

**Supplementary Material 1. Search strategy.**

The literature search was performed on June 26 2014. The databases searched were: Pubmed Medline, Embase, Scopus, Web of Science, Cochrane Database of systematic reviews, Database of Abstracts of Reviews of Effect (DARE), and Cochrane Central Register of Controlled Trials. The search term used was constructed for MEDLINE and adjusted in accordance with the syntax rules of the other databases:

Medline search strategy: (juvenile idiopathic arthritis) OR (juvenile rheumatoid arthritis) OR (juvenile chronic arthritis) OR (juvenile idiopathic arthritides) OR (Still\* disease) OR (Still disease) OR JIA OR JCA OR JRA AND  
(temporomandibular joint) OR (temporomandibular joints) OR TMJ AND  
(risk factors) OR (risk factor) OR diagnosis OR diagnose OR predictors OR predictor OR prediction OR examination OR examinations OR sign OR signs OR symptom OR symptoms OR pain OR complaint OR complaints OR [(craniofacial OR dentoskeletal OR facial OR jaw) AND (morphology OR asymmetry OR symmetry)]

## **Supplementary Material 2. Data extraction criteria.**

Research question 1 and 2: With respect to monitoring patients with JIA and TMJ arthritis:

1. RQ 1: What is the general validity of the recommendation?
2. RQ 2: What is the level of evidence of the recommendation?

### Inclusion criteria:

- JIA, JRA, or JCA diagnosis.
- Studies involving assessment of orofacial clinical signs or symptoms by some kind of clinical orofacial examination; descriptive studies, observational studies, clinical studies dealing with intervention.
- Studies with a sufficient and clear description of the clinical outcome variable(s) examined.
- Majority of patients below 18 years of age or longitudinal cohort study where baseline data was from patients below the age of 18 years.
- Only English and German articles included.
- All articles presenting original research regardless of year of publication.

### Exclusion criteria:

- Dual publications with the exception of meta-analyses.
- Non-peer reviewed studies (e.g. conference abstracts).
- Review articles and animal studies.
- Studies on adults, case-reports or case series with less than 5 patients, dual publications.

Research question 3 and 4: With respect to diagnosis of TMJ arthritis:

3. RQ3: What is the diagnostic validity of the recommendation?
4. RQ4: What is the level of evidence of the recommendation with respect to diagnostic validity?

### Inclusion criteria:

- JIA, JRA, or JCA diagnosis.
- Studies presenting data on clinical outcome measures predicting TMJ inflammation and/or TMJ hard tissue abnormalities where diagnosis of TMJ inflammation is based on contrast-enhanced MRI and/or TMJ hard tissue abnormalities are diagnosed based on sufficient radiological techniques (tomograms, CBCT, CT).
- Majority of patients below 18 years of age.
- Only English and German articles included.
- All articles presenting original research regardless of year of publication.

### Exclusion criteria:

- Studies without measureable/objective clinical outcome variables.
- Studies without a direct description of the clinical findings and imaging/radiological findings.
- Dual publications with the exception of meta-analyses.
- Studies using insufficient imaging techniques to assess TMJ inflammation (MRI without contrast-enhancement).
- Studies using inconclusive radiological modalities for the assessment of TMJ hard tissue changes (panoramic and cephalometric images).
- Non-peer-reviewed studies (e.g. conference abstracts).
- Review articles, animal studies, descriptive studies.
- Studies on adults, case-reports or case series with less than 5 patients, dual publications.

**Supplementary Material 3. Outcome variable ratings:** Clinical outcome variables rated of “moderate and low importance” in the Delphi survey (median  $\leq 8$ , on a 10 point numerical scale, 0 = not important, 10 = of utmost importance); presented together with second round median score and 25<sup>th</sup>/75<sup>th</sup> percentiles. First round scores are illustrated in brackets.

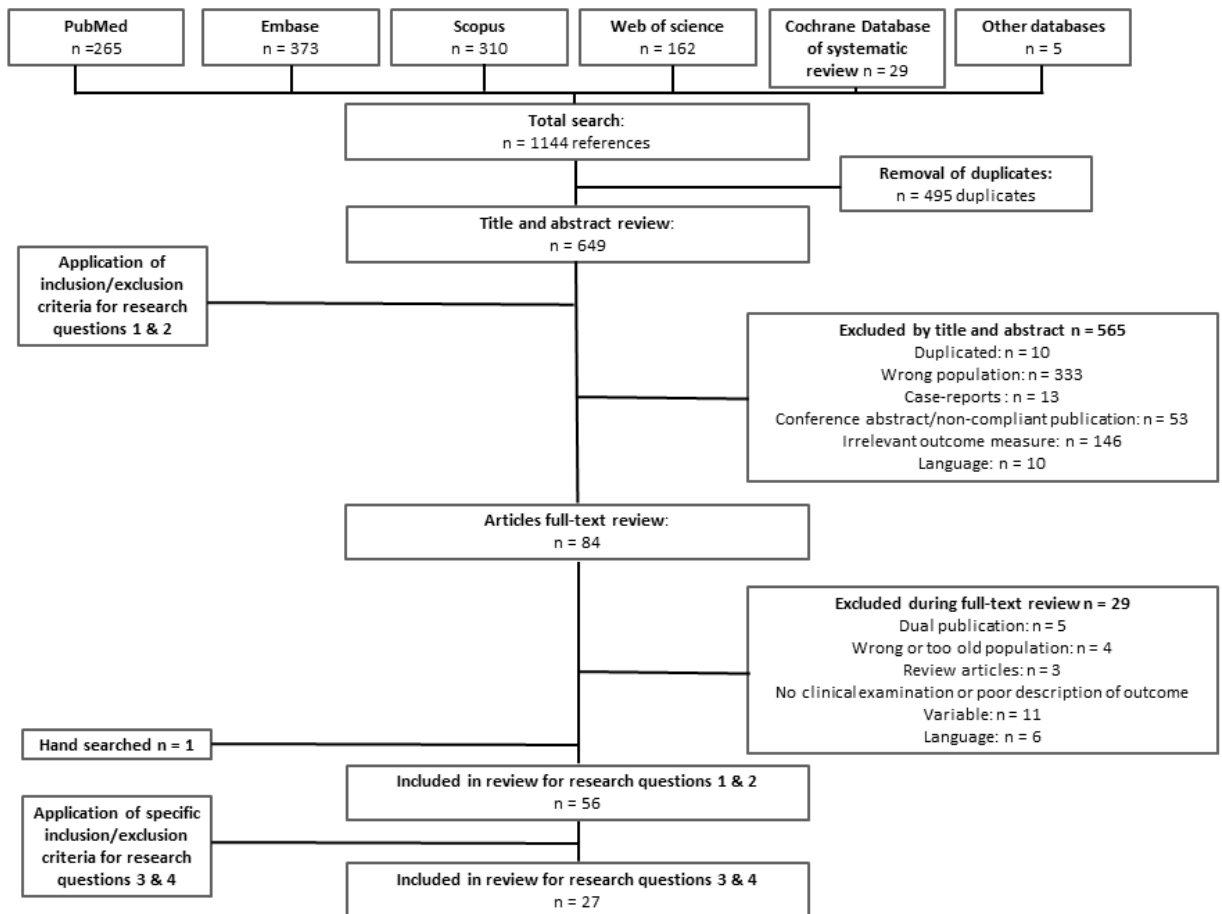
Outcome variables rated of “moderate importance” ( $6 \leq \text{median} < 8$ ) in the second Delphi round

Outcome variable	2 <sup>nd</sup> round median score	25 <sup>th</sup> /75 <sup>th</sup> percentiles
Symptom assessment variables		
Assessment of influence on sleep	7 (7)	6-8 (5-9)
Clinical examination variables		
Incisal overjet in centric position	6 (6)	4-7 (4-8)
Occlusion - distance between the intercuspidal and retruded mandibular position (sagittal plane)	6 (6)	3-7 (3-6)

Outcome variables rated of “low importance” (median  $< 6$ ) in the second Delphi round

Outcome variable	2 <sup>nd</sup> round median score	25 <sup>th</sup> /75 <sup>th</sup> percentiles
<u>Symptom assessment variables</u>		
Duration (when present)	5 (6)	4-8 (4-7)
Pain duration/ onset of pain	5 (6)	3-8 (4-7)
Associated symptoms (e.g. fatigue, headache, etc)	5 (6)	4-6 (4-8)
Emotional factors associated with the orofacial pain	4 (5)	3-5 (3-7)
Orofacial pain sensory descriptors	5 (5)	3-6 (3-8)
Level of unpleasantness	4 (5)	3-5 (3-7)
Influence on appetite	4 (5)	3-5 (2-7)
Influence on speech	5 (6)	3-7 (4-7)
Influence on social interactions	5 (5)	3-7 (3-7)
<u>Clinical examination variables</u>		
Joint sounds during mouth opening	5 (6)	4-7 (4-8)
Joint sounds/crepitation during laterotrusion	5 (6)	4-6 (4-7)
Intraoral muscle tenderness with palpation	5 (5)	3-6 (2-7)
Pain with palpation of shoulder and cervical spine	4 (5)	3-6 (3-7)

**Supplementary Material 4. Flowchart of the literature search process.**



**Supplementary Material 5. Articles included to answer research questions 1 and 2**

1. Abdul-Aziez OA, Saber NZ, El-Bakry SA, Mohammad AA, Abdel-Maksud SS, Ali Y. Serum S100A12 and temporomandibular joint magnetic resonance imaging in juvenile idiopathic arthritis Egyptian patients: a case control study. *Pak J Biol Sci* 2010;13:101-13.
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15. Habibi S, Ellis J, Strike H, Ramanan AV. Safety and efficacy of US-guided CS injection into temporomandibular joints in children with active JIA. *Rheumatology(Oxford)* 2011;51:874-77.

16. Hanna VE, Rider SF, Moore TL, Wilson VK, Osborn TG, Rotskoff KS, et al. Effects of systemic onset juvenile rheumatoid arthritis on facial morphology and temporomandibular joint form and function. *J Rheumatol* 1996;23:155-58.
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#### Articles included to answer research questions 3 and 4

1. Abdul-Aziez OA, Saber NZ, El-Bakry SA, Mohammad AA, Abdel-Maksud SS, Ali Y. Serum S100A12 and temporomandibular joint magnetic resonance imaging in juvenile idiopathic arthritis Egyptian patients: a case control study. *Pak J Biol Sci* 2010;13:101-13.
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17. Mussler A, Allozy B, Landau H, Kallinich T, Trauzeddel R, Schroder RJ. Comparison of magnetic resonance imaging signs and clinical findings in follow-up examinations in children and juveniles with temporomandibular joint involvement in juvenile idiopathic arthritis. *Rofo* 2010;182: 36-44.
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- effective therapy in children with juvenile idiopathic arthritis. *J Oral Maxillofac Surg* 2012;70:1802-7.
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## Supplementary Material 6. Detailed summary of the supporting evidence behind each of the recommendations

### Recommendation 1:

*The medical history should include: Sex, age at time of examination, JIA category, disease duration, previous/current medications, previous/current orthodontic treatment, and disease activity.*

*Validity and level of evidence for recommendation 1 with respect to monitoring patients with JIA (RQ 1 and RQ 2):*

The majority of all eligible articles included background information <sup>(1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46)</sup>. The information varied among the studies. The most consistently included items were: age at time of examination, JIA category, and disease duration. Information about medication or disease activity level was not consistently reported across the literature. The level of evidence for this recommendation was graded III (Table 2).

*Diagnostic validity and level of evidence of recommendation 1 (RQ 3 and RQ 4):*

A number of studies found that certain factors are associated with the presence of TMJ arthritis. This includes: early age at onset <sup>(6 9 18)</sup>; high disease activity <sup>(1 18)</sup>; and long disease duration <sup>(6 18 47)</sup>. In contrast, Stoll *et al.* reported that a shorter disease duration was associated with an increased risk of MRI-verified TMJ inflammation (OR 0.87, 95% CI 0.78-0.97) <sup>(37)</sup>. The discrepancy in findings of disease duration and TMJ inflammation might be explained by the fact that Stoll's group used contrast-enhanced MRI, in addition to an assessment of hard-tissue destruction, which offered the opportunity to detect early inflammatory soft-tissue changes. Previous studies used only conventional radiographic techniques and a variety of tomograms, which lacked the sensitivity to detect early changes, but instead showed chronic structural changes which would be expected to be positively correlated with a longer disease course. Several studies have also demonstrated an association between specific JIA categories and the presence of TMJ involvement. Cannizaro *et al.* found that with 3 specific categories of JIA increased the risk of MRI-verified TMJ inflammation: oligo extended, rheumatoid factor (RF) negative polyarticular, and the psoriatic (likelihood ratio 14.8) <sup>(9)</sup>. Additionally, the systemic and the polyarticular categories have been associated with the presence of TMJ osseous destruction <sup>(6 18)</sup>. With respect to diagnosis, the level of evidence for this recommendation was graded III (Table 2).

### Recommendation 2:

*The patient should be asked about the presence of orofacial symptoms. This should include location, intensity, frequency, character and situations in which the symptoms occur.*

*Validity and level of evidence of recommendation 2 with respect to monitoring patients with JIA (RQ 1 and RQ 2):*

Forty of the eligible articles included an assessment of orofacial symptoms <sup>(1 2 4 5 6 7 10 11 13 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 33 38 39 41 42 43 44 45 46 47 48 49 50 51 52 53)</sup>. The majority of the studies assessed specific pain/symptom characteristics (“in what situations do you feel pain?”), whereas intensity, duration, and location were less often assessed.

Cross-sectional case-control studies reported a significantly higher prevalence of orofacial symptoms in patients with JIA compared with non-JIA controls <sup>(11 19 31 33 46 50 53)</sup>. The reported prevalence varied greatly among the studies and seems to be associated with long disease duration and older patient age, and could therefore be mechanical related pain due to abnormal function in a deformed joint. Weiss *et al.* found that 71% of newly diagnosed patients with MRI-verified signs of acute TMJ inflammation were asymptomatic (median age 8.6 years) <sup>(45)</sup>, whereas a large cross-sectional study by Cederstrom *et al.* demonstrated a varying degree of symptoms in all JIA categories, with a prevalence of 32-78% and a mean disease duration at first study visit of 2.9 years (25/75 percentiles 0.4/5.4 years) <sup>(10)</sup>. In keeping with this, Leksell *et al.* reported that orofacial symptoms were a common finding, and, furthermore, 22% of patients with JIA reported that orofacial symptoms had a severe influence on their daily activities <sup>(19)</sup>. Orofacial symptoms were most often described as being of moderate intensity. Persistent pain was not a common finding, and seemed to be triggered during functional loading associated with activities such as mastication and maximal mouth opening <sup>(7 19 39 50)</sup>. Follow-up studies described large intra-individual fluctuation of orofacial symptoms over time <sup>(7 39 50)</sup>, and the prevalence of pain and dysfunction in patients with JIA seemed to increase with age <sup>(50)</sup>. The pain sites most often involved were the TMJ area in combination with the masseter muscle region <sup>(7 39 50)</sup>. The level of evidence for this recommendation was graded III (Table 2).

#### *Diagnostic validity and level of evidence of recommendation 2 (RQ 3 and RQ 4):*

Symptoms such as pain were not found to be reliable predictors of TMJ inflammation, <sup>(5 8 17 23 28 37 45)</sup> despite the fact that there was a high prevalence of orofacial symptoms in the JIA cohorts studied <sup>(11 19 31 33 46 50 53)</sup>. Only a few studies found self-reported pain/symptoms to be a predictor of TMJ inflammation or hard tissue deformity <sup>(1 24)</sup>. Arabshahi *et al.* found more pain in joints with no signs of effusion on MRI (80%) compared to joints with effusion (53%) <sup>(5)</sup>. In support of this, Weiss *et al.* reported that symptoms and TMJ inflammation were associated with high specificity (100), but low sensitivity (26) <sup>(45)</sup>. When assessing reliability of symptoms to predict TMJ damage, Ronning *et al.*, reported that less than 40% of patients with condylar lesions displayed clinical symptoms; furthermore, symptoms were also found in patients without radiological condylar lesions <sup>(32)</sup>. In keeping with this, Svensson *et al.* concluded that the presence of pain was not a reliable sign of TMJ destruction, based on histological sections from resected human condylar heads <sup>(42)</sup>. With respect to diagnosis, the level of evidence for this recommendation was graded III (Table 2).

### **Recommendation 3:**

*The clinical examination of orofacial signs should include; palpation of the temporomandibular joint (lateral pole) and masticatory muscles (masseter and temporalis muscles); assessment of pain on palpation, TMJ pain on mandibular movement, and assessment of joint sounds (listening or auscultation)*

#### *Validity and level of evidence of recommendation 3 with respect to monitor patients with JIA (RQ 1 and RQ 2):*

More than half of the included studies (n=37) assessed the presence of clinical signs included palpation of the TMJs and masticatory muscles <sup>(1 2 3 4 7 8 11 12 13 14 15 16 17 18 19 20 21 22 23 25 26 27 28 30 31 32 33 38 41 43 44 45 46 47 49 51 53)</sup>. The majority of studies used this examination modality to address pain/tenderness in addition to the presence of crepitation and joint clicking. Palpation of the TMJ was a more common outcome measure than palpation of the masticatory muscles.

Extrapolated evidence from case-control studies shows that tenderness on palpation is significantly higher in patients with JIA compared to healthy controls <sup>(19 46 54)</sup>. There was also significantly more TMJ crepitation and clicking observed in the patients with JIA compared to healthy controls <sup>(19 20 46 54)</sup>. In a large and controlled cross-sectional study, Koos *et al.* found TMJ pain and muscle pain on

palpation to be significantly more frequent<sup>(54)</sup> in JIA patients compared to controls (TMJ tenderness 40% vs 8%; muscle tenderness, 61% vs. 22%). TMJ clicking was also significantly more frequent in JIA patients compared to controls (22% vs. 12%)<sup>(54)</sup>. The level of evidence for this recommendation was graded III (Table 2).

*Diagnostic validity and level of evidence of recommendation 3 (RQ 3 and RQ 4):*

In the study by Koos *et al.*, MRI-verified TMJ inflammation based on clinical outcome measures was estimated<sup>(54)</sup>. Both items for pain on palpation yielded intermediate predictive values for TMJ inflammation (sensitivity 0.40 and specificity 0.86 for TMJ pain on palpation; sensitivity 0.61 and specificity 0.71 for masseter muscle pain on palpation). The least sensitive item was TMJ clicking (sensitivity 0.23, specificity 0.87)<sup>(54)</sup>. With respect to diagnosis, the level of evidence for this recommendation was graded III (Table 2).

**Recommendation 4:**

*The clinical examination of orofacial function should include assessment of temporomandibular joint function; e.g. maximal mouth opening, mouth opening deviation, protrusion, laterotrusion, and condylar translation during opening.*

*Validity and level of evidence of recommendation 4 with respect to monitoring patients with JIA (RQ 1 and RQ 2):*

This recommendation embraces clinical examination outcome variables related to the mobility of the TMJ including: maximal mouth opening capacity, lateral mandibular excursion, protrusion, joint translation and mouth opening deviation. Based on the current literature, assessment of TMJ function seems to be extremely important. Fifty of the eligible articles included assessment of the TMJ function<sup>(1 2 3 4 6 7 8 9 10 11 12 14 15 16 17 18 19 20 21 22 23 24 25 26 28 29 30 32 33 34 35 36 37 38 40 41 42 43 44 45 46 47 48 49 51 52 53 55)</sup>.

The most consistently reported clinical outcome variables across the included literature were mouth opening capacity and mouth opening deviation. In general, findings related to these clinical examination variables must be cautiously compared between studies. This is due to the wide age ranges examined, the differences in the way the actual clinical assessments were conducted, and different cut-off points used to define a reduced maximal mouth opening and/or mouth opening deviation. Several different assessment methods were applied to define reduced maximal mouth opening such as strict cut-off values (usually <40 mm); comparisons with historical normative values; patient perceived reduced opening capacity; or with less precise assessment methods like the “3-finger rule”. In addition, there was no general distinction between the assessment of mouth-opening capacity with or without pain, and only a few studies defined the criteria for the presence of mouth opening deviation<sup>(17 54)</sup>.

Even though comparison of findings across the literature calls for cautious interpretation, the evidence from a substantial number of articles indicate an increased prevalence of reduced TMJ function in patients with TMJ arthritis compared with healthy controls; reduced maximal mouth opening capacity in patients with JIA was reported in a significant number of articles<sup>(3 5 19 23 33 37 38 46)</sup> together with the presence of mandibular deviation upon mouth opening<sup>(3 23 37 43 44 54)</sup>. Additionally, findings such as reduced joint translation, laterotrusion, protrusion, and bite-force were also reported with a higher frequency in patients with JIA<sup>(11 31 33 46 53)</sup>. The level of evidence for this recommendation was graded III (Table 2).

*Diagnostic validity and level of evidence of recommendation 4 (RQ 3 and RQ 4):*

Several cross-sectional studies evaluated the association between maximal mouth opening capacity and MRI-verified TMJ arthritis with the purpose of establishing clinical predictors to aid early diagnosis of TMJ arthritis. These studies showed that reduced maximal mouth-opening capacity had only a limited predictive value when using cut-off values (abnormal<40mm, Stoll *et al.*: Sens. 0.32 and spec. 0.75 median age 9.2 years; Müller *et al.*: sens. 0.31 and spec. 1, median age 9.8 years; Koos *et al.*, sens. 0.21 and spec. 0.83, mean age 13.3 years)<sup>(23 37 54)</sup>. With a 45 mm cut-off value Müller *et al.* reported an improved predictive value (abnormal<45mm, sens. 0.47 and spec. 0.91, median age of 9.8 years) and concluded that restricted or decreased mouth opening should be considered a sign of

TMJ involvement even in the absence of additional clinical findings associated with TMJ arthritis <sup>(23)</sup>. In comparison with normative values, Abramowicz *et al.* reported that patients with a limited maximal mouth opening (2 standard deviations below age-related normative values) were 6.7 times more likely to have synovitis than those with normal opening capacity <sup>(3)</sup>. Currently, limited longitudinal data exists correlating disease course of TMJ inflammation with the age-related developmental increase in maximal mouth opening capacity <sup>(17 28)</sup>. Unfortunately, the current data is insufficient to determine whether longitudinal assessment with a sudden change in maximal mouth opening capacity would have diagnostic value.

The presence of mandibular deviation during mouth opening was reported to be one of the single most sensitive clinical findings for the prediction of TMJ arthritis: Abramowicz *et al.*, OR 4.9 (95% CI 0.47–52.16); Stoll *et al.*, OR 6.21 (95% CI 2.87–13.4); Twilt *et al.* OR 7.1 (95% CI 2.3–23.5) <sup>(3 37 44)</sup>. In support of this, Koos *et al.* reported that the presence of mouth opening deviation was the single most reliable clinical findings for diagnosis of TMJ inflammation among five clinical examination outcome variables (sens.0.65, spec.0.78) <sup>(54)</sup>. Combined findings of reduced maximal mouth opening (2 standard deviations below age-related normative values) and mouth opening deviation was reported to have a positive predictive value of 1.00 for the presence of MRI-verified synovitis <sup>(3)</sup>. The diagnostic values of other outcome variables, reflecting TMJ function, were less often reported across the literature. Variables reflecting capacities of translation, laterotrusion, protrusion, and bite-force were reported in JIA; however, the current knowledge is too limited to conclude on their diagnostic values. With respect to diagnosis, the level of evidence for this recommendation was graded III (Table 2).

## Recommendation 5:

*The clinical examination should include assessment of facial morphology and symmetry; mandibular sagittal position (convexity of the facial profile); and lower face asymmetry in the frontal plane. Validity and level of evidence of recommendation 5 with respect to monitoring patients with JIA (RQ 1 and RQ 2):*

Assessment of the facial morphology and symmetry was included in 24 of the eligible studies <sup>(2 3 5 9 11 13 19 20 21 23 25 27 30 31 33 34 37 41 43 45 48 49 51 52)</sup>. Facial symmetry was more often assessed than the profile of patients. Both of these outcome variables were most often reported with a binary outcome (e.g. presence of facial asymmetry or a convex profile yes/no).

Extrapolated evidence from the literature indicates that facial asymmetry based on clinical examination is more prevalent in patients with JIA compared to healthy controls <sup>(2 3 9 11 13 23 34 37 51)</sup>.

Cross-sectional studies also reported a convex profile to be a prevalent finding in JIA. There was a significantly higher prevalence of convex profiles in patients with JIA compared to controls (Leksell *et al.* 56% vs. 5%, Savioli 33% vs. 7%) <sup>(19 31 33)</sup>. Prevalence of facial asymmetry and the presence of a convex profile were both associated with the severity of the TMJ abnormality <sup>(11 31 55)</sup>. The level of evidence for this recommendation was graded III (Table 2).

*Diagnostic validity and level of evidence of recommendation 5 (RQ 3 and RQ 4):*

The association between facial asymmetry/convex profile and the presence of TMJ inflammation is not very well examined in the literature. However, older studies have reported an association between hard-tissue TMJ lesions and dysmorphic craniofacial findings <sup>(31 34 55)</sup>. Hu *et al.* found a correlation between facial asymmetry/chin deviation and the severity of the erosive changes <sup>(13)</sup>. In a study by Ronchezet *et al.*, all patients with severe condylar alterations had a convex profile (100%) whereas 50% of patients with mild condylar alterations had a convex profile <sup>(31)</sup>. With respect to diagnosis, the level of evidence for this recommendation was graded IV (Table 2).

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