	Prospective Comparing ceph and MRI	Precision of 24 measurements	ICC Bland-Altman plot analysis	Angular measures (-7.2, 4.5) Linear measures (-3.7, 3.1)
Koerich de Paula 2015	10	12.9 (11 - 15)	Comparing magnification and superimposition between CBCT-generated hemifacial and full-face LC to conventional LC	Reproducibility of 15 angles	ICC Bland-Altman plot analysis	Intraexaminer (-4.5, 4.6) Intraexaminer (-7.5, 5.7) Intraexaminer (-4.4, 5.6) Intraexaminer (-4.4, 2.0)

Liedtke G. 2012	30	17.5 (n/a)	Prospective Comparing ceph with total/half skull CBCT-MPR	Precision of 40 ceph factors	ICC Bland-Altman	Angular measures (-10.4, 9.8) Linear measures (-7.0, 6.9)
Swennen 2004	40	10.2 (9.2 - 11.0)	Retrospective evaluation of craniofacial morphology and growth patterns in patients with clefts.	Accuracy, reliability, and validity of 16 angles and 16 distances	Bland-Altman plot analysis	ss-n(s)-pog(s) was within 95% prn-sn-ls, 67.5% were outside of the 95% LOA

ADD: Anterior disk displacement. CBCT: Cone-beam computed tomography. CI: Confidence interval. Ceph: Cephalogram. Coeff var: Coefficient of variation. ICC: Intra-class correlation coefficient. LC: Lateral cephalogram. LOA: Level of agreement. MPR: Multiplanar reconstruction. MRI: Magnetic resonance imaging. RLC: Reconstructed lateral cephalogram. SD: Standard deviation. ss-n(s)-pog(s): Maxillary prominence. prn-sn-ls: Nasolabial angle.

Paper III

In children and adolescents with temporomandibular disorder assembled with juvenile idiopathic arthritis - no association were found between pain and TMJ deformities using CBCT.

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RESEARCH ARTICLE

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In children and adolescents with temporomandibular disorder assembled with juvenile idiopathic arthritis - no association were found between pain and TMJ deformities using CBCT

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Abstract

Background: Children and adolescents with juvenile idiopathic arthritis (JIA) may suffer from temporomandibular disorder (TMD). Due to this, imaging diagnosis is crucial in JIA with non-symptomatic TM joint (TMJ) involvement. The aim of the study was to examine the association between clinical TMD signs/symptoms and cone-beam computed tomography (CBCT) findings of TMJ structural deformities in children and adolescents with JIA.

Methods: This cross-sectional study is part of a longitudinal prospective multi-centre study performed from 2015–2020, including 228 children and adolescents aged 4–16 years diagnosed with JIA, according to the International League of Associations for Rheumatology (ILAR). For this sub-study, we included the Bergen cohort of 72 patients (32 female, median age 13.1 years, median duration of JIA 4.5 years). Clinical TMD signs/symptoms were registered as pain on palpation, pain on jaw movement, and combined pain of those two. The severity of TMJ deformity was classified as sound (no deformity), mild, or moderate/severe according to the radiographic findings of CBCT.

Results: Of 72 patients, 21 (29.2%) had pain on palpation at and around the lateral pole, while 41 (56.9%) had TMJ pain upon jaw movement and 26 (36.1%) had pain from both. Of 141 TMJs, 18.4% had mild and 14.2% had moderate/severe structural deformities visible on CBCT. CBCT findings were not significantly associated with either the pain on palpation or the pain on jaw movement. A significant difference was found between structural deformities in CBCT and the combined pain outcome (pain at both palpation and movement) for both TMJs for the persistent oligoarticular subtype ($p = 0.031$).

Conclusions: There was no association between painful TMD and CBCT imaging features of the TMJ in patients with JIA, but the oligoarticular subtype of JIA, there was a significant difference associated with TMJ pain and structural CBCT deformities.

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Keywords: Juvenile idiopathic arthritis, Temporomandibular joint arthritis, Temporomandibular disorder, Temporomandibular joint deformity, Cone-beam computed tomography

Background

Juvenile idiopathic Arthritis (JIA) is a heterogeneous condition that includes all forms of chronic arthritis of unknown origin with a duration of more than six weeks and an onset before 16 years of age [1, 2]. The reported prevalence is around 1–2 per 1000 children with girls more frequently affected than boys [3–5], and the condition is characterized by chronic synovial inflammation, with potential risk of developing progressive joint destruction and serious functional disability [1, 6, 7]. JIA includes seven subtypes (systematic arthritis, oligoarthritis (persistent or extended), rheumatoid factor negative polyarthritis, rheumatoid factor positive polyarthritis, psoriatic arthritis, and enthesitis-related arthritis) with different (though overlapping) characteristics. The estimated prevalence of temporomandibular joint (TMJ) arthritis in children and adolescents with JIA varies widely between 17 and 92%, of which a high proportion of cases appear to be clinically silent [8, 9]. TMJ arthritis is often combined with temporomandibular disorder (TMD), which is defined as muscular tensions from the surrounding muscles, or inflammation and/or destructive deformities in the TMJs of these patients, or a combination of the two [10]. Children and adolescents with JIA are more likely to suffer from TMD than their healthy peers, which means that children and adolescents with JIA are more likely to have impaired oral health [11–14]. In a recently published article from our multicentre study, we found that 40% of patients with JIA aged 6–16 years old experienced TMD [15]. An even higher TMD figure of 83% was reported in a cohort of Brazilian adolescents with JIA [16], while a Danish study revealed that 38–53% of patients with JIA (median age 6.6 years) experienced orofacial symptoms and dysfunction due to TMJ arthritis and/or muscular tensions [17]. Cone-beam computed tomography (CBCT) has been used as a 3D diagnostic modality for nearly two decades [18, 19] and the radiation doses are of this method are, in general, lower than that of conventional CT. For TMJ screening, CBCT imaging has been reported to require a 30% lower dosage and give a better image quality than CT [20]. In a retrospective study by Cho and colleagues including 282 children and adolescents aged 10 – 18 years, the authors found an association between TMJ condylar deformities and TMJ symptoms or reduced mouth opening capacity [21]. Another CBCT-based study showed that children and adolescents (10–19 years) with TMD had more erosive cortical bone changes than same-aged pre-orthodontic controls with malocclusion [22], and the same study also highlighted that pre-orthodontic participant with malocclusion presented solid radiographic signs. Although CBCT is the method of choice for assessing TMJ deformity, examples of CBCT use in children and adolescents with JIA-associated TMD are sparse. JIA may result in TMJ deformity and affect mandible development as well as chewing function. Therefore, early diagnosis and treatment of TMJ deformity are of clinical importance. However, there are no diagnostic guidelines available on whether CBCT is indicated for JIA patients or for which group of patients it is indicated. Clinical symptoms may serve as predictors for justified CBCT examination.

Therefore, the aim of this study is to examine the association between clinical signs/symptoms of TMD and structural TMJ deformities found from CBCT in this patient group.

Methods

We followed the strengthening the reporting of observational studies in epidemiology (STROBE) reporting guideline. This cross-sectional study is part of a longitudinal prospective multi-centre study performed from 2015–2020, including 228 children and adolescents aged 4–16 years, diagnosed with JIA according to the International League of Associations for Rheumatology (ILAR) [1]. Excluded from the study were those with congenital facial anomalies and/or major medical co-morbidities and those who did not consent to participate. The unselected material was retrieved from the Bergen NorJIA cohort of children and adolescents with JIA (n = 72) from 2015–2017 and included standardized assessments of TMD as part of a broader oral health examination.

Clinical TMD examinations were performed by using a shortened version of the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) Axis I [23] and the self-assessment questionnaire recommended by TMJaw for clinical TMJ assessment in patients diagnosed with JIA [24]. The reason for this combination of diagnostic tools is that the DC/TMD tool alone is reported to have weak validity for TMJ assessment. Therefore, this tool can also identify disc displacement (low sensitivity) and degenerative joint disease (low sensitivity and specificity). To avoid systemic error, reliability results from various calibration exercises in TMD diagnostic prior to and during the study period are described in our previous publication [15].

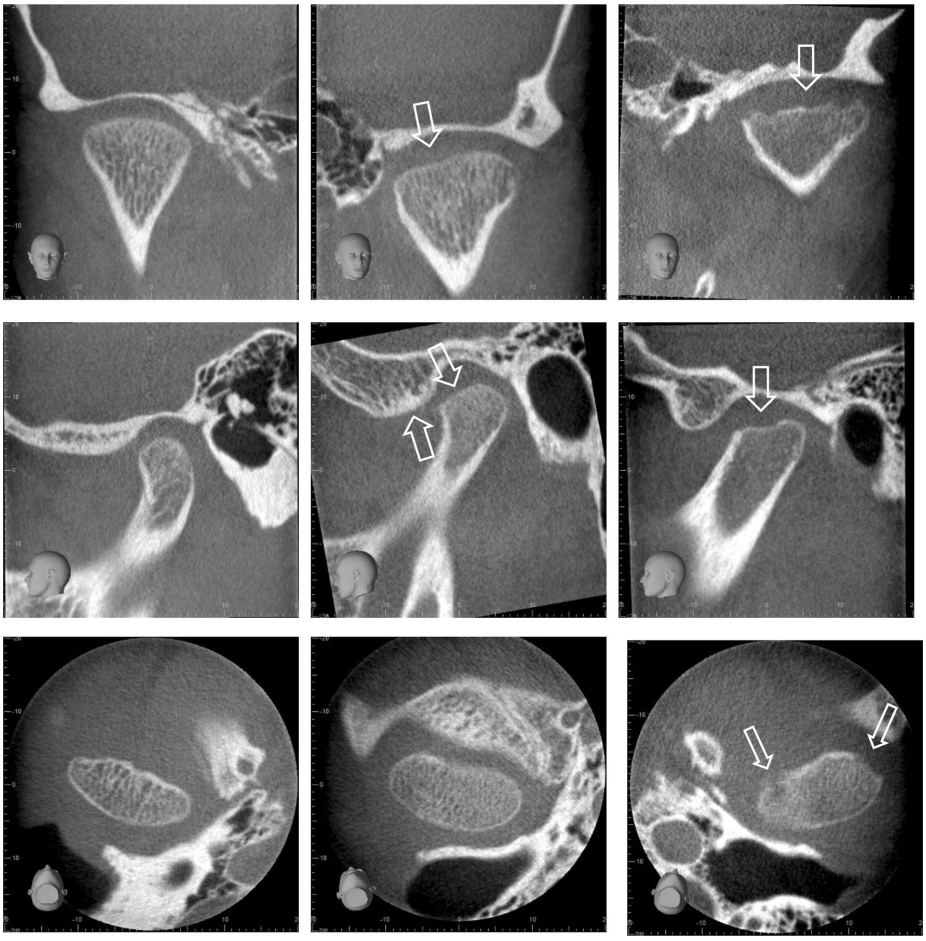

Fig. 1 Examples of temporomandibular joint (TMJ) deformity on cone-beam computed tomography (CBCT)

During clinical examination, we determined whether there was pain on direct palpation at and around the lateral pole. Moreover, we asked the patient whether he/she currently experienced TMJ and masticatory muscle symptoms on vertical, lateral, and or protrusive jaw movements, and we also registered combined pain (pain on palpation and pain on jaw movement). The CBCT examination was performed using a 3D Accuitomo 170 (Morita) with a field of view of 4×4 cm and a voxel size of 80 µm. The exposure parameters were adjusted for each individual patient. All images were exported into iDixel One Volume Viewer (Version 2.6.0 Morita), and analysed by an experienced paediatric radiologist (TAA, 13 years of experience in paediatric imaging) with additional information in the image masked. The overall impression of TMJ deformity was categorized into one of three groups based on the radiographic appearance in the condyle and temporal parts: sound = normal anatomical variation, mild = slight flattening of the fossa/eminence or condyle, or minor joint surfaces irregularities, moderate/severe = apparent deformation of fossa/eminence or condyle, apparent reduction of condyle volume or more severe joint surface irregularities. Examples of typical cases are shown in Fig. 1.

Statistical methods

Descriptive statistics were reported as mean with SDs, percentages, or median (ranges). For analyses, we dichotomized the TMJ deformity variable to absent or present due to low number of cases in the mild and moderate/severe groups. Associations between localized pain (TMD) and structural deformities visible in CBCT were examined using Fisher's exact/chi-square test and an independent/two-sample t-test as appropriate. Statistical analyses were performed using SPSS version 25 (IBM Corporation, New York, NY, USA). All tests were two-sided and statistical significance was set at 5% ($p \leq 0.05$).

Ethical considerations

Ethical approval for this study was obtained from the Regional Committee For Medical And Health Ethics (REC west), Universitetet i Bergen, Det medisinske fakultet, Postboks 7804, 5020 Bergen, reference number: 2012/542/REC west. Written informed consent was obtained from the parents or legal representatives of the children and adolescents. The study was registered in ClinicalTrials.gov (No: NCT03904459).

Results

A total of 72 children and adolescents (44% girls) and a median age of 13.1 years (range 5.9–16.5 years) were included (Table 1). The most prevalent ILAR categories were persistent oligoarthritis, present in 31 (43.7%) of the participants, and rheumatoid factor negative polyarthritis (RF-negative), present in 14 (18.3%) of the participants. None had rheumatoid factor positive polyarthritis. No statistically significant differences in the presence of TMD according to JIA category were observed ($p = 0.837$).

Outcome on patient level

Twenty-one of the 72 participants (29%, 12 girls) experienced pain on palpation at and around the lateral pole, while 41 (56.9%) reported TMJ pain on jaw movement (Fig. 2). Eighteen (25.0%) of the participants were positive to both findings. The reason for the inconsequent adding of the numbers are since the mentioned categories overlap and are not mutually exclusive. Mild or moderate/severe TMJ deformity was found in 19 of the 51 (26.4%) participants without pain on palpation at and around the lateral pole, while mild or moderate/severe TMJ deformity was found in 8 of the 21 (11.1%) patients with pain ($p = 0.711$). TMJ deformity was seen in 10 of the 31 (13.4%) participants without pain on jaw movement but 17 of 41 patients (23.6%) had pain ($p = 0.333$). No association was seen for either palpatory pain or for pain upon jaw movement between boys and girls ($p = 0$ 0.164, $p = 0.588$) and between right and left or both TMJ ($p = 0.784$, $p = 0.237$). CBCT findings grouped according to pain on palpation and painful jaw movement for right and left side (separately) are presented in detail in Figs. 3 and 4. The distribution of painful palpation of TMJs, painful jaw movements, and structural deformities is presented in Additional file 1: Table S1. Seventeen participants had CBCT findings of deformities in both TMJs, 12 of whom were girls ($p = 0.018$).

Outcome on joint level

Of 141 TMJs, 18.4% showed mild and 14.2% showed moderate/severe TMJ deformity visible in CBCT. No

Table 1 Characteristics of participants with juvenile idiopathic arthritis (JIA) in relation to temporomandibular disorder (TMD)

	Bergen cohort n = 72	TMD* n = 46	No TMD n = 26	p-value**
Girls, n (%)	32.0 (44.4)	21.0 (29.2)	11.0 (15.3)	0.784
Age at JIA onset, median (IQR)	7.0 (7.6, 3.0–10.7)	7.5 (7.3, 3.3–10.6)	6.6 (8.5, 2.6–11.1)	0.759
Age at clinical investigation, median (IQR)	13.1 (4.9, 10.2–15.1)	12.9 (4.3, 10.6–14.9)	13.6 (7.6, 7.8–15.4)	0.721
Disease duration, median (IQR)	4.5 (5.5, 2.2–7.7)	4.6 (5.5, 2.2–7.7)	4.1 (5.8, 2.1–8.0)	0.979
JIA categories, n (%)				
Oligoarthritis persistent	31.0 (43.7)	19.0 (39.1)	12.0 (52.0)	0.837
Oligoarthritis extended	6.0 (8.5)	3.0 (6.5)	3.0 (12.0)	
Systemic arthritis	1.0 (1.4)	1.0 (2.2)	0.0 (0)	
RF-negative polyarthritis	14.0 (18.3)	9.0 (19.6)	5.0 (16.0)	
Psoriatic arthritis	2 (2.8)	1.0 (2.2)	1.0 (4.0)	
Enthesitis-related arthritis	7.0 (9.9)	6.0 (13.0)	1.0 (4)	
Undifferentiated JIA	11.0 (15.5)	7.0 (17.4)	4.0 (12.0)	

* TMD is defined by painful palpation at or around the lateral pole of the TMJ and/or symptoms of painful jaw movements

** Chi^2 -test/Student's t-test

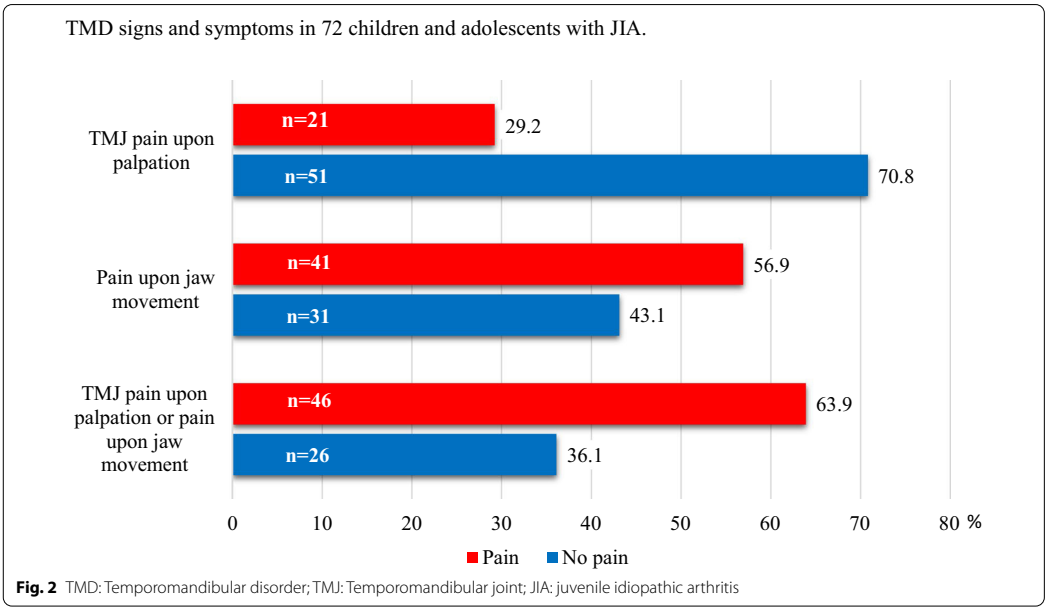

Fig. 2 TMD: Temporomandibular disorder; TMJ: Temporomandibular joint; JIA: juvenile idiopathic arthritis

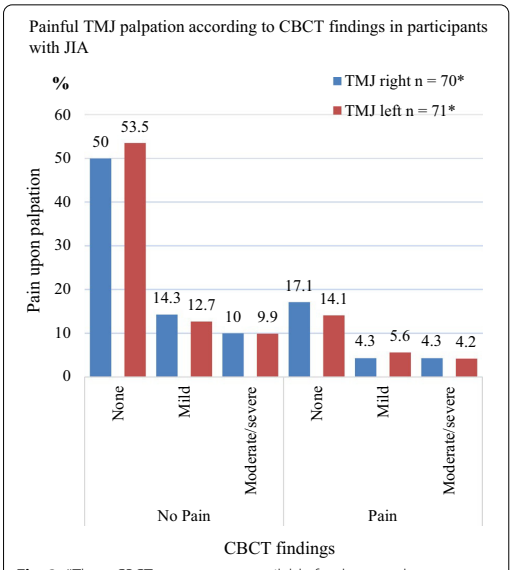

Fig. 3 *Three CBCT scans are not available for these analyses because the field of view did not cover the relevant structures. CBCT: Cone-beam computed tomography; TMJ: Temporomandibular joint

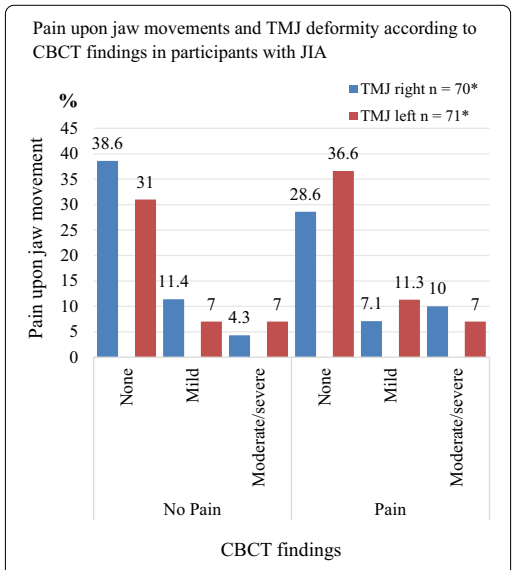

Fig. 4 *Three CBCT scans are not available for these analyses because the field of view did not cover the relevant structures

statistically significant associations were seen between pain on palpation and TMJ deformity visible in CBCT ($p=0.96$ right side and $p=0.38$ left side, respectively), or between pain on jaw movement and CBCT findings ($p=0.45$ right side and $p=0.84$ left side). No association between TMJ deformity and combined pain outcome (pain on both palpation and jaw movement) was seen, with p-values of 0.603 and 0.067 for the right and left TMJ, respectively. Statistical significance was found between CBCT findings and a combined pain outcome (pain at both palpation and jaw movement) in both TMJs for the persistent oligoarticular subtype ($p=0.031$).

Discussion

We have shown that nearly one-third of patients with JIA had pain on palpation at and around the lateral TMJ-pole, and that nearly 60% experienced painful jaw movements. Moreover, assessment by CBCT showed that one-third of the TMJs in these patients was associated with structural deformities, more often in girls than in boys. No associations were seen between pain on palpation of TMJs or painful jaw movements and structural deformities visible with CBCT. The persistent oligoarticular subtype of JIA revealed an association between structural deformities visible with CBCT and clinical signs and symptoms.

The lack of association between clinical signs/symptoms and structural deformity on CBCT in patients with JIA is in line with previous studies that used panoramic radiography as a diagnostic modality [25–27]. In addition, two older studies concluded that asymmetries of mandibular condyles and rami are part of the expected morphological variation in healthy children and adolescents [28, 29], and facial development that might be thought of as disadvantageous may be prevalent among healthy children without a diagnosis of JIA [30]. Only a few CBCT studies have examined structural changes and condylar 3D asymmetry in young individuals with JIA [31–33]. One case–control study of 23 patients with JIA (14 girls, mean age 13.6) using CBCT reported that 83% of the participants had severe structural changes, including cases of extreme deformity even if asymptomatic [31], although the authors did not categorize the extent of JIA.

In this study, we were able to define TMJ deformity in CBCT as either mild or moderate/severe because bony deformities on the condylar surfaces of young individuals are readily detectable using CBCT scans [34, 35]. Other studies have reported differences in terms of condylar flattening [16, 36, 37]. For example, a study of 15 young patients with JIA (mean age 16.3 years old) found signs and symptoms suggestive of TMD in 25 of the 30 TMJs, of which 67% showed condylar flattening based on CBCT scans of 1 mm slice thickness [16]. Similarly, Urtane and colleagues found that 95% of 65 patients with JIA (10–17 years old) had condylar surface flattening based on an even lower slice thickness of 0.3 mm and that there was a correlation (although weakly supported) between pain and condylar surface flattening visible in CBCT imaging [37]. Both studies depicted numerous CBCT scans with distinct anterior condylar flattening but neither of them analysed nor particularly highlighted this flattening. We would argue that this condylar flattening might represent normal variations, as previously shown in several studies [38–40]. In their recent study of panoramic radiographs of 65 children (mean age 12 years old), Cedströmer and colleagues pointed out that even minor bony deformities might hamper craniofacial development [41]. However, our study shows that there is a significant difference between the oligoarticular and polyarticular subtypes. Similar to the results reported by Twilt and colleagues in their panoramic radiograph study of 89 patients (mean age 11.5 years), TMJ deformity was more prevalent when arthritis had an oligoarticular and RF-negative course [42]. Divergent results for condylar deformities that have been generally reported in the literature are probably due to the use of different scoring systems and different patient populations [26, 43, 44]. Previous studies have also shown that TMJ symptoms and signs are not always predictive of TMJ arthritis or TMJ deformity [45, 46]. For example, asymptomatic patients with structural TMJ deformities were reported in a panoramic radiograph study by Billiau and colleagues (26), which included 46 patients (median age at 9.33 years), 28% of whom exhibited condylar deformity without clinical signs or symptoms, which is similar to our study results [26]. However, their study was based on the research diagnostic criteria RDC/TMD [47], which has been validated for ages 18 years and higher, and the young persons in our study were younger than that. A recent MRI study of 50 patients with JIA (9–16 years old) combined clinical variables related to pain and function, and observed TMJ deformity in 9 of 10 patients [48].

In their retrospective CBCT study of 19 JIA and 19 patients with idiopathic condylar resorption (both groups with a mean age of 15.3 years old), Alimanovic and colleagues [49] reported that 55.2% patients of the JIA cohort presented subjective TMJ symptoms, and 42.1% had pain upon TMJ palpation, similar to our results (Figs. 3 and 4). Furthermore, that paper showed that mildly deformed condyles were the most common CBCT finding in both JIA and idiopathic condylar resorption. In their comparative MRI study of 18 JIA patients and 18 patients with anterior disk displacement (ADD) (both groups 11–19 years old), Kellenberger and colleagues (46) reported significantly more TMJ pain upon clinical examination in the ADD-cohort than in JIA. However, deformity in terms of flattening of condylar and

temporal bone was more present in the JIA-cohort, and 72% of these had reduced glenoid fossa depth [50]. Those findings corroborate that TMJ arthritis in JIA may often be asymptomatic [51, 52]. Therefore, it is still unknown whether symptoms and signs originating from TMJ arthritis are associated with TMJ deformity.

Our study had some limitations. First, the number of patients with CBCT findings of structural deformities was relatively low. Second, we used a relatively crude CBCT score. The strengths are the meticulous calibration and standardization work performed for both TMD and CBCT assessments. Nonetheless, for this group of patients, longitudinal, prospective studies should be performed to evaluate deformities in pathologies of the TMJ over time.

Conclusions

There was no association between painful TMD and CBCT imaging features of the TMJ in patients with JIA, but in the subtype of JIA, persistent oligoarticular type, it was found statistical significance between symptoms and signs of TMJ pain and structural CBCT deformities.

Abbreviations

ADD: Articular disk displacement; CBCT: Cone-beam computed tomography; DC/TMD: Diagnostic criteria for temporomandibular disorder; ICR: Idiopathic condylar resorption; ILAR: International league of associations of rheumatology; JIA: Juvenile idiopathic arthritis; MRI: Magnet resonance imaging; RDC/TMD: Research diagnostic criteria for TMD; TMD: Temporomandibular disorder; TMJ: Temporomandibular joint; TMJaw: Temporomandibular Joint Juvenile Arthritis group.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12903-021-01870-z.

Additional file 1. Painful and painless TMJs upon jaw movement and palpation according to ILAR categories.

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Authors' contributions

JF conceived and designed the study, agreed to be accountable for all aspects of the work, ensure questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved, was involved in writing the manuscript, and approved the final version to be published. TAA, OA, MSS, KR, XQS, and AR contributed to the study design, analysed and interpreted data, were involved in drafting the manuscript and revising it critically for important intellectual content, and approved the final version to be published. KT, EGG, and ANÅ collected data and provided valuable comments. All authors have read and approved the final manuscript.

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Availability of data and materials

The datasets generated and analysed in this study are not publicly available because they contain information that could compromise the individual privacy of research participants. The datasets will be made available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the regional committees for medical and health research ethics (REC west, Universitetet i Bergen, Det medisinske fakultet, Postboks 7804, 5020 Bergen), reference number: 2012/542/REC west. Written informed consent was obtained from the parents or legal representatives of the children and adolescents. The study was registered in ClinicalTrials.gov (No: NCT03904459).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

13. Appendix I

CASE REPORT FORM - UNDERSØKELSE KJEVELEDD, VEKST OG TMD

Pasient-Id.nr: _ _ _ _ _ _ _ _ _ _ _ _

Senter: _ _ _ _ _ _ _ _ _ _ _ _

Undersøker: _ _ _ _ _ _ _ _ _ _ _ _

Dato: _ _ / _ _ / _ _ (DD / MM / ÅÅ)

1a. Lokalisasjon av smerte siste 30 dager

HØYRE SMERTE				VENSTRE SMERTE			
○ Ingen	○ Temporalis	○ Andre tyggem.	○ Ikke-tygge strukturer	○ Ingen	○ Temporalis	○ Andre tyggem.	Ikke-tygge strukturer
	○ Masseter	○ Kjeveledd			○ Masseter	○ Kjeveledd	

1b. Lokalisasjon av hodepine siste 30 dager

○ Ingen	○ Temporalis	○ Andre	○ Ingen	○ Temporalis	○ Andre

2. Åpningsbevegelser

A. Smertefri inc. åpning _ _ mm

B. Maksimal inc. ikke-assistert åpning _ _ mm

C. Maksimal inc. assistert åpning _ _ mm

	HØYRE SIDE				VENSTRE SIDE			
		Smerte	Gjenkjennbar smerte	Gjenkjennbar hodepine		Smerte	Gjenkjennbar smerte	Gjenkjennbar hodepine
B.	Temporalis	N J	N J	N J	Temporalis	N J	N J	N J
	Masseter	N J	N J		Masseter	N J	N J	
	Kjeveledd	N J	N J		Kjeveledd	N J	N J	
	Andre tyggem.	N J	N J		Andre tyggem.	N J	N J	
C.	Ikke-tyggem.	N J	N J		Ikke-tyggem.	N J	N J	

D. Maksimal ikke-assistert munnåpning (Maksimal ikke-assistert munnåpning = Maksimal incisal åpning +/- Vertikalt incisalt overbitt)

Maksimal incisal åpning *: _____ mm

Vertikalt incisalt overbitt + / - _____ mm

Maksimal ikke-assistert munnåpning: = _____ mm

Horisontalt incisalt overbitt registreres ved kjeveortopedisk undersøkelse.

*For å bedre målingens repeterbarhet, vennligst marker med en "x" de tannposisjoner som ble brukt under målingen.

○	11	○	12	○	13	○	21	○	22	○	23	○	51	○	52	○	53	○	61	○	62	○	63
○	41	○	42	○	43	○	31	○	32	○	33	○	81	○	82	○	83	○	71	○	72	○	73

3. Mandibula deviasjon ved maksimal munnåpning (≥ 3 mm):

Mandibula deviasjon til høyre side ☐

Mandibula deviasjon til venstre side ☐

Ingen deviasjon ☐

4. Laterale og protrusive bevegelser

		HØYRE SIDE				VENSTRE SIDE			
		Smerte	Gjenkjennbar smerte	Gjenkjennbar hodepine		Smerte	Gjenkjennbar smerte	Gjenkjennbar hodepine	
A. Høyre Lateral _ _ mm	Temporalis	N J	N J	N J	Temporalis	N J	N J	N J	
	Masseter	N J	N J		Masseter	N J	N J		
	Kjeveledd	N J	N J		Kjeveledd	N J	N J		
	Andre tyggem	N J	N J		Andre tyggem	N J	N J		
	Ikke-tyggem.	N J	N J		Ikke-tyggem.	N J	N J		
B. Venstre Lateral _ _ mm	Temporalis	N J	N J	N J	Temporalis	N J	N J	N J	
	Masseter	N J	N J		Masseter	N J	N J		
	Kjeveledd	N J	N J		Kjeveledd	N J	N J		
	Andre tyggem	N J	N J		Andre tyggem	N J	N J		
	Ikke-tyggem.	N J	N J		Ikke-tyggem.	N J	N J		
C. Protrusjon _ _ mm	Temporalis	N J	N J	N J	Temporalis	N J	N J	N J	
	Masseter	N J	N J		Masseter	N J	N J		
	Kjeveledd	N J	N J		Kjeveledd	N J	N J		
○ Om negativt HOB	Andre tyggem.	N J	N J		Andre-tyggem.	N J	N J		
	Ikke tyggem.	N J	N J		Ikke-tyggem.	N J	N J		

5. Kjeveleddslyder ved åpne- og lukkebevegelser

HØYRE Kjeveledd

	Undersøker		Pasient		Smerte v/klikkelyd	Gjenkjennbar smerte
	Åpne	Lukke				
Klikkelyd	N J	N J	N J	→ N J	N J	N J
Krepitasjon	N J	N J	N J			

VENSTRE Kjeveledd

	Undersøker		Pasient		Smerte v/klikkelyd	Gjenkjennbar smerte
	Åpne	Lukke				
Klikkelyd	N J	N J	N J	→ N J	N J	N J
Krepitasjon	N J	N J	N J			

6. Kjeveledd-lyder ved laterale & protrusive bevegelser

HØYRE Kjeveledd

	Undersøker	Pasient		Smerte v/klikkelyd	Gjenkjennbar smerte
Klikkelyd	N J	N J	→ N J	N J	N J
Krepitasjon	N J	N J			

VENSTRE Kjeveledd

	Undersøker	Pasient		Smerte v/klikkelyd	Gjenkjennbar smerte
Klikkelyd	N J	N J	→ N J	N J	N J
Krepitasjon	N J	N J			

7. Kjeveläsning

HØYRE Kjeveledd	Låsning	Reduksjon Pasient	Reduksjon Undersøker
Under åpning	N J	N J	N J
Fullt åpen posisjon	N J	N J	N J

VENSTRE Kjeveledd	Låsning	Reduksjon Pasient	Reduksjon Undersøker
Under åpning	N J	N J	N J
Fullt åpen posisjon	N J	N J	N J

8. Muskel- (2 sek. palp.tid) & kjeveleddssmerte (5 sek. palp.tid) ved palpasjon)

HØYRE SIDE (1 kg)	Smerte	Gjenkjennbar smerte	Gjenkjennbar hodepine
Temporalis (posterior)	N J	N J	N J
Temporalis (midtre)	N J	N J	N J
Temporalis (anterior)	N J	N J	N J
Masseter (utspring)	N J	N J	
Masseter (midtre)	N J	N J	
Masseter (feste)	N J	N J	

VENSTRE SIDE (1 kg)	Smerte	Gjenkjennbar smerte	Gjenkjennbar hodepine
Temporalis (posterior)	N J	N J	N J
Temporalis (midtre)	N J	N J	N J
Temporalis (anterior)	N J	N J	N J
Masseter (utspring)	N J	N J	
Masseter (midtre)	N J	N J	
Masseter (feste)	N J	N J	

Kjeveledd

HØYRE SIDE	Smerte	Gjenkjennbar smerte
Laterale pol **(0,5 kg)**	N J	N J
Omkring laterale pol **(1 kg)**	N J	N J

VENSTRE SIDE	Smerte	Gjenkjennbar smerte
Laterale pol **(0,5 kg)**	N J	N J
Omkring laterale pol **(1 kg)**	N J	N J

9. Kjeveledd smerte ved palpasjon:
Vennligst registrer om følgende kliniske funn er tilstede:

Smerte ved palpasjon med *lukket munn*:

- Ingen smerte □
- Høyre kjeveledd □
- Venstre kjeveledd □
- Begge kjeveledd □

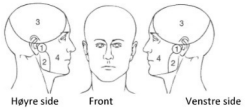
Smerte ved palpasjon med *åpen munn*:

- Ingen smerte □
- Høyre kjeveledd □
- Venstre kjeveledd □
- Begge kjeveledd □

10. Smerte summasjon (fra samordnet symptomskjema)

Smerte frekvens (spørsmål 4, EurTMJ1.): _____ poeng
Smerte intensitet (VAS 0-100, fra spørsmål 5, EurTMJ 2.): _____ mm
Smerte-index: (Smerte frekvens x Smerte intensitet, 0-400): _____ x _____ = _____

11. Klinisk vurdert smerte lokalisasjon (se spørsmål 2,4,8)



❑ 1.	❑ 1.
❑ 2.	❑ 2.
❑ 3.	❑ 3.
❑ 4.	❑ 4.

12. Frontal ansikts asymmetri: - Generelt intrykk av mandibulær symmetri:

- Symmetrisk mandibula □
- Asymmetrisk mot høyre side (høyre side er kortest) □
- Asymmetrisk mot venstre side (venstre side er kortest) □

Symmetrisk | Asymmetrisk deviasjon mot ha.side | Asymmetrisk deviasjon mot ve.side

13. Ansiktsprofil:

Velg nedenfor den bilde som passer best med pasientens profil:

□ Rett □ Mild konvex □ Moderat konvex □ Konvex mikrognatisk

14. Hevelse relatert til kjeveledd

❑ ja ❑ nei ❑ ikke vurdert

Hvis ja: ❑ høyre side ❑ venstre side ❑ bilateralt

Konklusjon med diagnoser:

Klinisk mistanke om aktiv kjeveleddsartritt

❑ ja ❑ nei ❑ ikke vurdert

❑ høyre side ❑ venstre side ❑ bilateralt

Bekreftet med MR med kontrast dato: _ _ / _ _ / _ _ (DD / MM / ÅÅ) ja ❑ nei ❑ ikke vurdert

Klinisk mistanke om gjennomgått kjeveleddsartritt

❑ ja ❑ nei ❑ ikke vurdert

❑ høyre side ❑ venstre side ❑ bilateralt

Bekreftet med MR med kontrast dato: _ _ / _ _ / _ _ (DD / MM / ÅÅ) ja ❑ nei ❑ ikke vurdert

Klinisk mistanke om TMD

Myalgi
❑ Ja ❑ Nei ❑ ikke vurdert
❑ høyre side ❑ venstre side ❑ bilateralt

Artralgia
❑ Ja ❑ Nei ❑ ikke vurdert
❑ høyre side ❑ venstre side ❑ bilateralt

Hodepine
❑ Ja ❑ Nei ❑ ikke vurdert
❑ høyre side ❑ venstre side ❑ bilateralt

Diskusdisplassering med reduksjon
❑ Ja ❑ Nei ❑ ikke vurdert
❑ høyre side ❑ venstre side ❑ bilateralt
Bekreftet med MR med funksjonsstatus dato: _ _ / _ _ / _ _ (DD / MM / ÅÅ) ja ❑ nei ❑ ikke vurdert

Diskusdisplassering med reduksjon og intermitterende låsning
❑ Ja ❑ Nei ❑ ikke vurdert
❑ høyre side ❑ venstre side ❑ bilateralt
Bekreftet med MR med funksjonsstatus dato: _ _ / _ _ / _ _ (DD / MM / ÅÅ) ja ❑ nei ❑ ikke vurdert

Diskusdisplassering uten reduksjon med redusert gapeevne - closed lock
❑ Ja ❑ Nei ❑ ikke vurdert
❑ høyre side ❑ venstre side ❑ bilateralt
Bekreftet med MR med funksjonsstatus dato: _ _ / _ _ / _ _ (DD / MM / ÅÅ) ja ❑ nei ❑ ikke vurdert

Diskusdisplassering uten reduksjon uten redusert gapeevne
❑ Ja ❑ Nei ❑ ikke vurdert
❑ høyre side ❑ venstre side ❑ bilateralt
Bekreftet med MR med funksjonsstatus dato: _ _ / _ _ / _ _ (DD / MM / ÅÅ) ja ❑ nei ❑ ikke vurdert

Kjeveleddsluksasjon
❑ Ja ❑ Nei ❑ ikke vurdert
❑ høyre side ❑ venstre side ❑ bilateralt
Bekreftet med MR med funksjonsstatus dato: _ _ / _ _ / _ _ (DD / MM / ÅÅ) ja ❑ nei ❑ ikke vurdert

Artrose / degenerativ sykdom i kjeveledd
❑ Ja ❑ Nei ❑ ikke vurdert
❑ høyre side ❑ venstre side ❑ bilateralt
Bekreftet med CBCT dato: _ _ / _ _ / _ _ (DD / MM / ÅÅ) ❑ ja ❑ nei ❑ ikke vurdert

DEFINISJONER

DIAGNOSE	Klinikk	SPØRSMÅL I SKJEMA		
		Case Report Form	Symptomskjema	Wilkes new category of TMJ**
Aktiv kjeveleddsartritt	hevelse over kjeveledd eller nedsatt funksjon med smerte/ømhet over kjeveledd*	Spm 2b, 2c , 2d nedsatt funksjon med smerte + gjenkjennbar smerte kjeveledd **og/eller** Spm 4a,4b,4c nedsatt funksjon med smerte kjeveledd + gjenkjennbar smerte kjeveledd **og/eller** Spm 14. Hevelse	7 (forverring) **og/eller** 8 ja **og/eller** 9 ja **og/eller** 11b ja	
Gjennomgått kjeveleddsartritt	krepitasjoner, vekstforstyrrelse; asymmetri eller mikrognati, deviasjoner ved gap	3 deviasjon ved gap **og** 5,6 krepitasjoner **og/eller** 12 asymmetrisk frontalt **og/eller** 13 moderat konvex, mikrognatisk	15 ja	
Myalgi	Smerte i en tyggemuskel **OG** Smerte ved kjevefunksjon eller parafunksjon	1a, 2, 8, 11 (Smerte + gjenkjennbar smerte i tyggemuskler) **OG** 4 (tyggemuskler funksjon)	3 **OG** 7	
Artralgia	Leddsmerte Smerte i tyggemuskelatur Smerte kjeveledd ved kjevefunksjon el. parafunksjon	1a (kjeveledd) **OG** 2 **OR** 4 (kjeveledd) **OG** 8,9,11 (kjeveledd)	3 **OG** 7	
Hodepine assosiert med TMD	Smerte i m.temporalis **OG** Hodepine utløst av kjeve-bevegelser / funksjon eller parafunksjon	1b **OG** 2b (ved maks. ikke-assistert munnåpning smerte i m.temporalis + kjent hodepine), 4a-c (laterotrusjon,protrusjon, 8 (kjent hodepine ved palp. m.temporalis),11(m.temporalis)	12, 14	
Diskusdisplassering med reduksjon	Reciprok klikking ved oppgap og lukking **eller** klikking ved oppgap el lukking **og** laterotrusjon eller protrusjon.	5:klikking (åpning & lukking) **eller** 5: klikking (åpning eller lukking) **og** 6: klikking (laterotrusjon eller protrusjon)	15	I.
Diskusdisplassering med reduksjon og intermitterende låsning	Som ovenfor + behov for manøver for å åpne munn (intermitterende låsning med redusert gap)	Som ovenfor + 7	15 18:ja 19:nei	II.
Diskusdisplassering uten reduksjon med redusert gapeevne – "closed lock"	Kjevesperre med redusert gap < 40 mm (passiv gap) Tyggeplager	2c < 40 mm inkl. Vertikal incisal overbitning	16 **OG** 17	III.
Diskusdisplassering uten reduksjon uten redusert gapeevne	Kjevesperre med gap ≥ 40 mm (passiv gap) Tyggeplager	2c ≥ 40 mm inkl. Vertikal incisal overbitning	16 **OG** 17	III. – IV.
Kjeveleddsluksasjon	Kjevesperre / låsning ved maksimalt gap, må lukke munn vha manøver	7	20 **OG** 21	II.
Artrose / degenerativ sykdom i kjeveledd	Krepitasjoner kjeveledd ved bevegelse rapportert av undersøker **eller** Undersøker+ pasient	5 eller 6 rapportert av undersøker **eller** Undersøker+ pasient	15 **Eller rapportert av pasient under undersøkelse**	V.

*Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. The Journal of rheumatology. 2004;31(2):390-2.

Dette undersøkelseskjema er basert på *Diagnostic Criteria for Temporomandibular Disorders (DC-TMD)*[1], *The EUROMJOINT Recommendations for Clinical Temporomandibular joint Assessment in Patients Diagnosed With Juvenile Idiopathic Arthritis*[2] samt Wilkes classifikation of TMJ[3,4] . For spesifikasjoner og beskrivelser, se referanser.

1. Schiffman E, Ohrbach R, Truelove E, Look J, Anderson G, Goulet JP, et al. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: Recommendations of the International RDC/TMD Consortium Network* and Orofacial Pain Special Interest Groupdagger. Journal of oral & facial pain and headache. 2014;28(1):6-27.

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** Wilkes stages of TMJ

Staging of Internal Derangement of TMJ (12, 13)

STAGE	CLINICAL	IMAGING	SURGICAL
I. EARLY	Painless clicking No restricted motion	Slightly forward disc, reducing* Normal osseous contours	Normal disc form Slight anterior displacement Passive incoordination (clicking)
II. EARLY/ INTERMEDIATE	Occasional painful clicking Intermittent locking Headaches	Slightly forward disc, reducing Early disc deformity Normal osseous contours	Anterior disc displacement Thickened disc
III. INTERMEDIATE	Frequent pain Joint tenderness, headaches Locking Restricted motion Painful chewing	Anterior disc displacement, reducing early progressing to non-reducing* late Moderate to marked disc thickening Normal osseous contours	Disc deformed & displaced Variable adhesions No bone changes
IV. INTERMEDIATE/ LATE	Chronic pain, headache Restricted motion	Anterior disc displacement, non-reducing Marked disc thickening Abnormal bone contours	Degenerative remodeling of bony surfaces Osteophytes Adhesions, deformed disc without perforation
V. LATE	Variable pain Joint crepitus Painful function	Anterior disc displacement, non-reducing with perforation and gross disc deformity Degenerative osseous changes	Gross degenerative changes of disc and hard tissues; Perforation Multiple adhesions

* refers to disc position in relation to the condyle when the mouth is open

Table 2. New TMJ surgical classification[4**]

Category	Clinical presentation	Radiological features	Diagnosis	Treatment
Category 1.	TMJ pain No joint noises No history of locking or dislocation Full range of jaw movement Normal chewing	OPG – normal condyles MRI – normal TMJ	Joint contusion – acute trauma Myofascial pain Ear pathology – otalgia Neuropathic, Psychogenic	Medication +/- splint Surgery has no role
Category 2.	Intermittent joint pain Joint clicking Occasional locking	OPG – normal condyles MRI – disc displacement with reduction Disc and condyle normal contour	Early TMJ internal derangement Joint inflammation/adhesions	TMJ arthrocentesis TMJ arthroscopic lavage
Category 3.	Painful chronic closed lock Recurrent joint swelling Painful recurrent dislocation	OPG – normal condyles MRI – disc displacement without reduction Disc normal or mildly deformed contour Prominent eminence	Moderate TMJ internal derangement Recurrent TMJ dislocation TMJ synovial chondromatosis Dislocated condylar fracture	TMJ arthroscopy (operative) TMJ arthroplasty – disc plication/ repositioning +- eminectomy
Category 4.	Constant joint pain Painful crepitus Mildly limited mouth opening Painful chewing	OPG – early condylar changes CT scans – mild to moderate condylar degeneration MRI – severely degenerated, displaced and deformed disc Early condylar changes – osteophytes, flattening	Advanced TMJ internal derangement Rare TMJ disorder – metabolic, inflammatory or developmental joint disease	TMJ discectomy +- condyloplasty/shave Debridement of glenoid fossa Reduction of eminence
Category 5.	Intolerable low grade pain Constant crepitus Locking Malocclusion Unable to chew anything solid	OPG – obvious degenerative changes to condyle MRI – disc destroyed/difficult to see CT scan – condyle severely degenerate	TMJ osteoarthritis TMJ condylysis TMJ ankylosis TMJ tumour	TMJ resection TMJ total joint replacement

Table 2. New TMJ surgical classification[4**]

Category	Clinical presentation	Radiological features	Diagnosis	Treatment
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14. Appendix II

The EURO^{tm}JOINT Recommendations for Clinical Temporomandibular joint Assessment in Patients Diagnosed With Juvenile Idiopathic Arthritis

Final and proof-read version

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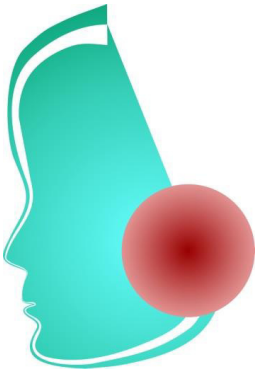

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This info will be completed when we have decided on the full context of the manuscript

Introduction

Within the past decade, increased attention has been paid to the consequences of temporomandibular joint (TMJ) inflammation in patients diagnosed with juvenile idiopathic arthritis. Several clinical studies have been conducted. However, no uniform and standardized criteria on functional clinical TMJ examination outcome measures have been proposed.

The objective of this work is to propose terminology and to develop standardized recommendations for the minimal amount of clinical TMJ examination outcome measures to be assessed in the daily routine evaluation of the TMJ, as well as clinical studies in patients diagnosed with JIA. The recommendations were developed by the international Euro^{tm}Joint network, based on the current scientific knowledge of TMJ arthritis in JIA patients. Our guidelines therefore only reflect the current consensus recommendations. We plan to conduct revisions to the recommendations as our understanding of TMJ arthritis improves.

The recommendations proposed in this paper describe the assessment of orofacial pain and dysfunction, symptomatic changes, and craniofacial symmetry. To evaluate outcome measures related to TMJ inflammation we refer to the imaging modalities suitable for the assessment of the specific research question of interest. It must be emphasized that the primary aim of this paper is to standardize the *clinical* examination in patients receiving treatment for an existing TMJ arthritis condition or JIA patients receiving a routine orofacial clinical evaluation. An important focus for future research will be the assessment of the correlation between TMJ inflammation and the clinical examination items proposed in the present recommendations.

Since the treatment of TMJ arthritis involves an interdisciplinary approach, a primary goal of our recommendations was to create guidelines to measure clinical outcome that can be used by practitioners without dental training, or specialized training in the examination of the temporomandibular joint.
Detailed instructions for how to perform each clinical measure can be found in the appendix.

The EuroTMJoint Recommendations for Clinical Temporomandibular Joint Assessment in Patients Diagnosed With Juvenile Idiopathic Arthritis

---

General information:
This form consists of three sections:
Part 1. To be filled out by your doctor. This will provide us with some of your medical history.
Part 2. To be filled out by you. This will help us understand how your temporomandibular joint arthritis affects you. Feel free to consult the staff if you have questions about this part of form
Part 3. To be filled out by your doctor. This will provide us with your doctor's physical examination findings.

Part 1: General information (to be filled out by the doctor)

Date: **Examiner:**

Patient ID: **Age (years and months):**

Treatment, Protocol: _____ **Age at onset of JIA (years and months):**

JIA subtype:

□	Oligoarticular persistent	□	Oligoarticular extended
□	Psoriatic	□	Systemic
□	RF-negative polyarticular	□	RF-positive polyaticular
□	Enthesitis Related Arthritis (ERA)	□	Undifferentiated
□	Subtype not confirmed		

Information in this form regards:

		Date day/month/year		
□	Routine clinical examination	-- / -- / ----		
□	BI: Baseline information (pre-intervention)	-- / -- / ----		
□	T0: Intervention	-- / -- / ----	BI – T0	weeks
□	T1: Follow up 1 post-intervention	-- / -- / ----	T0 – T1	weeks
□	T2: Follow up 2 post-intervention	-- / -- / ----	T1 – T2	weeks
□	T3: Follow up 3 post-intervention	-- / -- / ----	T2 – T3	weeks
	T__Follow up			

Current medication and dosage (name of drug, dosage used and duration of therapy):

		Name	Dosage / frequency	Date started	Date ended
□	No medication				
□	NSAID				
□	Analgesics (e.g. Acetaminophen)				
□	DMARDs (e.g. Methotrexate)				
□	Biologics				
□	Systemic corticosteroids				
□	TMJ intra-articular corticosteroids				
□	Other:				

TMJ imaging - TMJ inflammation

Signs of acute TMJ inflammation based on recent MRI (e.g. joint effusion, synovial enhancement, synovial thickening, bone marrow edema)?

Yes □
No □
No contrast enhanced MRI available □

Location

Right TMJ □
Left TMJ □
Both TMJs □

Date of MRI: ― ― / ― ― / ― ― ― ― (day/month/year)

Time since the latest MRI: _____

Chronic TMJ alterations

Signs of chronic TMJ alterations based on recent radiological/imaging findings (e.g. bony alterations such as condylar flattening, erosive changes, bone fragmentation)

Yes □
No □
No radiographic/imaging material available □

Location

Right TMJ □
Left TMJ □
Both TMJs □

Date of last radiological/imaging examination: ― ― / ― ― / ― ― ― ― (day/month/year)

Time since the latest radiographic examination: _____

Radiographic technique used:

□	CT	□	MRI
□	Cone-beam CT	□	Tomograms
□	OPG (panoramic)	□	Other

Part 2 (to be filled out by patient or guardian)

Patient History

Introduction: We would like to know how much pain you have from your TMJ arthritis. Please tell us about your symptoms within the past 2 weeks.

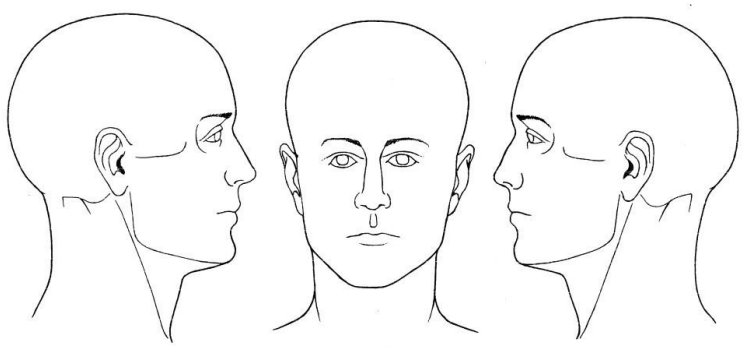
1. Pain frequency:
How often have you felt face or jaw pain within the last 2 weeks?

All the time:	□ (4 points)
Several times a day	□ (3 points)
Several times a week	□ (2 points)
Less than once a week	□ (1 point)
Never	□ (0 point)

2. Pain intensity:
How severe has your average face or jaw pain been within the last 2 weeks?

0	10
No pain	Worst pain possible

3. Pain locations
Use this figure to circle all the locations where you have felt pain within the last 2 weeks. Please take care to mark the left and right sides correctly



Right side Front Left side

4. Jaw function:
Was the function of your jaw affected within the last 2 weeks (e.g. eating, yawning, talking)?

No □
Yes □

If "yes" please use the scale below to document how much your jaw was affected?

0	10
Not affected	severely affected

5. Symptoms/Main complaints
Please mark off all statements that apply to you within the last 2 weeks. You are allowed to choose more than one statement.

	Yes
I feel pain when I chew	□
I avoid hard or chewy foods because it hurts my face or jaw.	□
I feel pain when I open my mouth wide (e.g. yawning)	□
I feel stiffness in my jaw muscles in the morning	□
I feel that my jaw gets stuck in the open or closed position	□
I feel pain in my jaw when I talk for a long time	□

6. Changes in face and jaw pain:
Please indicate the change in your face or jaw pain since your last clinic visit:

No change	□
Improved (less pain)	□ (Please elaborate in 6.a)
Worse (more pain)	□ (Please elaborate in 6.b)

6.a Please use the scale below to quantify the amount of improvement since the last clinic visit

0	10
No change	Best change possible

6.b Please use the scale below to quantify the amount of worsening since the last clinic visit

0	10
No change	Worst change possible

7. Changes in jaw function:

Please indicate the changes in your jaw function since your last clinic visit:

No change □
Improved (better function) □ (Please elaborate in 7.a)
Worse (Reduced function) □ (Please elaborate in 7.b)

7.a Please use the scale below to quantify the amount of improvement since the last clinic visit

|_____|
No change Best imaginable change

7.b Please use the scale below to quantify the amount of worsening since the last clinic visit

|_____|
No change Worst imaginable change

Part 3 (to be filled out by the clinician)

TMJ Clinical Examination Form

8. Pain summary (from the patient questionnaire)

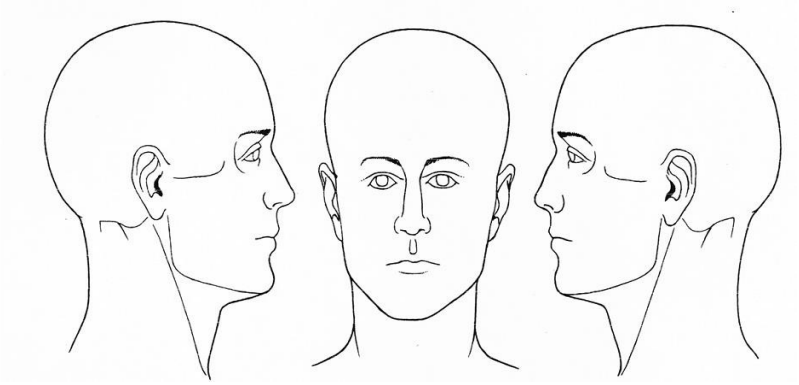
Pain frequency (question 1): _____ points

Pain intensity (VAS 0-100, from question 2): _____ mm

Pain-index: (Pain frequency x Pain intensity, 0-400): _____ x _____ = _____

9. Clinician assessed pain location

Ask the patient to use his/her finger to point out all the locations of orofacial pain on their face within the last 2 weeks. *Please* mark an "X" to indicate these areas on the face-map (Note: to be filled out by the clinician, not the patient).



10. TMJ pain on palpation:

Please indicate if the following clinical findings are present:

Pain on palpation with closed mouth:

None	□
Right TMJ	□
Left TMJ	□
Both TMJs	□

Pain on palpation with open mouth:

None	□
Right TMJ	□
Left TMJ	□
Both TMJs	□

11. Mandibular deviation at maximal mouth opening (≥ 3 mm)*:

Mandibular deviation to the right	□
Mandibular deviation to the left	□
No deviation*	□

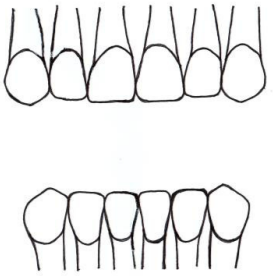
12.
Maximal unassisted mouth opening:
(Maximal unassisted mouth opening = Maximal incisal opening + Vertical incisal overlap)

Maximal incisal opening*: _____ mm

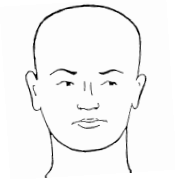
Vertical incisal overlap: + _____ mm

Maximal unassisted mouth opening: = _____ mm

*In order to improve reproducibility please put an "x" to mark the teeth and the positions on the teeth used for the measurement.

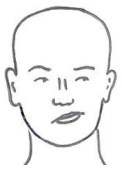


13. Frontal facial asymmetry:
Overall impression of mandibular symmetry:
Symmetric mandible: □
Asymmetric toward the right side (the right side is smallest) □
Asymmetric toward the left side (the left side is smallest) □



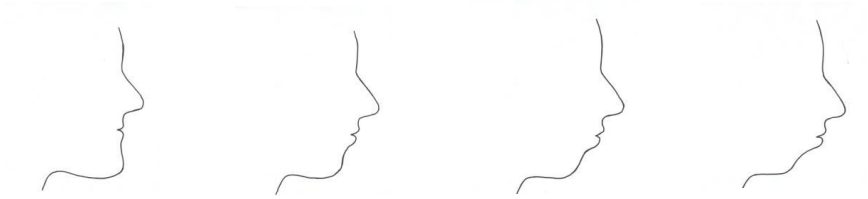
Symmetric

Asymmetric deviating towards the right



Asymmetric deviating towards the left

14. Facial profile:
Choose the picture below that matches the profile of the patient the best.



□ *Straight*

□ *Mild convex*

□ *Moderate convex*

□ *Convex micrognathic*

Instructions

General information about the form

- All items on the form must be completed. If the patient refuses or is unable to answer one or more of the items in the form, please write NA (Not Available).
- Patient information (Part 1) and the TMJ clinical examination (Part 3) are filled out by the examiner. The patient's history (part 2) is filled out by the patient/guardian prior to the clinical examination.
- Complete the questions in accordance with the instructions described below.

Part 1: Patient information

To be filled out by clinician

- Complete every item on the form carefully.
- Try to be as accurate as possible about age of the patient and age at time of JIA diagnosis.
- Please choose one of the listed JIA sub-types:
- It is preferable for baseline information to be as close to the time of intervention as possible.
- Current medication: please list all of the patient´s current medications anddosages.

Part 2: Patient History

To be filled out by the patient (or guardian)

Note: For the relevant questions, please ensure that you use age-appropriate Visual Analogue Scales (VAS). Please make sure that the patient/ guardian is familiar with the VAS.

Patients are asked to describe symptoms they have had within the 2 weeks prior to their clinic visit)

Please have the patient complete the questionnaire prior to the clinical examination. If the patient is unable to complete the questionnaire, ask their guardian to help.

1. **Pain frequency:** The patient should assess how often he/she has experienced orofacial pain within the last 2 weeks.

2. **Pain intensity**: The patient should assess how intense his/her orofacial pain has been within the last 2 weeks.

3. **Pain location:** The patient should use the illustrations of the head to mark the sites of pain/. For bilateral symptoms, the patient should use both lateral head illustrations to indicate sites of pain(p 9). Please v**e**rify that the patient understands the left and right side of the face.

4. **Jaw Function:** The patient should assess how much the jaw function (eg eating, yawning, and talking) has been affected within the last two weeks.
5. **Symptoms/complaints:** Instruct the patient to indicate all situations where symptoms (ie facial or jaw pain, difficulty chewing, etc) occurred within the last two weeks. The patient is allowed to choose more than one of the statements listed.
6. **Changes in face and jaw pain**: The patient should compare current visit to the last clinic visit as a reference for this assessment. Disregard this question if this is the first visit, or pre-intervention information.
7. **Changes in jaw function:**. Notice that the patient should compare current visit to the last clinic visit as a reference for this assessment. Disregard this question if this is the first visit, or pre-intervention information.

Part 3: TMJ clinical examination

8. **Pain Summary:** Record the information documented on the patient's questionnaire. Calculate the pain-index by multiplying pain intensity (mm) and pain frequency (points). The pain-index is an outcome measure indicating the overall patients' pain profile (a measure including both intensity and frequency).

9. **Pain Location:**
    - Ask the patient to point out all the areas where orofacial pain has been experienced within the last two weeks. Emphasize that all areas should be pointed out.
    - The examiner fills out the face-maps corresponding to all areas on the face pointed out by the patient (use X).

10. **TMJ pain on palpation:**

    Note: there is a distinct difference between discomfort and pain. Please document pain only, and NOT discomfort. Verify with the patient that reported pain is similar to the pain that the patient indicated in the questionnaire. This will help to differentiate between pain and discomfort from palpation.
    - Use the pad of your index finger and place it anteriorly to the tragus of the ear.
    - While having your index finger in this position ask the patient to open and close the mouth in order to localize the precise position of the lateral pole of the mandibular condyle.

Closed mouth position:

- After localizing the TMJ, ask the patient to close the mouth but avoid contact between upper and lower teeth.
- Palpate with firm pressure.
- Ask about and document the presence of pain. Only document pain if the patient reports that the pain they feel is comparable to the pain that is typically associated with their TMJ discomfort (”familiar pain”). This helps to distinguish between TMJ pain, and referred pain from another source such as a middle ear infection or a dental abcess.

Open mouth position:

- Ask the patient to open the mouth almost as wide as possible (submaximum mouth opening).
- While the mouth is open, apply a firm pressure on the lateral pole of the mandibular condyle.
- Ask about and document the presence of pain. Only document pain if the patient reports that the pain they feel is comparable to the pain that is typically associated with their TMJ discomfort (”familiar pain”). This helps to distinguish between TMJ pain, and referred pain from another source such as a middle ear infection or a dental abcess.

  Note that there is a distinct difference between discomfort and pain. Please document pain only, NOT discomfort.

11. **Mandibular deviation at maximal mouth opening end point:** Assess this variable in the following way:
    - Ask the patient to put the mandible in a position where the posterior teeth are in contact/occlusion (figure 1a).
    - Assess the dental midline of the upper and lower jaw by placing the thumb under the lower lip, and retracting the lower lip so that the lower incisors are revealed.
    - Notice any dental and/or chin-point midline deviation in the closed mouth position. Assess the mid chin-point in relation to a vertical reference midline perpendicular to the inter-pupilar line. Use this vertical midline as your reference during the following assessment.
    - Ask the patient to open the mouth as much as possible, even though he/she feels pain.
    - Ask the patient to hold the position of the mandible at maximal mouth opening and use the dental midline and/or chin-point in relation to the vertical midface reference line.
    - Document whether the mandible has deviated to the left or to the right side, or if the mandible is positioned straight in relation to the vertical midface reference line (figure

1bc). Mandibular sideways excursions *during* mouth opening should *not* be noted; the mandibular position should only be assessed at the maximal mouth opening end-point.

- Only deviations ≥ 3 mm are recorded.
- Corrected mandibular deviations are recorded as 'no deviation'. Corrected deviation is defined as a mandibular lateral excursion during the mouth opening procedure that is corrected and absent at maximal mouth opening. This means that the mandible does not deviate from the vertical reference midline at maximal mouth opening (Figure 1ab)

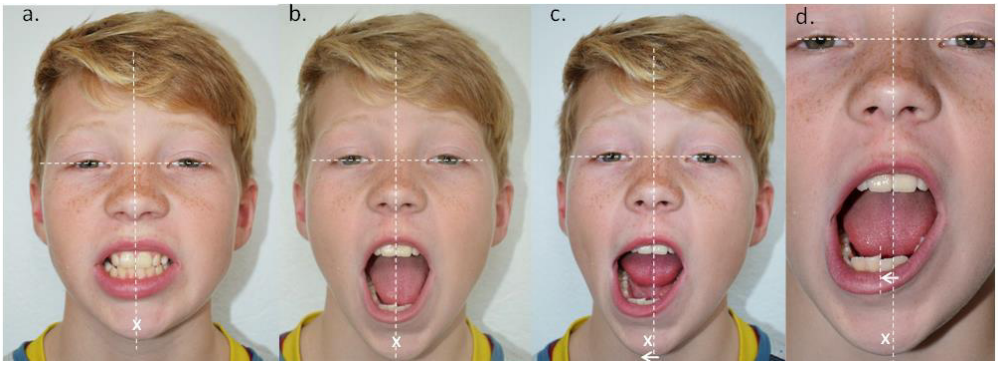


Figure 1. a) Teeth are in contact. Assess the chin-point (indicated by an "x") in relation to a vertical reference midline perpendicular to the inter-pupilar line. b) No mandibular deviation at maximal mouth opening. Notice how the chin-point corresponds with the vertical reference midline. c) Mandibular deviation to the right side at maximal mouth opening. The chin-point translates to the right and no longer corresponds with the vertical reference midline. d) Close-up of mandibular deviation to the right side at maximal mouth opening. Notice how both the lower dental midline and the chin reference-point are deviated to the right.

12. **Maximal unassisted mouth opening:**

To determine the actual maximal mouth opening, it is important to recognize that this measurement requires information about two variables:

1) The maximal incisal opening,

2) The vertical incisal overlap in the closed-mouth position.

The maximal incisal opening

- Ask the patient to open and close two times as a warming up exercise. Use the third opening as the score to be recorded.
- Ask the patient to open the mouth as much as possible, even if he/she feels pain. Place a ruler on the incisal edge of the lower right incisor and record the number of mm measured between the lower right and upper right incisal edge on the form (Figure 2).

Note: It is very important for the examiner to instruct the patient to open as wide as possible, since patients tend to open until they feel discomfort or pain without reaching their maximal mouth opening.
In case of missing incisors use the right canines for the assessment of the maximal mouth opening

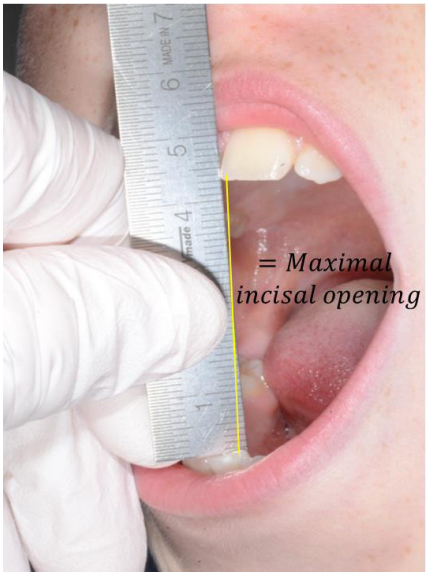


Figure 2. Maximal incisal opening of 43 mm

Vertical incisal overlap

- The mandible should be in a position where the teeth are in contact (Figure 3)

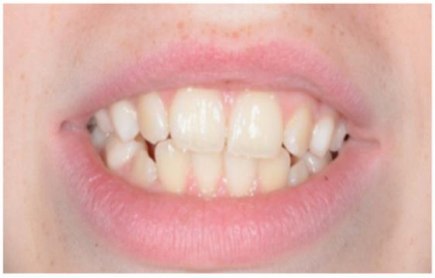


Figure 3. Closed mouth position with teeth together (in occlusion)

- In the closed-mouth position, assess the vertical incisal overlap. Position your thumb under the incisal edge of the central upper incisors (figure 4) and ask the patient to open the mouth. Measure the amount of overlap with a ruler (figure 5). Record this amount on

the form. Always measure the distance between the two incisal points having the biggest overlap (deepest overbite).

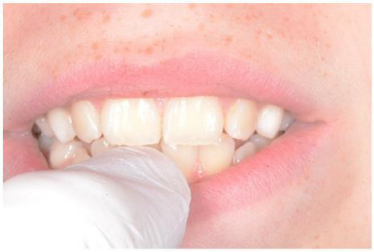


Figure 4

Figure 5

- In case of an anterior open bite (missing overlap of the incisors), assess vertical incisor distance as follows: use a ruler to measure the incisal opening between the upper and the lower incisor with the posterior teeth in contact (fig 6) and measure the number of mm between the incisal edges. Record the anterior open bite (the interincisor distance in closed mouth position) with a negative digit. (e.g. -2 mm). Note: an anterior open bite may be the result of chronic TMJ involvement

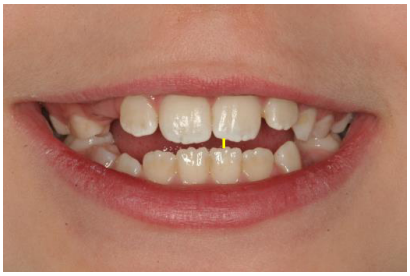


Figure 6. Open bite with missing incisal overlap (yellow line)

Calculate the maximal unassisted mouth opening as follows:

Maximal unassisted mouth opening = maximal incisal opening + vertical overlap

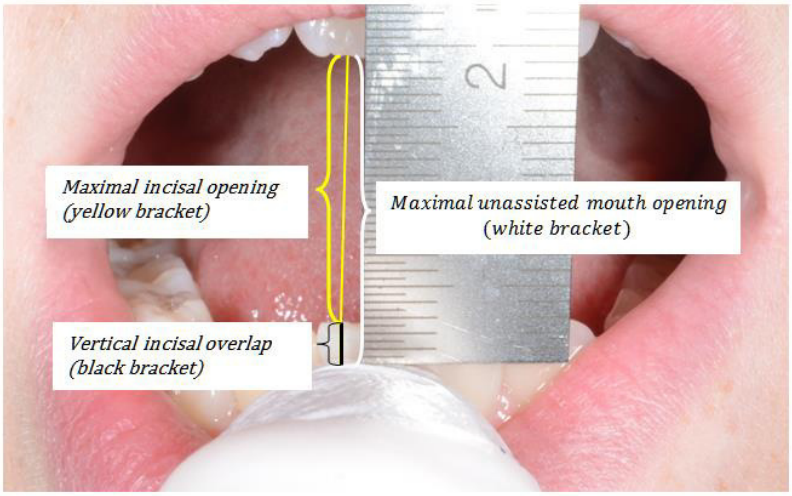


Figure 7. Example: a patient has a maximal incisal opening movement of 16 mm (yellow bracket) and a vertical incisal overlap of 3 mm (black bracket). The maximal unassisted mouth opening of this patient is 16 mm + 3 mm = 19 mm (yellow bracket + black bracket). In case the patient had an anterior incisal open bite of 2 mm instead, the maximal unassisted mouth opening of this patient would be: - 2mm +16 mm = 14 mm.

13. **Frontal facial asymmetry:** The variables are assessed with the patient positioned in front of you:
    - Ask the patient to sit upright, close the mouth and relax the lips.
    - Position your index fingers on the mandibular angle (gonion point) on each site (white arrow).
    - Use the position of the index fingers to assess any noticeable left-right difference in mandibular ramus height (white lines) with reference to the pupilar line.
    - Assess if the inter-commisura line and/or the inter-gonion line are parallel to the pupilar line. If not this indicates a clinical facial asymmetry.
    - As an aid, you can ask the patient to bite on a spatula and assess the canting of the spatula in relation to the inter-pupil line.
    - Based on these findings record the overall impression of the mandibular asymmetry on the form.
    - It is important to recognize that the assessment above is only a clinical assessment of craniofacial skeletal asymmetry. Thorough assessment of skeletal craniofacial asymmetry requires radiological assessment of variables of craniofacial growth, occlusal development and dentoalveolar relations.

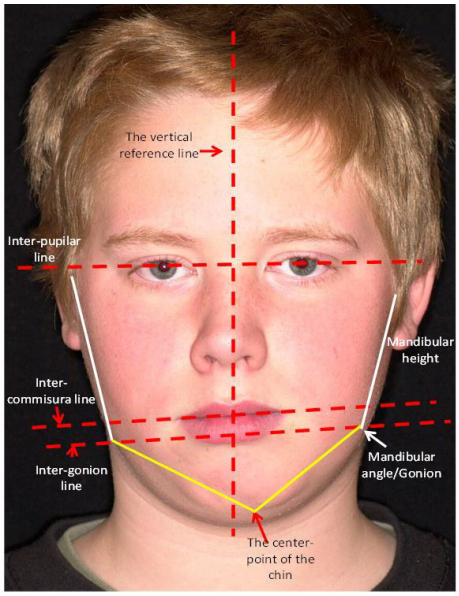


Figure 8. Facial asymmetry assessment. The white arrow indicates the mandibular angle - the point of intersection between the vertical (white lines) and the horizontal part (yellow lines) of the mandible. The white vertical lines indicate the mandibular ramus height which is defined as the distance between the TMJ and the mandibular angle. The red lines illustrate the lines used to assess frontal asymmetry. The obvious facial left side asymmetry of this patient is illustrated by the left side canting of the inter-commisura line/inter-gonion line in relation to the inter-pupilar reference line. The left mandibular ramus height is reduced compared with the right mandibular ramus height. Additionally, a left side chin-point deviation is seen in relation to the vertical reference line also indicating a left-right mandibular ramus height asymmetry. A chin-point deviation in relation to the vertical reference line is not always obvious in JIA patients. Clinically this means, that the chin point may be centered symmetrically despite the presence of mandibular ramus height asymmetry.

14. Patients' facial profile

- Position the patient in an upright position.
- Ask the patient to look straight ahead to a point on the wall.
- Assess the profile in accordance with the illustrations presented.

15. Appendix III

Samordnet symptomskjema

Pasient-Id.nr: _ _ _ _ _ _ _ _ _ _ _ _

Senter: _ _ _ _ _ _ _ _ _ _ _ _

Undersøker: _ _ _ _ _ _ _ _ _ _ _ _

Dato: _ _ / _ _ / _ _ (DD / MM / ÅÅ)

NorJIA
Norwegian JIA Study – Imaging, oral health and quality of life in children with juvenile idiopathic arthritis (JIA)

SMERTE

1. Har du noen gang hatt smerte i kjeve, tinning, i øret eller foran øret på en av sidene? **Nei** ☐ **Ja** ☐

Hvis du svarte NEI, så hopp videre til spørsmål 12.

2. For hvor mange år eller måneder siden begynte smertene første gang i kjeven, **tinning, i øret eller foran øret?** .....år .....måneder

3. I de siste 30 dager, hvilket av følgende beskriver best en eventuell smerte i kjeve, tinning, i øret eller foran øret på den ene eller andre siden?

Velg ETT svar

- ☐ Ingen smerte
- ☐ Smerten kommer og går
- ☐ Smerten er der alltid

Hvis du svarte NEI på spørsmål 3 og ikke har smerte (verken de siste 30 dager eller siste 14 dager), så hopp videre til spørsmål 12.

KJEVELEDD

Pasientens historie (Fylles ut av pasient eller foresatte)

Vi vil gjerne vite hvor mye smerte du har fra dine kjeveledd. Vennligst fortell oss om dine symptomer i løpet av *de siste to ukene*.

4. Smertefrekvens

Hvor ofte har du følt smerter i ansikt eller kjeve i løpet av de siste to ukene?

- ❑ Hele tiden (4 poeng)
- ❑ Flere ganger om dagen (3 poeng)
- ❑ Flere ganger i uken (2 poeng)
- ❑ Ikke hver uke (1 poeng)
- ❑ Aldri (0 poeng)

5. Smerteintensitet

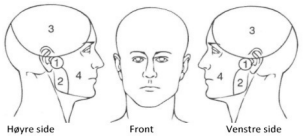
Hvor store smerter i ansikt eller kjeve har du hatt i løpet av de siste to ukene?

(= **Ingen smerte,** = **Verst mulig smerte**)

Ingen smerte — Verst mulig smerte

6. Områder med smerter

Bruk denne figuren til å markere alle områder hvor du har følt smerte i løpet av de to siste ukene. Vennligst vær nøye med å markere høyre og venstre side korrekt.



Høyre side — Front — Venstre side

❑ 1.	❑ 1.
❑ 2.	❑ 2.
❑ 3.	❑ 3.
❑ 4.	❑ 4.

7. I de siste 30 dager, førte følgende aktiviteter til endring av smerte (det vil si, til forbedring eller forverring) i din kjeve, tinning, i øret eller foran øret på den ene eller andre siden?

		Nei	Ja
A.	Tygging av hard eller grov mat	☐	☐
B.	Åpning av munnen eller ved bevegelse av kjeven fremover eller til siden	☐	☐
C.	Kjevevaner som det å bite sammen, bite hardt sammen eller gnisse tenner, eller tygge tyggegummi	☐	☐
D.	Andre kjeveaktiviteter slik som snakking eller gjesping	☐	☐

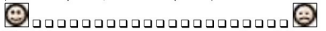
8. Kjevens funksjon

Har kjevens funksjon vært påvirket i løpet av de siste to ukene? (f.eks. spising, gjesping, snakking)?

❑ Nei
❑ Ja

Hvis "ja" , bruk skalaen under for å vise hvor mye påvirket.

( = Ikke påvirket,  = Svært påvirket)



Ikke påvirket Svært påvirket

9. Symptomer/vanligste plager

Marker alle utsagnene som stemmer overens med deg i løpet av de siste to ukene. Du kan velge flere enn ett utsagn.

	Ja
Det gjør vondt når jeg tygger	❑
Jeg unngår hard eller seig mat fordi det gjør vondt i ansiktet eller kjeven når jeg tygger	❑
Det gjør vondt når jeg gaper høyt (f.eks gjesping)	❑
Jeg er stiv i kjevemusklene om morgenen	❑
Jeg føler at kjeven låser seg når jeg gaper eller lukker munnen	❑
Det gjør vondt i kjeven når jeg snakker lenge	

For Tromsø som har pasienter som tidligere har rutiner med klinisk undersøkelse av denne pasientgruppen. Ikke aktuelt for Bergen og Trondheim.

10. Endringer i ansikts- og kjevesmerte

Marker endringen i din ansikts- eller kjevesmerte siden ditt forrige besøk ved klinikken:

Ingen endring ❑
Forbedring (mindre smerte) ❑ (Utdyp dette i 10.a)
Forverring (mer smerte) ❑ (Utdyp dette i 10.b)

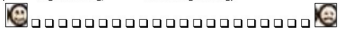
10.a Bruk skalaen under til å vise graden av forbedring siden ditt forrige klinikkbesøk

( =Ingen endring,  = Best mulig endring)

Ingen endring Best mulig endring

10.b Bruk skalaen under til å vise graden av forverring siden ditt forrige klinikkbesøk

( =Ingen endring,  = Verst mulig endring)



Ingen endring Verst mulig endring

11. Endringer i kjevens funksjon

Marker endringen i din kjevefunksjon siden ditt forrige besøk ved klinikken:

Ingen endring ❑
Forbedring (bedre funksjon) ❑ (Utdyp i 11.a)
Forverring (redusert funksjon) ❑ (Utdyp i 11.b)

11.a Bruk skalaen under til å vise graden av forbedring siden forrige klinikk besøk

(=Ingen endring, = Best mulig endring)

Ingen endring Best mulig endring

11.b Bruk skalaen under til å vise graden av forverring siden forrige klinikk besøk

(=Ingen endring, = Verst mulig endring)

Ingen endring Verst mulig endring

HODEPINE

12. I de siste 30 dager, har du da hatt noe hodepine som involverer tinningene? **Nei** ☐ **Ja** ☐

Hvis du svarte NEI på spørsmål 12, så hopp videre til spørsmål 15.

13. For hvor mange år eller måneder siden begynte hodepinen første gang i tinningen?

.....år .....måneder

14. I de siste 30 dager, førte følgende aktiviteter til endring av hodepinen (det vil si, forbedring eller forverring) i din tinning på den ene eller andre siden?

	Nei	Ja
A. Tygging av hard eller grov mat	☐	☐
B. Åpning av munnen eller ved bevegelse av kjeven fremover eller til siden	☐	☐
C. Kjevevaner som det å bite sammen, bite hardt sammen eller gnisse tenner, eller tygge tyggegummi	☐	☐
D. Andre kjeveaktiviteter slik som snakking eller gjesping	☐	☐

LYDER FRA KJEVELEDDENE

			Undersøker notater		
15. I de siste 30 dager, har du hatt noe lyder fra kjeveleddet(-ene) når du beveget eller brukte kjeven din?	**Nei** ☐	**Ja** ☐	**R** ☐	**L** ☐	**DNK**

LUKKET KJEVELÅSNING

	Nei	**Ja**	**R**	**L**	**DNK**
16. Har du noen gang hatt kjevelåsning eller en hindring av kjeven, om enn for et øyeblikk, slik at den ikke ville åpne seg HELT OPP?	☐	☐	☐	☐	☐

Hvis du svarte NEI på spørsmål 16, så hopp videre til spørsmål 20.

17.	Var kjevelåsningen eller hindringen alvorlig nok til å begrense din kjeveåpning og forstyrre din spiseevne?	☐	☐	☐	☐	☐
18.	I de siste 30 dager, var kjevelåsningen slik at du ikke kunne åpne HELT OPP, om enn for et øyeblikk, for så å frigjøre seg slik at du kunne åpne HELT OPP?	☐	☐	☐	☐	☐

Hvis du svarte NEI på spørsmål 18, kan du hoppe videre til spørsmål 20.

19.	Er din kjeve for øyeblikket låst eller begrenset slik at din kjeve ikke vil åpne HELT OPP?	☐	☐	☐	☐	☐

ÅPEN KJEVELÅSNING

20.	I de siste 30 dager, når du åpnet munnen helt opp, har det oppstått en kjevelåsning eller en hindring av kjeven, om enn for et øyeblikk, slik at du ikke har kunnet lukke igjen fra denne fullt åpne posisjonen?	☐	☐	☐	☐	☐

Hvis du svarer NEI på Spørsmål 20, så er du ferdig.

21.	I de siste 30 dager, da kjeven din ble låst eller forble i en fullt åpen posisjon, måtte du da gjøre noe for å få den lukket, inkludert hvile, bevegelse, pressing eller manøvrering?	☐	☐	☐	☐	☐

Takk for at du deltok!

16. Appendix IV

Forespørsel om deltakelse i forskningsprosjektet

«Barn og unge med leddgikt (Juvenil Idiopatisk Artritt)» (REK-nr 2012/542)
Foreldre (Barn <12 år)

Bakgrunn og hensikt
Dette prosjektet er et tverrfaglig forskningsprosjekt hvor forskere fra Tannhelsetjenestens Kompetansesenter Vest Hordaland (TkVest- tannlegespesialister) og fra Haukeland Universitetssykehus (legespesialister) deltar. Hovedmålet med forskningen er å kartlegge tidlige tegn på leddgikt i kjeveledd og undersøke i hvilken grad leddgikt påvirker munnhelsen, skjelletthelsen og livskvaliteten. Du lurer sikkert hvorfor du blir bedt om å la barnet ditt delta i et forskningsprosjekt som dette, for barnet ditt har jo ikke leddgikt. Grunnen er at man i forskning ofte har behov for å sammenligne syke og friske for å påvise forskjeller mellom gruppene, og derved få ny kunnskap om sykdommen. Siden ditt barn er friskt, spør vi deg derfor om å la barnet ditt delta i prosjektet vårt som del av den "friske" gruppen.

Hva innebærer det å delta?
Hvis du vil delta, betyr dette at barnet ditt - i tillegg til den vanlige tannhelsesjekken (som han/hun nå er innkalt til) - vil få undersøkt tyggemuskulatur, kjeveledd og bittforhold. Vi vil også måle barnets høyde og vekt, samt ta fotografier. Undersøkelsen vil bli utført av en tannlege som er vant med barn, og foregår på seksjonen for barnetannpleie, Institutt for klinisk Odontologi, Årstadveien 19, 1. etasje. Du og barnet ditt vil også bli bedt om å besvare noen spørreskjema. Undersøkelsen foregår to ganger med to års mellomrom. Du har allerede samtykket i at ditt barn deltar ved det første besøket, og nå spør vi om ditt barn vil delta på oppfølgingsbesøket. I tillegg spør vi om barnet ditt kan delta på en MR-undersøkelse av kjeveleddene (en bildeundersøkelse som gjøres liggende på en benk i en trommel og tar ca 30 minutter). Disse undersøkelsene vil foregå ved Haukeland Universitetssykehus, og barnet vil bli innkalt en tid etter tannhelseundersøkelsen.

Mulige fordeler og ulemper
Fordelen med deltakelse er at barnet ditt vil få en noe grundigere undersøkelse enn ellers hos tannlegen, ved unormale funn vil du bli varslet av studieledelsen og henvist til videre oppfølging i helsetjenesten. Ulempen er at undersøkelsene samlet sett vil ta litt lengre tid.

Hva skjer med informasjonen om barnet?
Prosjektet er vurdert og godkjent av Regional komité for medisinsk og helsefaglig forskningsetikk Vest (REK III), og ingen opplysninger om barnet ditt vil bli lest av utenforstående. Alle opplysninger vil bli oppbevart på vanlig måte, etter gjeldende regelverk for lagring av helsedata, og i en egen forskningsdatabase. Ved prosjektets slutt vil navnet til barnet ditt bli slettet fra forskningsdatabasen og de kliniske opplysningene om tannhelsen vil bli lagret i tannlegejournalen. Hvis du sier ja til å la barnet ditt delta i studien, gir du også ditt samtykke til at avidentifiserte opplysninger utleveres til samarbeidende forskere ved foretakene i Helse Midt og NTNU, samt forskere i Tromsø. Enhver utlevering av opplysninger til samarbeidende forskere vil bli lagt frem for REK.

Frivillig deltakelse
Det er frivillig å delta i studien. Du kan også velge om barnet bare skal delta på noen av tilleggsundersøkelsene. Du kan når som helst og uten å oppgi noen grunn, trekke ditt samtykke om å delta i studien. Dette vil ikke få konsekvenser for behandlingstilbudene i Den offentlige tannhelsetjenesten eller i helsetjenesten for øvrig. Ønsker du å trekke deg eller har spørsmål om studien, kontakter du en av undertegnende.

Ved ytterligere spørsmål, kontakt forskningsleder Johannes Fischer, tannlege ved Institutt for klinisk Odontologi (tlf. 55586676/96855033) eller overlege/professor Karen Rosendahl, Haukeland Universitetssykehus (tlf. 91183832).

Karen Rosendahl
Overlege/professor,
Seksjon for Barne- og ungdomsradiologi
Haukeland Universitetssykehus

Johannes Fischer
Forskningsleder
Institutt for klinisk Odontologi

Samtykke til deltakelse i forskning på barneleddgikt

Jeg/vi har forstått hva samtykket til deltakelse i denne studien innebærer for mitt barn.
Jeg/vi har mottatt informasjon og har hatt anledning til å stille spørsmål.

Jeg/vi er villig til å la mitt barn …….
(barnets navn og fødselsdato)

- ☐ delta i tannhelsestudien
- ☐ delta i MR-undersøkelsen

(Navn og signatur, foreldre/foresatte, dato)

Telefonnummer for avtale om tidspunkt for undersøkelsene: _____

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)

Informasjonsskriv, Barn og unge med leddgikt, versjon 10.11.18 (Foreldre, friske kontroller)

Forespørsel om deltakelse i forskningsprosjektet

«Barn og unge med leddgikt (Juvenil Idiopatisk Artritt)»
(REK-nr 2012/542) Foreldre og Ungdom 12-16 år

Bakgrunn og hensikt
Du lurer sikkert på hvorfor du blir bedt om å delta i et forskningsprosjekt som dette, for du har jo ikke leddgikt. Grunnen er at man i forskning ofte har behov for å sammenligne syke og friske; i vårt prosjekt betyr det at vi vil sammenligne barn med og uten leddgikt. Siden du er frisk spør vi deg om hjelp. Vi ønsker å kartlegge tidlige tegn på leddgikt i kjeveleddene, og undersøke i hvilken grad leddgikt påvirker munnhelsen, skjeletthelsen og livskvaliteten. Ved å delta i studien, hjelper du oss med å nå målene våre.

Hva innebærer det å delta?
Hvis du vil delta, betyr dette at du i tillegg til den vanlige tannhelsesjekken (som du nå er innkalt til), vil få undersøkt tyggemuskulatur, kjeveledd og bittforhold. Vi vil også måle høyden og vekten din, samt ta fotografier. Undersøkelsen vil bli gjort av en tannlege som er vant med barn og ungdom, og foregår på seksjonen for barnetannpleie, Institutt for klinisk Odontologi, Årstadveien 19, 1. etasje. Du (og foresatte) vil også bli bedt om å svare på noen spørreskjema. Undersøkelsen foregår to ganger med to års mellomrom. Dine foresatte har allerede samtykket i deltakelse ved det første besøket, og nå spør vi om du vil delta på oppfølgingsbesøket.

I tillegg spør vi om du kan delta på en MR-undersøkelse av kjeveleddet (en bildeundersøkelse som gjøres liggende på en benk i en trommel og tar ca. 40 minutter). Denne undersøkelsen vil foregå ved Haukeland Universitetssykehus, i MR-senteret på Pækeringsdekket (Sentralblokken, Lab. P2), og du (og dine foresatte) vil få tilbud om en time relativt snarlig.

Mulige fordeler og ulemper
Fordelen med deltakelse er at du vil få en noe grundigere undersøkelse enn ellers hos tannlegen. Ved unormale funn vil du bli varslet av studieledelsen og henvist til videre oppfølging i helsetjenesten. Ulempen er at du må regne med at undersøkelsen vil ta litt lengre tid.

Hva skjer med informasjonen vi samler inn om deg?
Prosjektet er vurdert og godkjent av Regional komité for medisinsk og helsefaglig forskningsetikk Vest (REK III), og ingen opplysninger om deg vil bli lest av utenforstående. Alle opplysninger om deg vil bli oppbevart på vanlig måte, etter gjeldende regelverk for lagring av helsedata, samt i en egen forskningsdatabase. Ved prosjektets slutt vil navnet ditt bli slettet fra forskningsdatabasen og opplysningene om deg vil bli lagret i tannlegejournalen. Hvis du sier ja til å delta i studien, gir du også ditt samtykke til at ikke-identifiserte opplysninger utleveres til samarbeidende forskere ved foretakene i Helse Vest og Universitetet i Bergen, samt forskere i Tromsø. Enhver utlevering av opplysninger til samarbeidende forskere vil bli lagt frem for REK.

Frivillig deltakelse
Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn, trekke ditt samtykke om å delta i studien. Dette vil ikke få konsekvenser for behandlingstilbudene i Den offentlige tannhelsetjenesten eller i helsetjenesten for øvrig. Ønsker du å trekke deg eller har spørsmål om studien, kontakter du (og foresatte) en av undertegnende.

Ved ytterligere spørsmål, kontakt Forskningsleder Johannes Fischer, tannlege ved Institutt for klinisk Odontologi (tlf. 55586676/96855033) eller overlege/professor Karen Rosendahl, Haukeland Universitetssykehus (tlf. 91183832).

Karen Rosendahl
Overlege/professor
Seksjon for Barne- og ungdomsradiologi
Haukeland Universitetssykehus/UiB

Johannes Fischer
Forskningsleder
Institutt for klinisk Odontologi

Samtykke til deltakelse i forskning på barneleddgikt

Jeg/vi har forstått hva samtykket til deltakelse i denne studien innebærer for mitt barn.
Jeg/vi har mottatt informasjon og har hatt anledning til å stille spørsmål.

Jeg/vi er villig til å la mitt barn ……
(barnets navn og fødselsdato)

- ☐ delta i tannhelsestudien
- ☐ delta i MR-undersøkelsen

(Navn og signatur - barn/ungdom), dato)
"Foresatte skal være informert og samtykke til deltakelse i forskningsprosjekter for ungdom over 12 år, med mindre pasienten av forhold som bør respekteres ønsker noe annet."

(Navn og signatur, foreldre/foresatte, dato)

Telefonnummer for avtale om tidspunkt for undersøkelsene: _____

UNIVERSITETET I BERGEN
Det medisinsk-odontologiske fakultet

Forespørsel om deltakelse i forskningsprosjektet

«Barn og unge med leddgikt (Juvenil Idiopatisk Artritt)» (REK-nr 2012/542).
16- 18 år

Bakgrunn og hensikt
Du lurer sikkert på hvorfor du blir bedt om å delta i et forskningsprosjekt som dette, for du har jo ikke leddgikt. Grunnen er at man i forskning ofte har behov for å sammenligne syke og friske, slik at vi kan påvise forskjeller mellom gruppene, og derved få ny kunnskap om sykdommen. I denne sammenhengen betyr det barn og unge med og uten leddgikt. Siden du er frisk, spør vi deg derfor om å delta i prosjektet vårt som del av den "friske" gruppen. Vi ønsker å kartlegge tidlige tegn på leddgikt i kjeveleddet, samt undersøke i hvilken grad leddgikt påvirker munnhelsen og livskvaliteten. Ved å delta i studien, hjelper du oss med å nå målene våre; som takk for hjelpen får du to kinobilletter.

Hva innebærer det å delta?
Hvis du vil delta, betyr dette at du i tillegg til den vanlige tannhelsesjekken (som du nå er innkalt til), vil få undersøkt tyggemuskulatur, kjeveledd og bitt-forhold. Vi vil også måle høyden og vekten din, samt ta noen fotografier. Undersøkelsen vil bli gjort av en tannlege som er vant med barn og ungdom, og som møter opp på din lokale tannklinikk. Du vil også bli bedt om å svare på noen spørreskjema. Grunnen til at vi må informere deg om dette er at tannhelsedataene dine vil bli benyttet i forskningssammenheng. Vi er derfor avhengige av at du skriver under på det vedlagte skjemaet.

Mulige fordeler og ulemper
Fordelen med deltakelse er at du vil få en noe grundigere undersøkelse enn ellers. Ulempen er at du må regne med at undersøkelsen samlet sett vil ta litt lengre tid.

Hva skjer med informasjonen vi samler inn om deg?
Prosjektet er vurdert og godkjent av Den regionale komité for medisinsk forskningsetikk i Helseregion Vest (REK III), og ingen opplysninger om deg vil bli lest av utenforstående. Alle opplysninger om deg vil bli oppbevart på vanlig måte, ihht gjeldende regelverk for lagring av helsedata, samt i en egen forskningsdatabase ved Universitetet i Bergen. Ved prosjektets slutt, vil navnet ditt bli slettet fra forskningsdatabasen og de kliniske opplysningene bli lagret i tannlegejournal for senere bruk. Hvis du sier ja til å delta i studien, gir du også ditt samtykke til at avidentifiserte opplysninger utleveres til samarbeidende forskere ved foretakene i Helse Vest og Universitetet i Bergen, samt forskere i Trondheim og i Tromsø. Enhver utlevering av opplysninger til samarbeidende forskere vil bli lagt frem for REK.

Frivillig deltakelse
Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn, trekke ditt samtykke om å delta i studien. Dette vil ikke få konsekvenser for din videre behandling eller for behandlingstilbudene i Den offentlige tannhelsetjenesten. Ønsker du å trekke deg, gir du beskjed til en av undertegnende, også om du bare har spørsmål om studien.

Ved ytterligere spørsmål, kontakt
1.amanuensis/spesialist pedodonti Marit Slåttelid Skeie, Universitetet i Bergen (tlf. 55 586576).

Marit Slåttelid Skeie
Førsteamanuensis/
Spesialist pedodonti

Karen Rosendahl
Prof./ Overlege/Barnerøntgen

Karin Tylleskär
Overlege/ Barneklinikken

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Versjon 21.5.15

Samtykke til deltakelse i studien

Jeg er villig til å delta i studien

(Navn og signatur, dato)

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)

Errata for

Subjective symptoms, clinical signs and imaging features related to temporomandibular disorder in juvenile idiopathic arthritis

Johannes M. Fischer

Thesis for the degree philosophiae doctor (PhD)
at the University of Bergen
2022

6. Juli 2022 Johannes Fischer
(date and sign. of candidate)

(date and sign. of faculty)

Errata

Page 6 Full stop missing: “A subset of 90 children and adolescents with JIA underwent a MRI, CBCT of the TMJs and ceph The agreement of continuous measurements was assessed with a 95% limit of agreement according to Bland-Altman and MDC at an individual level.” –corrected to “A subset of 90 children and adolescents with JIA underwent a MRI, CBCT of the TMJs and ceph. The agreement of continuous measurements was assessed with a 95% limit of agreement according to Bland-Altman and MDC at an individual level.”

Page 9 Missing abbreviation: Geometric morphometrics = GMMs

Page 9 Missing abbreviation: Magnetic resonance tomography = MR

Page 10 Missing abbreviation: T1 weighted = T1-w

Page 15 Missing words: In a previous clinical approach, Lövgren and colleagues validated three pain screening questions in relation to DC/TMD [16].” – corrected to “In a previous clinical approach, Lövgren and colleagues validated three pain screening questions in relation to the diagnostic criteria of temporomandibular disorder (DC/TMD) [16].”

Page 16 Abundant words: “Among the classifications mentioned above, the RDC/TMD, established by Dworkin and colleagues, has hitherto been the most widely used protocol in TMD research groups of experts, also called the “Consortium Network” based on The International Association of Dental Research and The International Association for the Study of Pain Association of Dental Research and The International Association for the Study of Pain [28].” – corrected to “Among the classifications mentioned above, the RDC/TMD, established by Dworkin and colleagues, has hitherto been the most widely used protocol in TMD research groups of experts, also called the “Consortium Network” based on The International Association of Dental Research and The International Association for the Study of Pain [28].

Page 17 Full stop missing: “Graue and colleagues also conducted an examination based on the DC/TMD criteria, finding a TMD prevalence of 11.9%, with a peak at 16 years of age is significantly higher in the 20–40-year age group (reproductive period) compared to other age groups and that TMD seems to be far more prevalent in the female population [40].” – corrected to “Graue and colleagues also conducted an examination based on the DC/TMD criteria, finding a TMD prevalence of 11.9%, with a peak at 16 years of age.”

Page 18 Missing words: “is significantly higher in the 20–40-year age group (reproductive period) compared to other age groups and that TMD seems to be far more prevalent in the female population [40].” – corrected to “Multiple cross-sectional studies have revealed that the overall prevalence of TMD is significantly higher in the 20–40-year age group (reproductive period) compared to other age groups and that TMD seems to be far more prevalent in the female population [40].”

Page 18 Punctuation error: “A recent systematic review pointed out that catastrophic thinking in terms of rumination and exaggeration of an existing or foreseen painful act or stimuli has a significant impact on the intensity of TMD pain [41] .” – corrected to “A recent systematic review pointed out that catastrophic thinking in terms of rumination and exaggeration of an existing or foreseen painful act or stimuli has a significant impact on the intensity of TMD pain [41].”

Page 18 Punctuation error: “An overview of the available literature on this topic revealed that occlusal adjustments or equilibration in terms of TMD management is critical [11, 44] .” – corrected to “An overview of the available literature on this topic revealed that occlusal adjustments or equilibration in terms of TMD management is critical [11, 44].”

Page 21 Punctuation error: “In children and adolescent patients, severe TMJ OA may lead to facial growth disturbances seen in reduced condylar width and height, which can negatively impact dental occlusion. [73].” – corrected to “In children and adolescent patients, severe TMJ OA may lead to facial growth disturbances seen in reduced condylar width and height, which can negatively impact dental occlusion [73].”

Page 28 Punctuation error: “The fluctuating episodes represent the dynamic and insidious character of JIA[131].” – corrected to “The fluctuating episodes represent the dynamic and insidious character of JIA [131].”

Page 30 Incorrectly abbreviated word: “More recently, the potential of MRI for the evaluation of growth disturbances secondary to TMJ involvement has been addressed, using T1-weighted 3D sequences to construct oblique sections through the mandible on which measurements are based [156-158].” – corrected to “More recently, the potential of MRI for the evaluation of growth disturbances secondary to TMJ involvement has been addressed, using T1- weighted (T1-w) 3D sequences to construct oblique sections through the mandible on which measurements are based [156-158].”

Page 30 Misspelling: “The x-ray source and image receptor rotate around the patient’s head, and a curved focal trough of dentation and surrounding bones is created after exposure.” – corrected to “The x-ray source and image receptor rotate around the patient’s head, and a curved focal trough of dentition and surrounding bones is created after exposure.”

Page 35 Misspelling: “The Case Report Form (CRF) (shown in Appendix I) contains assessment procedures, which were standardised and based on two shortened versions of diagnostic tools: the “Axis I Clinical Examination for DC/MD” [29] and “The EuroTMJoint Recommendations for Clinical TMJ Assessment in Patients Diagnosed With JIA” (shown in Appendix II) currently termed the Temporomandibular Joint Juvenile Arthritis (TMJAW) group.” – corrected to “The Case Report Form (CRF) (shown in Appendix I) contains assessment procedures, which were standardised and based on two shortened versions of diagnostic tools: the “Axis I Clinical Examination for DC/TMD” [29] and “The EuroTMJoint Recommendations for Clinical TMJ Assessment in Patients Diagnosed With JIA” (shown in Appendix II) currently termed the Temporomandibular Joint Juvenile Arthritis (TMJAW) group.”

Page 38 Incorrectly abbreviated word: “In Paper II, a sagittal T1-weighted MPRAGE (ultrafast gradientecho 3D) sequence (TR/TE/FA/SL =2000/2.26/8/1) was used.” – corrected to “In Paper II, a sagittal T1-w MPRAGE (ultrafast gradientecho 3D) sequence (TR/TE/FA/SL =2000/2.26/8/1) was used.”

Page 38 Missing word: “Figure 5. a) Total mandibular length measured between the most cranial point of the condyle (Co) and the most anterior/inferior border of the chin in the mandibular midline (Gn) and b) Posterior mandibular ramus length measured between the most cranial point of the condyle and gonion (Co-Go).” – corrected to “Figure 5. a) Total mandibular base length measured between the most cranial point of the condyle (Co) and the most anterior/inferior border of the chin in the mandibular midline (Gn) and b) Posterior mandibular ramus length measured between the most cranial point of the condyle and gonion (Co-Go).”

Page 41 Punctuation error: “Familiar pain symptoms, the calculation of pain frequency/intensity (stage 10), the analyses of frontal asymmetry (stage 12) and profile of the face (stage 13) and finally swelling of the TMJ (stage14). exhibited low values and have been excluded from statistics.” – corrected to “Familiar pain symptoms, the calculation of pain frequency/intensity (stage 10), the analyses of frontal asymmetry (stage 12) and profile of the face (stage 13) and finally swelling of the TMJ (stage14) exhibited low values and have been excluded from statistics.”

Page 46 Abundant word: “This cross-sectional design of Study III study addressed potential associations between TMD and findings on CBCT.” – corrected to “This cross-sectional design of Study III addressed potential associations between TMD and findings on CBCT.”

Page 47 Misspelling: “* 3 CBCT scans are not available for these analyzes as the field of view (FOV) did not cover the relevant structures.” – corrected to “* 3 CBCT scans are not available for these analyses as the field of view (FOV) did not cover the relevant structures.”

Page 53 Incorrectly abbreviated word: “For MRI, all the measurements were performed on multiplanar reconstructed T1 weighted images as described in Paper II.” – corrected to “For MRI, all the measurements were performed on multiplanar reconstructed T1-w images as described in Paper II.”

Page 54 Punctuation error: “The MDC was defined as a change that falls outside the limits of agreement of the Bland Altman method, i.e., limits of agreement give information about MDC [217].” – corrected to “The MDC was defined as a change that falls outside the limits of agreement of the Bland-Altman method, i.e., limits of agreement give information about MDC [217].”

Page 55 Incorrectly abbreviated word: “By adding a 3D T1 weighted sequence to the standard protocol, a measurement to evaluate potential growth disturbances is gained.” – corrected to “By adding a 3D T-w sequence to the standard protocol, a measurement to evaluate potential growth disturbances is gained.”

Page 56 Misspelling: “Sharpened diagnostic tools are key for instigating the best treatment available.” – corrected to “Sharpened diagnostic tools are key for investigating the best treatment available.”

Page 58 Error in reference: “3. Clinical and Experimental Dental Research.” – corrected to “Clin Exp Dent Res,”

Page 58 Error in reference: “4. Clinical Journal of Pain,” – corrected to “Clin J Pain,”

Page 58 Error in reference: “5. Oral Diseases,” – corrected to “Oral Dis,”

Page 58 Error in reference: “6. New England Journal of Medicine,” – corrected to ”N Engl J Med,”

Page 58 Error in reference: “7. Journal of Pain,” – corrected to “J Pain, p. T27-45. “

Page 58 Error in reference: “9. Journal of Orofacial Pain,” – corrected to “J Orofac Pain, **19**(2): p. 144-50.”

Page 58 Error in reference: “10. J Orofac Pain,” – corrected to “J Orofac Pain,”

Page 58 Error in reference: “15. Journal of Orofacial Pain.” – corrected to “J Orofac Pain,”

Page 58 Error in reference: “16. Journal of Oral Rehabilitation,” – corrected to “J Oral Rehabil,”

Page 59 Error in reference: “17. Pain Medicine.,” – corrected to “Pain Med,”

Page 59 Error in reference: “23. Journal of Oral Rehabilitation,” – corrected to “J Oral Rehabil,”

Page 59 Error in reference: “26. Swedish dental journal,” – corrected to “Sven Tandlak Tidskr,”

Page 59 Error in reference: “28. Journal of craniomandibular disorders: facial & oral pain,” – corrected to “J Craniomandib Disord,”

Page 59 Error in reference: “29. *Group†.* Journal of Oral & Facial Pain and Headache,” – corrected to “*Groupdagger.* J Oral Facial Pain Headache,”

Page 59 Error in reference: “30. J Orofac Pain.,” – corrected to “30. Journal of Orofacial Pain, **26**(1): p. 17-25.”

Page 59 Error in reference: “31. Angle Orthodontist,” – corrected to “Angle Orthod,”

Page 60 Error in reference: “32. Clinical Oral Investigations,” – corrected to “32. Clin Oral Investig,”

Page 60 Error in reference: “33. Pesquisa odontologica brasileira = Brazilian oral research,” – corrected to “Braz Oral Res,”

Page 60 Error in reference: “35. Journal of Orofacial Orthopedics” – corrected to “J Orofac Orthop, : p. 6-8, 10-8.”

Page 60 Inadequate reference: “36. *Determinants for craniofacial pains in children 6–8 years of age: the PANIC study.* Acta Odontologica Scandinavica, 2017.” – corrected to “*Clinical Signs of Temporomandibular Disorders and Various Pain Conditions*

Among Children 6 to 8 Years of Age: The PANIC Study. Journal of Orofacial Pain, 2012. **26**(1): p. 17-25."

Page 60 Error in reference: "37. de Paiva Bertoli, F.M.," – corrected to "Bertoli, F.M.P., : p. e0192254."

Page 60 Error in reference: "38. Acta Odontologica Scandinavica," – corrected to "Acta Odontol Scand,"

Page 60 Error in reference: "40. Journal of Oral Rehabilitation," – corrected to "J Oral Rehabil,"

Page 60 Error in references: "41. Journal of Oral & Facial Pain and Headache," – corrected to "J Oral Facial Pain Headache,"

Page 60 Error in reference: "42. Journal of Oral Rehabilitation," – corrected to "J Oral Rehabil, **48**(11): p. 1193-1200."

Page 60 Error in reference: "43. Cranio - Journal of Craniomandibular Practice," – corrected to "Cranio,"

Page 60 Error in reference: "45. American Journal of Orthodontics and Dentofacial Orthopedics," – corrected to "Am J Orthod Dentofacial Orthop,"

Page 60 Error in reference: "46. Angle Orthodontist," – corrected to "Angle Orthod,"

Page 61 Error in reference: "47. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics," – corrected to "Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontology,"

Page 61 Inadequate reference: "48. Manfredini, D., L. Lombardo, and G. Siciliani, *Dental occlusion and temporomandibular disorders.* Evidence-Based Dentistry, 2017. **18**(3): p. 86-87." -923." – corrected to "48. Manfredini, D., et al., *Orthodontics is temporomandibular disorder-neutral.* Angle Orthod, 2016. **86**(4): p. 649-54."

Page 61 Error in reference: "50. 2010. p. 430-451" – corrected to "J Oral Rehabil, 2010. **37**(6): p. 430-51."

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Page 61 Error in reference: "58. Journal of Rheumatology," – corrected to "J Rheumatol,"

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Page 61 Error in reference: “62. International Review of Cytology,” – corrected to “Int Rev Cytol, (Iv):”

Page 62 Error in reference: “American Journal of Orthodontics and Dentofacial Orthopedics,” – corrected to “Am J Orthod Dentofacial Orthop,”

Page 62 Error in reference: “65. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics,” – corrected to “Oral Surg Oral Med Oral Pathol Oral Radiol Endod, : p. 372-8.”

Page 62 Error in reference: “67.” – corrected to “: p. 428-32.”

Page 62 Error in reference: “69. Journal of Oral Rehabilitation,” – corrected to “J Oral Rehabil,”

Page 62 Error in reference: “73. American Journal of Orthodontics and Dentofacial Orthopedics,” – corrected to “Am J Orthod Dentofacial Orthop,”

Page 62 Error in reference: “75.” – corrected to “Int J Oral Maxillofac Surg, 2007. **36**(7): p. 571-6.”

Page 62 Error in reference: “76. Journal of the Royal Society of Medicine,” – corrected to “Proc R Soc Med,”

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Page 63 Error in reference: “82. Journal of Oral and Maxillofacial Surgery,” – corrected to “J Oral Maxillofac Surg,”

Page 63 Error in reference: “83. Orthodontics and Dentofacial Orthopedics,” – corrected to “Am J Orthod Dentofacial Orthop,”

Page 63 Error in reference: “85. European Journal of Orthodontics,” – corrected to “Eur J Orthod,”

Page 63 Error in reference: “86. American Journal of Orthodontics and Dentofacial Orthopedics,” – corrected to “Am J Orthod Dentofacial Orthop, **98**(1): p. 29-32.”

Page 63 Error in reference: “87. Journal of Rheumatology,” – corrected to “J Rheumatol, **22**(10): p. 1956-61.”

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Page 63 Error in reference: “89. Acta radiologica: diagnosis,” – corrected to “Acta Radiol Diagn (Stockh), **22**(5): p. 593-9.”

Page 63 Error in reference: “European Radiology,” – corrected to “Eur Radiol, : p. 2512-7.”

Page 63 Error in reference: “92. BMC Medical Imaging,” – corrected to “BMC Med Imaging, : p. 28.”

Page 63 Error in reference: “93. Pediatric Radiology,” – corrected to “Pediatr Radiol,”

Page 63 Error in reference: “94. Scientific Reports,” – corrected to “Sci Rep,”

Page 64 Error in reference: “97. *Mayer S. Diamantberger (1864-1944). Erstbeschreiber der juvenilen chronischen Arthritis.* Zeitschrift fur Rheumatologie, 2009. **68**(3): p. 264-270.” – corrected to “*[Mayer S. Diamantberger (1864-1944). The first person to describe juvenile chronic arthritis].* Z Rheumatol,”

Page 64 Error in reference: “98. The Journal of rheumatology,” – corrected to “J Rheumatol,”

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Page 64 Error in reference: “110.” – corrected to “Clin Exp Rheumatol, **17**(3):”

Page 64 Error in reference: “111. PEDIATRICS” – corrected to “Pediatrics, **121**(2): p. e299-306.”

Page 64 Error in reference: “112.” – corrected to “Best Pract Res Clin Rheumatol, **23**(5):”

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Page 65 Error in reference: “114.” – corrected to “Best Pract Res Clin Rheumatol, **23**(5):”

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Page 65 Error in reference: “117. European Journal of Clinical Microbiology and Infectious Diseases,” – corrected to “Eur J Clin Microbiol Infect Dis,”

Page 65 Error in reference: “118. Pediatric Rheumatology,” – corrected to “Pediatr Rheumatol Online J,”

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Page 65 Error in reference: “120. Scandinavian Journal of Rheumatology,” – corrected to “ Scand J Rheumatol,”

Page 65 Error in reference: “122. Journal of Rheumatology,” – corrected to “J Rheumatol,”

Page 65 Error in reference: “123. Pediatric Rheumatology,” – corrected to “Pediatr Rheumatol Online J, : p. 47.”

Page 65 Error in reference: “125. The Journal of rheumatology,” – corrected to “J Rheumatol,”

Page 65 Error in reference: “126. Rheumatology,” – corrected to “Rheumatology (Oxford),”

Page 65 Error in reference: “127. Journal of Rheumatology,” – corrected to “J Rheumatol, : p. 1774-9.”

Page 65 Error in reference: “128. Journal of Interferon and Cytokine Research,” – corrected to “J Interferon Cytokine Res,”

Page 66 Error in reference: “129.” – corrected to “Nat Rev Immunol, **14**(9): ”

Page 66 Error in reference: “130. Elsevier B.V.” – corrected to “Lancet, 2011. **377**(9783):”

Page 66 Error in reference: “131. The Journal of rheumatology,” – corrected to “J Rheumatol,”

Page 66 Error in reference: “132. Olsen-Bergem, H., T. Bjornland, and J.E. Reseland,” – corrected to “Olsen-Bergem, H.,”

Page 66 Error in reference: “133.” – corrected to “Curr Rheumatol Rep, 2017. **19**(12): p. 75.”

Page 66 Error in reference: “135. 2011, Arthritis Care Res (Hoboken).” – corrected to “Arthritis Care Res (Hoboken), 2011. **63**(4):”

Page 66 Error in reference: “136. 2011.” – corrected to “Arthritis Care Res (Hoboken), 2011. **63**(7):”

Page 66 Error in reference: “137. Journal of Rheumatology,” – corrected to “J Rheumatol,”

Page 66 Error in reference: “138.” – corrected to “Pediatr Rheumatol Online J, **18**(1): p. 75.”

Page 66 Error in reference: “139. Journal of rheumatology,” – corrected to “J Rheumatol,”

Page 66 Error in reference: “140. Journal of Rheumatology,” – corrected to “J Rheumatol, : p. 190-197.”

Page 66 Error in reference: “141. 2018, Elsevier.” – corrected to “Lancet Child Adolesc Health, 2018. **2**(5):”

Page 66 Error in reference: “142. British Medical Bulletin,” – corrected to “Br Med Bull, **40**(2):”

Page 66 Error in reference: “144. Pediatric Rheumatology,” – corrected to “Pediatr Rheumatol Online J, : p. 8.”

Page 67 Error in reference: “146. Arthritis Care & Research, 2021: p. 0-3.” – corrected to “Arthritis Care Res (Hoboken), 2022. **74**(2): p. 308-316.”

Page 67 Error in reference: “147. Dentomaxillofacial Radiology,” – corrected to “Dentomaxillofac Radiol,”

Page 67 Error in reference: “148 British Journal of Radiology,” – corrected to “Br J Radiol,”

Page 67 Error in reference: “149. Dentomaxillofacial Radiology,” – corrected to “Dentomaxillofac Radiol, : p. 20190272.”

Page 67 Error in reference: “152. Radiology,” – corrected to “Radiology,”

Page 67 Error in reference: “154. Annals of the Rheumatic Diseases,” – corrected to “Ann Rheum Dis,”

Page 67 Error in reference: “155. Journal of Rheumatology,” – corrected to “J Rheumatol,”

Page 67 Error in reference: “156. European Journal of Orthodontics,” – corrected to “Eur J Orthod,”

Page 67 Error in reference: “157. Progress in Orthodontics,” – corrected to “Prog Orthod, : p. 40.”

Page 67 Error in reference: “158. Rheumatology,” – corrected to “. Rheumatology (Oxford),”

Page 67 Error in reference: “159.” – corrected to “Acta radiol, **32**(2-3):, illust.”

Page 68 Error in reference: “161. Oral Surg Oral Med Oral Pathol Oral Radiol Endod,” corrected to “Oral Surg Oral Med Oral Pathol Oral Radiol Endod,”

Page 68 Error in reference: “162. Seminars in Arthritis and Rheumatism,” – corrected to “Semin Arthritis Rheum,”

Page 68 Error in reference: “163. Journal of Rheumatology,” – corrected to “J Rheumatol,”

Page 68 Error in reference: “164. Acta Odontologica Scandinavica,” – corrected to “Acta Odontol Scand,”

Page 68 Error in reference: “165. Angle Orthodontist,” – corrected to “Angle Orthod, : p. 388-93.”

Page 68 Error in reference: “166. Dentomaxillofacial Radiology,” – corrected to “Dentomaxillofac Radiol, : p. 34.”

Page 68 Error in reference: “167.” – corrected to “Dentomaxillofac Radiol, **44**(1): p. 20140235.”

Page 68 Error in reference: “168. American Journal of Orthodontics and Dentofacial Orthopedics,” – corrected to “Am J Orthod Dentofacial Orthop,”

Page 68 Error in reference: “169. The European Journal of Orthodontics,” – corrected to “Eur J Orthod,”

Page 68 Error in reference: “170. Journal of Cranio-Maxillofacial Surgery,” – corrected to “J Craniomaxillofac Surg,”

Page 68 Error in reference: “171. Minerva stomatologica,” – corrected to “Minerva Stomatol,”

Page 68 Error in reference: “173. Journal of Oral and Maxillofacial Surgery, 1343.e1-1343.e8.” – corrected to “J Oral Maxillofac Surg, 1343 e1-8.”

Page 68 Error in reference: “174. American Journal of Orthodontics and Dentofacial Orthopedics,” – corrected to “Am J Orthod Dentofacial Orthop,”

Page 68 Error in reference: “175. Progress in Orthodontics,” – corrected to “Prog Orthod, : p. 32.”

Page 69 Error in reference: “176. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology,” – corrected to “Oral Surg Oral Med Oral Pathol Oral Radiol Endod,”

Page 69 Error in reference: “177. European Journal of Orthodontics,” – corrected to “Eur J Orthod,”

Page 69 Error in reference: “178. Angle Orthodontist,” – corrected to “Angle Orthod, : p. 396-403.”

Page 69 Error in reference: “179. American Journal of Orthodontics,” – corrected to “Am J Orthod,”

Page 69 Error in reference: “180. European Journal of Orthodontics,” – corrected to “Eur J Orthod,”

Page 69 Error in reference: “181. Dentomaxillofacial Radiology,” – corrected to “Dentomaxillofac Radiol, : p. 100-6.”

Page 69 Error in reference: “182. Dentomaxillofacial Radiology,” – corrected to “Dentomaxillofac Radiol,”

Page 69 Error in reference: “183. J Orofac Orthop,” – corrected to “J Orofac Orthop,”

Page 69 Error in reference: “184. Cleft Palate-Craniofacial Journal,” – corrected to “Cleft Palate Craniofac J,”

Page 69 Error in reference: “185. Medical Decision Making,” – corrected to “Med Decis Making,”

Page 69 Error in reference: “186. BMC Oral Health,” – corrected to “BMC Oral Health, : p. 285.”

Page 69 Error in reference: “190. Scandinavian Journal of Rheumatology,” – corrected to “Scand J Rheumatol,”

Page 69 Error in reference: “191. The Journal of Prosthetic Dentistry,” – corrected to “ J Prosthet Dent,”

Page 70 Error in reference: “192. 2018.” – corrected to “**2018**: p. 7474608.”

Page 70 Error in reference: “194. The Journal of Rheumatology, 2019: p. jrheum.190661-jrheum.190661.” – corrected to “J Rheumatol, 2020. **47**(9): p. 1397-1404.”

Page 70 Error in reference: “195. Journal of Chiropractic Medicine,” – corrected to “J Chiropr Med,”

Page 70 Error in reference: “196. Swedish Dental Journal,” – corrected to “Swed Dent J,”

Page 70 Error in reference: “198. Cranio - Journal of Craniomandibular Practice,” – corrected to “Cranio,”

Page 70 Error in reference: “200. The Journal of Rheumatology,” – corrected to “J Rheumatol,”

Page 70 Error in reference: “202. The Journal of rheumatology,” – corrected to “J Rheumatol,”

Page 70 Error in reference: “203. Journal of Oral Rehabilitation, 2021.” – corrected to “J Oral Rehabil, 2022. **49**(1): p. 37-46.”

Page 70 Error in reference: “204. European Journal of Pain (United Kingdom),” – corrected to “Eur J Pain,”

Page 70 Error in reference: “206. Academic Radiology,” – corrected to “Acad Radiol,”

Page 70 Error in reference: “207. American Journal of Orthodontics,” – corrected to “Am J Orthod,”

Page 71 Error in reference: “208. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology,” – corrected to “Oral Surg Oral Med Oral Pathol Oral Radiol Endod,”

Page 71 Error in reference: “209. Arif, C.A., et al., *Journal* of Oral and Maxillofacial Surgery, 2021.” – corrected to “Celebi, A.A., et al., J Oral Maxillofac Surg, 2022. **80**(3): p. 422-430.”

Page 71 Error in reference: “211. Pediatric Rheumatology, 1-14.” – corrected to “Pediatr Rheumatol Online J, 106.”

Page 71 Error in reference: “212. Angle Orthodontist,” – corrected to “Angle Orthod,”

Page 71 Error in reference: “213. European Journal of Orthodontics,” – corrected to “Eur J Orthod,”

Page 71 Error in reference: “214. American Journal of Orthodontics and Dentofacial Orthopedics, 546.e1-546.e8.” – corrected to “Am J Orthod Dentofacial Orthop, 546 e1-8; discussion 546-7.”

Page 71 Error in reference: “215. Cevidanes, L.H.S., American Journal of Orthodontics and Dentofacial Orthopedics,” – corrected to “Cevidanes, L.H., Am J Orthod Dentofacial Orthop,”

Page 71 Error in reference: “216.” – corrected to “216. Nephron Clin Pract, **120**(3): p. c162-7.”

Page 71 Error in reference: “218. Oral surgery, oral medicine, oral pathology and oral radiology,” – corrected to “Oral Surg Oral Med Oral Pathol Oral Radiol,”

Page 71 Error in reference: “219. Journal of orofacial orthopedics” – corrected to “J Orofac Orthop, 506-19.”

Page 71 Error in reference: “220. Dentomaxillofacial Radiology,” – corrected to “Dentomaxillofac Radiol, : p. 20170305.”

Page 71 Error in reference: “221. Journal of Pain,” – corrected to “J Pain,”

Page 71 Error in reference: “225. European Journal of Pain,” – corrected to “Eur J Pain, 49-56.”

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