SYSTEMATIC REVIEW

Three-dimensional imaging of soft and hard facial tissues in patients with craniofacial syndromes: a systematic review of methodological quality

Arianne Lewyllie, Maria Cadenas De Llano-Pérula, Anna Verdonck and Guy Willems

Department of Oral Health Sciences - Orthodontics, KU Leuven and Dentistry, University Hospitals Leuven, Leuven, Belgium

Objectives: To systematically review the methodological quality of three-dimensional imaging studies of patients with craniofacial syndromes and to propose recommendations for future research.

Methods: PubMed, Embase and Cochrane databases as well as Grey literature were electronically searched. Inclusion criteria were patients with genetic syndromes with craniofacial manifestations and three-dimensional imaging of facial soft and/or hard tissues. Exclusion criteria consisted of non-syndromic conditions or conditions owing to environmental causes, injury or trauma, facial soft and hard tissues not included in the image analysis, case reports, reviews, opinion articles. No restrictions were made for patients' ethnicity nor age, publication language or publication date. Study quality was evaluated using the Methodological Index for Non-Randomized Studies (MINORS).

Results: The search yielded 2228 citations of which 116 were assessed in detail and 60 were eventually included in this review. Studies showed a large heterogeneity in study design, sample size and patient age. An increase was observed in the amount of studies with time, and the imaging method most often used was CT. The most studied craniofacial syndromes were Treacher Collins, Crouzon and Apert syndrome. The articles could be divided into three main groups: diagnostic studies (34/60, 57%), evaluation of surgical outcomes (21/60, 35%) and evaluation of imaging techniques (5/60, 8%). For comparative studies, the median MINORS score was 13 (12–15, 25–75th percentile), and for non-comparative studies, the median MINORS score was 8 (7–9, 25–75th percentile).

Conclusions: The median MINORS scores were only 50 and 54% of the maximum scores and there was a lack of prospective, controlled trials with sufficiently large study groups. To improve the quality of future studies in this domain and given the low incidence of craniofacial syndromes, more prospective multicentre controlled trials should be set up.

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Introduction

Craniofacial syndromes can be considered as a collective term for a wide group of congenital, genetic disorders with multiple anomalies and major symptoms in the craniofacial area. All of these syndromes are relatively

rare with only few live births per year. Some of the most studied craniofacial syndromes are those associated with early closure of the cranial sutures (Pfeiffer, Apert, Crouzon syndrome) together with Treacher Collins and Goldenhar syndrome.

There is a wide variety in the severity of the craniofacial manifestations between the syndromes, ranging

Correspondence to: Dr Guy Willems, E-mail: guy.willems@kuleuven.be

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from a clear deformity of the entire craniofacial skeleton to much more subtle asymmetries. To determine the extensiveness of the deformity, medical imaging is often performed for diagnosis or in relation to surgical interventions. Originally, two-dimensional (2D) images and measurements were made. However, a face is intrinsically a three-dimensional (3D) object. Preservation of this nature has been made possible since the introduction of 3D imaging methods, which are now widely and frequently used to give a detailed representation of the craniofacial structures.¹ However, some imaging procedures like CT or cone beam CT (CBCT) make use of ionizing radiation and their potential to harm developing tissues should be taken into account, especially in young children. In contrast, non-invasive imaging methods like MRI and 3D ultrasonography are also available and have their specific indications.² Another non-invasive 3D modality is facial surface scanning, which provides imaging of the external facial soft tissues. This technique has been increasingly used to investigate the relation between facial morphology and the underlying genes, the so-called “*phenotype–genotype interaction*”.

The primary aim of this review was to evaluate the methodological quality of 3D imaging studies of subjects with different craniofacial syndromes. The secondary aim was to make recommendations for performing future studies. We included a broad range of syndromes to gather as much information as possible on 3D imaging. We additionally evaluated the following:

- (1) Which 3D imaging methods were used?
- (2) What were the indications for taking these images?
- (3) What was the evolution over time of the study design and type of imaging methods?

Methods and materials

The protocol for this review followed a review structure developed prior to the literature search. Reporting follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines³ and the Population, Intervention, Comparison and Outcome of Interest process.⁴

Eligibility criteria

P. Patients with craniofacial syndromes

I. 3D imaging

C. 2D imaging technique, no comparison or other comparison group (non-affected side or healthy controls)

O. Assessment of facial soft and/or hard tissues

Publications using 3D imaging techniques for assessing facial soft and hard tissues in patients with genetic syndromes with craniofacial manifestations were eligible for inclusion. Exclusion criteria were: articles with a study group consisting only of patients with non-syndromic conditions or conditions owing to environmental causes (like non-syndromic cleft palate or obstructive sleep apnoea syndrome (OSAS), injury or trauma, facial soft and hard tissues not included in the

image analysis, case reports, reviews, opinion articles. No restriction was made for patients' ethnicity nor age because in patients with craniofacial syndromes images are often taken prior to surgical interventions, and these interventions are commonly performed in early childhood. Also, no restriction was made for publication language nor publication date.

Information sources

Until the 15th of April 2017, literature was electronically searched using the PubMed, EMBASE and Cochrane databases. In addition, reviews on the subject and bibliographies of articles included in this review were manually checked for references (further referred to as 'other sources'). Grey literature was also searched through the GreyLit database (www.greylit.org).

Search and study selection

A search strategy was developed with the help of an experienced librarian specialized in health sciences and affiliated with the biomedical library of the KU Leuven, Belgium. The search strings used for PubMed, Embase and Cochrane databases are shown in [Table 1](#).

After the removal of duplicate records, the initial study selection was based on titles and abstracts. Then, the full text was retrieved for all the selected studies and studies with unclear abstracts. In case the full text could not be accessed online, the corresponding authors were contacted. The collection of data and reviewing of the collected studies were performed by the first author (A.L). Additional reviewing and cross checking of findings were performed by the second author (M.C.) independently. Disagreements were resolved by discussion and consensus.

Data extraction

After the final study sample was determined, data from all studies were extracted into an Excel data sheet. This included: first author, year of publication, study design, number of subjects in both study and/or control group, age range and mean age of subjects and/or controls, used 3D imaging method, main subject and assessed syndrome(s). These data are structured in [Table 2](#).

Quality assessment

A quality assessment of the included articles was conducted to evaluate their methodological quality. Therefore, the validated Methodological Index for Non-Randomized Studies (MINORS) was used (detailed in [Table 3](#)).⁶⁵ This instrument was originally developed to review surgical research, where randomization is not always feasible. Studies on craniofacial syndromes are seldom randomized controlled trials (RCTs) due to ethical reasons and often have small study groups because of the low incidence of these syndromes. However, it was still useful to systematically review the existing literature and answer questions in that particular field. Taking into account all the above,

Table 1 Search strategy

a. PubMed

"Imaging, Three-Dimensional"[Mesh] OR "Four-Dimensional Computed Tomography"[Mesh] OR ((3D[tiab] OR 3 D[tiab] OR three dimensional[tiab] OR 3 dimensional[tiab]) AND (imag*[tiab] OR scan*[tiab])) OR 4D[tiab] OR 4 D[tiab] OR four dimensional[tiab] OR 4 dimensional[tiab] OR "Cone-Beam Computed Tomography"[Mesh] OR cone beam[tiab] OR cbct[tiab] OR computed tomography[tiab] OR CT[tiab] OR "Photogrammetry"[Mesh] OR Stereophotogrammetr*[tiab] OR "Magnetic Resonance Imaging"[Mesh:NoExp] OR Magnetic Resonance imag*[tiab] OR MR[tiab] OR MRI[tiab] OR NMR[tiab] AND "Craniofacial Abnormalities"[Mesh] OR ((Craniofacial[tiab] OR mandibulofacial[tiab] OR maxillofacial[tiab] OR dentofacial[tiab]) AND (abnormal*[tiab] OR Dysostosis[tiab] OR Dysostoses[tiab] OR deform*[tiab])) AND "Syndrome"[Mesh] OR syndrom*[tiab] OR syndromes[tiab]

b. Embase

'Three dimensional imaging'/exp OR '3 dimensional imaging':ab,ti OR '3 d imaging':ab,ti OR '3d imaging':ab,ti OR 'three dimensional imaging':ab,ti #1
'Four dimensional computed tomography'/exp OR 'four dimensional imaging':ab,ti OR '4 dimensional imaging':ab,ti OR '4 d imaging':ab,ti OR '4d imaging':ab,ti #2
#1 OR #2 #3
'Cone beam computed tomography'/exp OR 'cone beam':ab,ti OR 'cbct':ab,ti OR 'computed tomography':ab,ti OR 'ct':ab,ti #4
'Stereophotogrammetry'/exp OR stereophotogrammetr*:ab,ti #5
'Nuclear magnetic resonance imaging'/exp OR 'magnetic resonance':ab,ti OR 'mr':ab,ti OR mri:ab,ti OR nmr:ab,ti #6
#3 OR #4 OR #5 OR #6 #7
'Craniofacial malformation'/exp OR [craniofacial:ab,ti OR mandibulofacial:ab,ti OR maxillofacial:ab,ti OR dentofacial:ab,ti AND (abnormal*:ab,ti OR dysostosis:ab,ti OR dysostoses:ab,ti OR deform*:ab,ti)] #8
'Syndrome'/exp OR syndrom*:ab,ti OR syndromes:ab,ti #9
#7 AND #8 AND #9 #10

c. Cochrane database

MeSH descriptor: (Syndrome) explode all trees #1
MeSH descriptor: (Craniofacial Abnormalities) explode all trees #2
MeSH descriptor: (Imaging, Three-Dimensional) explode all trees #3
{(Craniofacial or mandibulofacial or maxillofacial OR dentofacial) and (abnormal* or Dysostosis or Dysostoses or deform*)} #4
#2 or #4 #5
Syndrom* or syndromes #6
#6 or #1 #7
[("3D" or "3 d" or "3 dimensional" or "three dimensional") and (imag* or scan*)] #8
#3 or #8 #9
MeSH descriptor: (Four-Dimensional Computed Tomography) explode all trees #10
[("four dimensional" or "4D" or "4 d" or "4 dimensional") and (imag* or scan*)] #11
#10 or #11 #12
MeSH descriptor: (Cone-Beam Computed Tomography) explode all trees #13
Cone beam or "cbct" or "computed tomography" #14
#13 or #14 #15
MeSH descriptor: (Photogrammetry) explode all trees #16
Stereophotogrammetr* #17
#16 or #17 #18
MeSH descriptor: (Magnetic Resonance Imaging) explode all trees #19
Magnetic resonance imag* or "MR" or "NMR" or "MRI" #20
#19 or #20 #21
#21 or #18 or #15 or #12 or #9 #22
#22 and #7 and #5 #23

we considered the MINORS index as the most appropriate quality assessment index to evaluate the articles of this systematic review. According to this scale, the articles were divided into comparative and non-comparative studies with different scorings for both groups. Each item of the scale was given a score of 0 (not reported), 1 (reported but inadequate) or 2 (reported

and adequate). For non-comparative studies, 8 items have to be scored, so the global ideal score is 16, while for comparative studies, there are 4 additional items so, the global ideal score for comparative studies is 24. The first author (A.L.) scored all the included articles and the second author (M.C.) was consulted in case of doubt. Judging of the used statistical analysis of the

Table 2 Data extraction sheet

a. Comparative studies										
First author	Year	Study group		Control group		3D method	Study subject	Volume	Syndrome(s)	
		Sample size	Age range	Mean age	Sample size					Age range
Tucunduva et al ⁵	2016	10	NM	15	5	NM	15	CBCT	D	Treacher Collins
Mingo et al ⁶	2016	42	0.02–0.6	0.09	10	0.02–0.6	0.09	CT	S	Stickler
Solem et al ⁷	2016	9	8–16.6	12.4	20	8.9–16.8	12.15	CBCT	D	Craniofacial microsomia ^a
Tuin et al ⁸	2015	44	NM	NM	94	NM	NM	CT	D	Goldenhar ^a
Cruz et al ⁹	2015	43	0.5–13.4	5.1	23	NM	5.6	CT	D	Crouzon, Apert
Antunes et al ¹⁰	2015	20	3.39–26.15	15.5	67	NM	NM	CT	S	Crouzon, Apert
Ma et al ¹¹	2015	30	1–15	4.9	35	1–12	4.4	CT	D	Treacher Collins
Ma et al ¹²	2015	30	1–15	4.9	35	1–13	4.4	CT	D	Treacher Collins
Forte et al ¹³	2014	19	NM	5.53	17	NM	5.87	CT	D	Crouzon, Apert
Crombag et al ¹⁴	2014	10	12–21	NM	13	NM	NM	CT	S	Apert
Prasad et al ¹⁵	2014	21	6–19	11	21	6–12	11.1	Scan	D	22q11 DS
Hopper et al ¹⁶	2013	9	8.2–14.8	11	11.1	7.6–14.3	9.56	CT	S	Apert, Crouzon
Wink et al ¹⁷	2013	9	12–17	15	9	12–18	15	CT	D	Apert
Nikkhah et al ¹⁸	2013	6	2–15	8	26	NM	NM	CT	D	Treacher Collins
Herlin et al ¹⁹	2013	4	6–20	12.5	20	6–20	12.5	CT	S	Treacher Collins
Wong et al ²⁰	2013	12	NM	5	17	NM	5	CT	D	Treacher Collins
Travieso et al ²¹	2013	10	NM	5.5	14	NM	5.7	CT	D	Treacher Collins
Wilamowska et al ²²	2012	43	0.8–39	4.75	43	0.8–39	4.75	Scan	D	22q11 DS
Chung et al ²³	2012	10	NM	4.63	6	NM	5	CT	D	Treacher Collins
Fan et al ²⁴	2012	^b	NM	0.17	^b	NM	0.18	CT	S	Treacher Collins
Heude et al ²⁵	2011	8	0.3–16.6	7.9	NAS	0.3–16.6	7.9	CT	D	Treacher Collins, Nager, Stickler
Wang et al ²⁶	2009	21	7–16	11.3	20	10–16	11.8	CT	D	Hemifacial microsomia ^a
Heike et al ²⁷	2009	20	5–21	10.9	20	4–50	24.5	Scan	R	22q11 DS
Song et al ²⁸	2009	40	^b		44	^b		CT	D	Crouzon, Hemifacial microsomia ^a
Keller et al ²⁹	2007	11	0.29–0.45	0.36	12	0.3–1.3	0.64	CT	D	Muenke
Hammond et al ³⁰	2005	379	NM	NM	317	NM	NM	Scan	R	Noonan, 22q11 DS, Williams, Smith Magenis
Sforza et al ³¹	2005	28	12.8–45.1	26.8	429	NM	NM	Scan	D	Down
Hirschfelder et al ³²	2004	16	7–23	NM	NAS	7–23	NM	CT	D	Oculoauriculovertebral spectrum (hemifacial microsomia) ^y
Hammond et al ³³	2004	150	0.6–56	NM	280	0.03–56	NM	Scan	D	22q11 DS, Noonan
Ferrario et al ³⁴	2004	28	12–45	26.9	449	NM	NM	Scan	D	Down
Kaga et al ³⁵	2003	7	2–18	9	13	NM	NM	CT	D	Treacher Collins
Rotten et al ³⁶	2002	38	18–28 WPN		371	22–24 WPN		3D ultasound	D	Down, Treacher Collins
Cutting et al ³⁷	1995	5	NM	NM	9	NM	NM	CT	D	Crouzon
Posnick et al ³⁸	1995	26	0.25–17	NM	407	NM	NM	CT	D	Treacher Collins

(Continued)

Table 2 (Continued)

<i>a. Comparative studies</i>									
First author	Year	Study group		Control group		3D method		Study subject	Syndrome(s)
		Sample size	Age range	Mean age	Sample size	Age range	Mean age		
Moffat <i>et al</i> ³⁹	1994	24	0.1–16	5.25	449	NM	NM	CT D	Frontonasal and craniofrontonasal dysplasia
Posnick <i>et al</i> ⁴⁰	1994	8	0.75–1.9	1.1	401	NM	NM	CT S	Apert
Posnick <i>et al</i> ⁴¹	1993	14	0.5–3.4	1.2	542	NM	NM	CT S	Crouzon
Carr <i>et al</i> ⁴²	1992	36	NM	0.25	75	<1	NM	CT D	Apert, Crouzon
b. Non-comparative studies									
First author	Year	Study group		Mean age	3D method	Study subject	Volume	Syndrome(s)	
		Sample size	Age range						
Smektala <i>et al</i> ⁴³	2015	6	NM	10.8	CT	S	V	Crouzon, Apert, Binder ^a , Tyabi-Rubenstein, Pfeiffer, Marshal-Stickler	
Wery <i>et al</i> ⁴⁴	2015	10	7–19	14	CT	S		Apert, Crouzon, Pfeiffer	
Wood <i>et al</i> ⁴⁵	2015	17	0.75–12.6	5.2	CT	D		Crouzon, Pfeiffer, Saethre-Chotzen, Apert, Achondroplasia	
De Oliveira <i>et al</i> ⁴⁶	2014	11	0.3–14	5.3	CT	S		Crouzon, Apert, Pfeiffer Type I	
Arango <i>et al</i> ⁴⁷	2013	28	19–33 WPN	NM	MRI	R		Syndromic CL(P)	
Al Kaissi <i>et al</i> ⁴⁸	2013	7	NM	NM	CT	D		Cleidocranial dysplasia	
Chan <i>et al</i> ⁴⁹	2013	12	6–14	10.1	Scan	S	V	Apert, Crouzon, Pfeiffer, Saethre-Chotzen	
Wang <i>et al</i> ⁵⁰	2013	8	17–28	NM	CT	S		Binder ^a	
Birgfeld <i>et al</i> ⁵¹	2013	50	0.16–20	NM	Scan	R		Craniofacial microsomia ^a , Goldenhar ^a , Hemifacial microsomia ^a	
Lee <i>et al</i> ⁵²	2012	6	5–14	7.2	CT	S		Crouzon	
Manganaro <i>et al</i> ⁵³	2011	27	19–33 WPN	23.7 WPN	MRI	R		Syndromic CL(P)	
Miloro <i>et al</i> ⁵⁴	2010	35	36 WPN-4	0.3	CT	S		Treacher Collins, Stickler, Opitz, Down, Goldenhar ^a	
Bannink <i>et al</i> ⁵⁵	2010	11	4.1–23.1	14.9	CT	S	V	Apert, Crouzon, Pfeiffer	
Kaban <i>et al</i> ⁵⁶	2009	13	1.25–39	11.9	CT	S		Treacher Collins, Nager, Craniofacial microsomia ^a , Syndromic micrognathia ^a	
Oyama <i>et al</i> ⁵⁷	2009	40	0.7–16	4.5	CT	S		Crouzon, Apert, Pfeiffer	
Eley <i>et al</i> ⁵⁸	2009	25	0.3–19	10	CT	S		Crouzon, Apert, Pfeiffer	
Ponniah <i>et al</i> ⁵⁹	2008	10	0.3–15	9.81	CT	S		Crouzon, Apert	
Albuquerque and Cavalcanti ⁶⁰	2004	5	2–4	3.5	CT	D		Apert	
Santos <i>et al</i> ⁶¹	2003	10	0–19	6.4	CT	D	V	Oculoauriculovertebral spectrum (hemifacial microsomia) ^a	
Reinhart <i>et al</i> ⁶²	2003	13	0.24–3.56	1.39	CT	D		Muenke	
Roth <i>et al</i> ⁶³	1997	10	2.5–19	7.47	CT	S	V	Goldenhar ^a , Craniofacial microsomia ^a , Nager, Treacher Collins	
Marsh <i>et al</i> ⁶⁴	1986	14	0.01–49	13.18	CT	D		Treacher Collins	

NM, not mentioned; D, diagnostic study; NAS, non affected side; S, study evaluating surgical outcomes; V, volumetric measurements included in the analysis; Scan, 3D facial surface scanning; R, study evaluating the reliability of an imaging method; WPN = weeks pre-natal.

^aGenetic background not clear.

^bDependent of which part of the study.

Table 3 MINORS**a. Scoring for comparative studies**

<i>First author</i>	<i>Year</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>	<i>8</i>	<i>9</i>	<i>10</i>	<i>11</i>	<i>12</i>	<i>Score^a</i>
Tucunduva et al ⁵	2016	2	1	1	2	1	2	0	0	1	1	0	2	13
Mingo et al ⁶	2016	2	0	1	2	0	2	0	0	1	2	0	2	12
Solem et al ⁷	2016	2	0	1	2	0	2	2	1	1	1	2	2	16
Tuin et al ⁸	2015	2	2	1	2	0	2	0	0	1	2	1	2	15
Cruz et al ⁹	2015	2	0	0	2	0	2	0	0	2	0	2	2	12
Antunes et al ¹⁰	2015	2	1	1	2	0	2	0	0	2	0	0	2	12
Ma et al ¹¹	2015	2	0	1	2	2	2	0	0	2	0	2	2	15
Ma et al ¹²	2015	2	1	1	2	2	2	0	0	2	0	2	2	16
Forte et al ¹³	2014	2	0	1	2	1	2	0	1	2	0	2	2	15
Crombag et al ¹⁴	2014	2	1	0	2	0	2	0	0	2	1	1	2	13
Prasad et al ¹⁵	2014	1	1	2	2	1	2	0	0	2	2	1	2	16
Hopper et al ¹⁶	2013	2	0	1	2	0	2	2	0	1	0	1	2	13
Wink et al ¹⁷	2013	2	1	1	2	0	0	0	0	2	0	2	2	12
Nikkhah et al ¹⁸	2013	2	1	0	2	0	2	1	0	2	1	2	2	15
Herlin et al ¹⁹	2013	2	1	0	2	0	2	0	0	2	0	0	1	10
Wong et al ²⁰	2013	2	0	1	2	0	2	0	0	2	0	1	2	12
Travieso et al ²¹	2013	2	2	1	2	2	2	0	0	2	0	2	2	17
Wilamowska et al ²²	2012	2	1	0	2	1	2	0	0	2	0	2	2	14
Chung et al ²³	2012	2	0	1	2	0	2	0	0	2	0	2	2	13
Fan et al ²⁴	2012	2	2	0	2	0	2	0	0	2	0	1	2	13
Heude et al ²⁵	2011	2	0	0	2	0	2	0	0	1	2	2	2	13
Wang et al ²⁶	2009	2	0	0	2	1	0	0	0	1	0	2	2	10
Heike et al ²⁷	2009	2	0	0	2	1	2	0	0	2	2	1	2	14
Song et al ²⁸	2009	2	0	0	2	1	2	0	0	2	0	2	2	13
Keller et al ²⁹	2007	2	0	0	2	1	2	0	0	1	0	1	2	11
Hammond et al ³⁰	2005	2	0	2	2	0	2	0	0	2	0	0	2	12
Sforza et al ³¹	2005	2	0	1	2	0	2	0	0	2	1	2	2	14
Hirschfelder et al ³²	2004	2	0	0	2	0	0	0	0	1	2	2	2	11
Hammond et al ³³	2004	2	1	0	2	0	2	0	1	2	2	1	2	15
Ferrario et al ³⁴	2004	2	0	1	2	1	2	0	0	2	1	2	2	15
Kaga et al ³⁵	2003	2	0	0	2	0	2	0	0	2	1	1	0	10
Rotten et al ³⁶	2002	2	2	0	2	1	2	0	0	2	2	2	2	15
Cutting et al ³⁷	1995	2	0	0	2	0	2	0	0	2	1	2	2	13
Posnick et al ³⁸	1995	2	0	0	2	1	2	0	0	2	1	2	2	14
Moffat et al ³⁹	1994	2	0	0	2	1	2	0	0	2	1	2	1	13
Posnick et al ⁴⁰	1994	2	2	0	2	0	2	0	0	2	1	2	1	14
Posnick et al ⁴¹	1993	2	2	0	2	0	2	0	0	2	0	1	2	13
Carr et al ⁴²	1992	2	1	1	2	1	2	1	0	2	2	2	2	18
b. Scoring for non-comparative studies														
Smektala et al ⁴³	2015	2	0	1	2	2	2	0	0					9
Wery et al ⁴⁴	2015	2	1	1	2	1	2	0	0					9
Wood et al ⁴⁵	2015	1	1	1	2	0	2	0	0					7
De Oliveira et al ⁴⁶	2014	1	2	1	2	0	2	2	0					10
Arangio et al ⁴⁷	2013	1	0	1	2	0	2	0	0					6
Al Kaissi et al ⁴⁸	2013	1	0	0	2	0	2	0	0					5
Chan et al ⁴⁹	2013	2	0	0	2	0	2	2	0					8
Wang et al ⁵⁰	2013	1	0	0	2	0	0	0	0					3
Birgfeld et al ⁵¹	2013	2	2	0	2	2	2	0	0					10

(Continued)

Table 3 (Continued)*a. Scoring for comparative studies*

<i>First author</i>	<i>Year</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>	<i>8</i>	<i>9</i>	<i>10</i>	<i>11</i>	<i>12</i>	<i>Score^a</i>
Lee <i>et al</i> ⁵²	2012	2	0	1	2	0	2	1	0					8
Manganaro <i>et al</i> ⁵³	2011	2	0	2	2	0	2	0	0					8
Miloro <i>et al</i> ⁵⁴	2010	2	2	1	2	0	2	2	0					11
Bannink <i>et al</i> ⁵⁵	2010	2	1	1	2	0	2	1	0					9
Kaban <i>et al</i> ⁵⁶	2009	2	2	1	2	0	1	1	0					9
Oyama <i>et al</i> ⁵⁷	2009	2	1	1	2	0	2	2	0					10
Eley <i>et al</i> ⁵⁸	2009	2	2	0	2	2	2	1	0					11
Ponniah <i>et al</i> ⁵⁹	2008	2	0	0	2	0	1	0	0					5
Albuquerque and Cavalcanti ⁶⁰	2004	2	0	0	2	0	2	0	0					6
Santos <i>et al</i> ⁶¹	2003	2	0	0	2	1	2	0	0					7
Reinhart <i>et al</i> ⁶²	2003	2	0	0	2	0	2	1	0					7
Roth <i>et al</i> ⁶³	1997	2	0	0	2	0	2	2	0					8
Marsh <i>et al</i> ⁶⁴	1986	2	2	0	2	0	2	0	0					8

Correspondence of the numbers (taken from Slim *et al*):³ 1, a clearly stated aim; 2, inclusion of consecutive patients; 3, prospective collection of data; 4, endpoints appropriate to the aim of the study; 5, unbiased assessment of the study endpoint; 6, follow-up period appropriate to the aim of the study; 7, loss to follow up less than 5%; 8, prospective calculation of the study size. Additional criteria in the case of comparative studies: 9, an adequate control group; 10, contemporary groups; 11, baseline equivalence of groups; 12, adequate statistical analyses.

^aThe items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The global ideal score being 16 for non-comparative studies and 24 for comparative studies.

comparative studies was performed by the two main reviewers (A.L and M.C), consulting a professional statistician in case of doubt.

Results

Study selection

The electronic search of PubMed, EMBASE and Cochrane Library yielded 2226 citations. Two additional records were found through other sources. After removing duplicates and selection on titles and abstracts, the full text of the 116 remaining articles was assessed. Reasons for excluding studies after full text reading were: facial structures not included in the analysis, only 2D imaging, articles were case reports, reviews or opinions. The final selection comprised 60 articles which were summarized in Table 2. The PRISMA flow diagram is shown in Figure 1.

Study characteristics

The assessment of the methodological quality revealed that there were 22 non-comparative and 38 comparative studies with a median MINORS score of 8 over 16 (7–9, 25th–75th percentile) and 13 over 24 (12–15, 25–75th percentile) for both groups respectively (Table 3). Topics that were consistently scored as “not reported” in the majority of the studies were Item 7 “loss to follow-up less than 5%” and Item 8 “prospective calculation of the study size”. However, when a follow-up period was not included in a study but was also not required to meet

the aim of that study, Item 6 of the scale was scored “reported and adequate” and Item 7 was scored as “not reported” which contributed to the low scores on Item 7. Of the comparative studies, 76% (29/38) had an adequate control group. When the non-affected side or a historical control group was used for control, this was scored as inadequate.

The aim and outcome of the articles were heterogeneous, but three general subject matters could be distinguished: controlled and non-controlled diagnostic studies, surgical outcomes and evaluation of imaging techniques. More than half of the publications (34/60, 57%) could be considered as diagnostic studies describing phenotypes and craniofacial features in patients with craniofacial syndromes, often in comparison with healthy controls. About one third of the articles (21/60, 35%) was related to surgical outcomes or the description of surgical techniques. Distraction osteogenesis was the most evaluated surgical procedure in this group (17/21, 81%).

The last and smallest group (5/60, 8%) contained articles relating to the reliability or usefulness of specific imaging methods such as MRI and facial surface scanning. In two publications of the same study group, the ability of MRI to detect craniofacial anomalies in foetuses was pointed out and compared with standard 2D ultrasound examination.^{47,53} In three other publications, facial surface scanning was the used imaging method. The reliability of the 3dMDface system (3dMD, Atlanta, GA) in patients with 22q11.2 deletion syndrome in comparison with direct calipre measurements was

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

investigated in the first of these studies.²⁷ The intra- and interrater reliability were good to excellent and the technical error of measurement was less than 1 mm for most measurements. The main conclusion of this study was that interlandmark measurements on facial scans were accurate and showed good to excellent concordance with the direct measurements. Nevertheless, according to their results, landmark identification on 3D scans was more difficult in patients with facial hair and the ears were not always completely captured. In another study, 2D photographs were compared with 3D facial surface scans in patients with craniofacial macrosomia, microtia or Goldenhar syndrome to evaluate

facial morphology.⁵¹ An assessment tool developed by the authors was used to score all images. There was an agreement of over 90% between the ratings of both imaging methods. The quality of the images was also comparable, except for mandibular symmetry and soft tissue asymmetry, where the 3D ratings were higher and for ear morphology, macrostomia and eye abnormalities, where 2D images had higher ratings. Studying facial characteristics on 3D facial scans to develop statistical models for diagnostic discrimination between subjects with 22q11.2 deletion syndrome, Williams, Smith-Magenis and Noonan syndrome was the main objective of the third study.³⁰ The discrimination performance of the

full face for control–syndrome and syndrome–syndrome comparisons for children ranged from 87 to –97%. It was suggested that visualizations of 3D face-shape variations could be used to train physicians to recognize the key components of particular syndromes.

In the majority of the included studies (46/60, 77%), CT was used as the imaging modality. Other methods used were: facial surface scanning (9/60, 15%), MRI (2/60, 3%), CBCT (2/60, 3%) and ultrasonography (1/60, 2%).

In 17 out of 60 studies (28%), volumes were calculated as part of the analysis. 11 of these studies were diagnostic studies in which the volume of a certain anatomical structure like the condylar head, maxillary sinus, muscles or even the entire maxillary or mandibular body was calculated and compared with a control group. In the other six studies, volumes were calculated before and after maxillofacial surgery. The studies are indicated with a ‘V’ in the column ‘‘Volume’’ of Table 2.

Three craniofacial syndromes were by far more studied than others, namely: Treacher Collins, Crouzon and Apert syndrome in 16, 18 and 18 studies, respectively. In 19 out of the 21 surgical outcome studies (90%), patients with one of these syndromes were included. In the other studies, conditions were sometimes included which have not yet been clearly described in literature as genetically based syndromes but they were, however, treated as such and were often studied together with other known syndromes. This was the case in 12 of the 60 studies (20%) and the conditions included were: hemifacial microsomia and Goldenhar syndrome, craniofacial microsomia, Binder syndrome and syndromic micrognathia. These studies are identified in Table 2 with the letter (a).

The median of the reported mean ages of patients was 7.3 years (4.8–11.2, 25–75th percentile). However, the age range of patients both within and between studies was often wide, ranging from only a few weeks to adulthood. Three studies focussed on prenatal diagnosis of craniofacial anomalies and, therefore, fetuses in the third trimester were included in these studies. Also for sample size, a large variability between the studies existed, ranging from 4 to 375 subjects in the study group.

The included studies were published between 1986 and 2016. With regard to evolutions of the included studies over time, the following trends were noticed (reflected in Figures 2 and 3 and Table 2):

- There was an increase in the amount of studies with time (Figure 2).
- CT was the imaging method most often used, although from 2002 onwards, other modalities were involved, of which non-invasive facial surface scanning was described most frequently (Figure 3).

As a result of the information gathered from the included studies, a number of considerations to improve

Figure 2 Number of studies per publication period.

the methodological quality and reporting of future research projects have been summarized in Table 4 and are discussed with more detail in the ‘‘Discussion’’ section.

Discussion

The result of this systematic review was a heterogeneous collection of articles about 3D imaging in patients with craniofacial syndromes of moderate methodological quality, as the median MINORS scores were only 50 and 54% of the maximum scores. The low incidence of craniofacial syndromes makes it difficult to build up large study groups and randomized controlled trials are often not possible owing to ethical reasons. Also, the absence of blinding and a lack of information on dropouts contributed to the moderate scores on the MINORS scale. For comparative studies, control groups of healthy subjects, matched for age, gender and ethnicity were considered as the reference standard for comparison (score 2 on Item 9 of the MINORS scale). This was the case in 29 studies (29/38, 76%). In two studies on hemifacial microsomia, the non-affected side was used for comparison.^{25,32} This provided control for confounding environmental factors; however, there may have been unknown influences of the genetic condition on the non-affected side, resulting in a score 1 (‘‘reported but inadequate’’) on Item 9 (‘‘adequate control group’’) of the MINORS scale. Some studies made use of a historical control group, previously described in

Figure 3 Imaging method per publication period.

Table 4 Recommendations for future research**Recommendations for future research**

Study group

- Clear eligibility criteria
- Inclusion of consecutive patients
- Limited age range
- Prospective calculation of the study size

Study design

- Prospective studies
- Contemporary, matched control group
- Multicentre studies
- Similar protocols in different centres

Imaging

- Standard protocol for image taking
- Appropriate imaging method for study objective
- Avoidance of unnecessary radiation exposure
- Research records should coincide with records for treatment planning or monitoring

Reporting

- Present study in the appropriate format
- Report dropouts

Statistics

- Confidence intervals
- Statistical significance

literature. This also was considered as inadequate on the MINORS scale because there is no control over the different variables that could be affecting its comparability and, therefore, there is no way of controlling the possible bias.

CT was the imaging method most often used in the past as well as in recent studies. Of all methods available to produce 3D images of the craniofacial area, CT has the highest radiation exposure. Young individuals are especially vulnerable to the harmful effects of X-rays, so adaptation of the projection and radiation exposure according to the area of interest and age of the patient is mandatory. Depending on what information is required, less-invasive CBCT allows for a significant reduction in radiation exposure compared with conventional CT.⁶⁶ CBCT renders 3D images of the craniofacial area and is mainly used in the fields of dentistry, maxillofacial surgery and otorhinolaryngology. In this review, only one article was included in which CBCT was used (to investigate the area of the mandible between the mental foramina).⁵

Non-radiation methods are undoubtedly preferable over invasive methods but they have their specific indications. 3D facial surface scanning was the second most used imaging method in the studies of this review. It provides highly accurate images of the external facial

morphology so this could be an appropriate method for diagnostic purposes as well as to evaluate facial soft tissue changes after surgery.^{27,67} The fact that it is more and more used by researchers and clinicians shows a positive trend towards a reduction in the use of radiation methods.

Images can be evaluated both qualitatively and quantitatively by performing measurements on them. Besides, 3D images have the unique advantage of allowing for volumetric measurements. In total, there were 17 studies with volumetric measurements (17/60, 28%). In the group of diagnostic studies, volumes were calculated in 11 studies (11/34, 32%). In the remaining 23 studies, images were used to perform 2D linear or angular measurements or to assess asymmetries, atrophy or aplasia of certain elements. Depending on what information is needed, the least invasive imaging method should be selected. For instance, if only skeletal measurements need to be made in the sagittal plane, it would be more appropriate to take a conventional lateral cephalogram than a CT, as one could wonder what is the real advantage in using only 2D measurements in a 3D projection.^{23,26}

The subject matters of the included articles could be divided in three major groups: controlled and non-controlled diagnostic studies, evaluation of surgical outcomes and evaluation of 3D imaging methods.

The largest group contains diagnostic studies, where aims were highly variable and go from a general description of the facial area in a certain craniofacial syndrome to a detailed measuring of a specific anatomical structure, such as the masseteric muscle or the condylar head. Sixty-five percent (22/34, 65%) of studies in this group were comparative, quantitative studies. Diagnostic studies without a control group (6/34, 18%) can only attempt to describe the craniofacial phenotype in the studied population. Especially when sample sizes are small, care should be taken in extrapolating the results to a larger group.

A second group existed of articles relating to surgical interventions. The deformity of the craniofacial skeleton can be very complex and severe in patients with craniofacial syndromes and correction is endeavoured using advancing procedures. Distraction osteogenesis in early childhood is often performed for this purpose. In 17 out of 21 articles in this group (81%), distraction osteogenesis was evaluated with 3D imaging. The imaging method was CT in all studies except one. Images were taken prior to surgery to prepare the surgical procedure and to measure pre-operative values. After surgery, a follow-up image was often taken as well to perform post-operative measurements and evaluate the resulting anatomy in an objective way. By postponing the second image to a moment later in time when the results of the surgery are thought to be stable rather than taking an image immediately after the distraction has ended, a third image for follow up could be avoided and radiation exposure would, therefore, be further reduced. Again,

when the mean age of subjects is only a few weeks or months old, this certainly needs to be taken into account. One surgical evaluation study did successfully assess soft and hard tissue gain after distraction osteogenesis using facial surface scanning.⁴⁹

The third group contained articles in which the reliability of an imaging method was tested. Such articles can be of great value to provide scientific evidence about new imaging and measuring techniques.

Treacher Collins, Apert and Crouzon were the syndromes most studied. Interestingly, nearly all studies concerning surgical interventions (19/21, 90%) were performed in patients with one of these syndromes. This could be owing to the extensively aberrant morphology associated with these syndromes demanding one or more surgical interventions.

The genetic background of these three syndromes is well known. Owing to the rapidly progressing developments in the field of human genetics, even more information becomes available. However, this is not the case for other less frequently studied conditions, such as hemifacial microsomia or Goldenhar syndrome, where the underlying genetic origin is far less clear. In our study, we included genetically based, congenital syndromes with oral and craniofacial manifestations and we chose to exclude conditions such as non-syndromic oral clefts or OSAS because of them being genetically based but non-syndromic or non-syndromic but genetically based. Owing to the lack of knowledge and need for further investigation of these “unlabelled” conditions, it remains to be discussible which of them can be regarded as craniofacial syndromes and which not, a fact that could be considered as a limitation of this systematic review.

Further genetic research may help to clarify this. The aim of this review was to collect evidence about the use and developments of 3D imaging methods in patients with congenital anomalies. By including a wide range of diseases, our intent was not to miss valuable information.

Owing to the limited amount and large heterogeneity of the available literature, we were not able to perform statistical tests on the gathered data. Therefore, the focus lied on the methodological quality of the articles and on describing and summarizing the information of the different studies.

Remarks for future research

To allow for a more detailed and meta-analytic evaluation of the scientific literature about this topic, a significant improvement in study quality is necessary and could be achieved if some aspects of research would become more standard. We attempted to formulate some recommendations with the aim of improving future research and care of patients with craniofacial syndromes (summarized in [Table 4](#)). These recommendations were based on the MINORS scale and on the Eurocleft consensus guidelines⁶⁸ about imaging. The

Eurocleft project was held between 1996 and 2000 and its major aim was to improve the effectiveness and efficiency of care for European children with cleft lip/palate. To do so, information about treatment protocols of different European cleft teams was gathered and subsequently transformed into guidelines describing minimum standards for care of patients with clefts. A specific topic about record taking was also part of the Eurocleft report and this we now applied to patients with craniofacial syndromes.

Regarding the study group, clear eligibility criteria should be formulated. All patients potentially fitting for inclusion should be included, so selection bias could be minimized. On the other hand, age range should be limited because of its influence on study results, especially when sample sizes are small. For example, when a study group consists of children as well as adults, the influence of growth is difficult to incorporate when outcomes are generalized. In that perspective, the study aim should be adapted to the age range of patients. To empower the significance of study results, a prospective calculation of study size is mandatory. To reach a substantial group of patients within a limited age range and taking into account the low incidences of craniofacial syndromes it will be necessary to set up multicentre studies. In this way, data obtained following similar protocols can be gathered. This is why prospective trials are much preferred over retrospective studies, since standard protocols can be set in advance and followed within one and between different centres to augment the comparability of outcomes. Additionally, results of the study group should be compared with a contemporary, matched control group ideally composed of non-affected individuals.

Also, for the image taking itself, it is important that a protocol exists and is followed by every person who takes an image. In this way, the comparability and quality of the obtained images will be higher, retakes will be much less needed and there will be less missing data because of bad image quality. Before taking an image, it should be clear what it will be used for so the appropriate imaging method can be selected. In case of radiological images, the field of view and exposure time should also be adjusted to avoid excessive radiation exposure.

Children with craniofacial syndromes are often treated by practitioners of several disciplines and go through many interventions and surgical procedures from an early age. Without a doubt, images can thereby be very helpful. However, the need for these images should match as much as possible between different professionals, which should be a priority of the multidisciplinary team. For the patient, in particular, this would be beneficial because radiation exposure, amount of visits and additional burden would be reduced. Subsequently, records for research goals should coincide with records for treatment planning or monitoring as well.

Concerning the reporting of a study, dropouts and subjects that are lost during follow up should be

mentioned. Furthermore, the study should be presented in the appropriate format. Mainly, the distinction between a case series and a clinical trial should be clear. Last, the statistical analysis of results should not be forgotten, and confidence intervals and statistical significance should be provided when possible.

Conclusion

In this systematic review about 3D imaging of facial soft and hard tissues in children with craniofacial syndromes 60 articles were included. The overall methodological quality of the articles was moderate,

indicated by median MINORS scores around 50% of the maximum score. Main subjects of the included articles were diagnostic studies, evaluation of surgical outcomes and evaluation of 3D imaging methods. Studies showed a large heterogeneity in sample size, age range and study design, making statistical analysis not possible. Even though randomization and blinding are often difficult in this domain, other measures could be taken to improve the quality of future research as proposed in the present article. Collaboration between different disciplines and even different centres would be the key component to accomplish this together with standard protocols for image taking and study set up.

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