# RELATION BETWEEN SOFT AND HARD TISSUE CHANGES FOLLOWING MAXILLARY OSTEOTOMIES IN CLEFT LIP AND PALATE PATIENTS: A META-ANALYSIS

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# ABSTRACT

## RELATION BETWEEN SOFT AND HARD TISSUE CHANGES FOLLOWING MAXILLARY OSTEOTOMIES IN CLEFT LIP AND PALATE PATIENTS: A META-ANALYSIS

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**AIM:** To systematically investigate the available literature regarding the relation between soft and hard tissue changes following maxillary osteotomies in cleft lip and palate patients that could be used as an aid in lateral cephalometric radiographic prediction.

**MATERIALS AND METHOD**: Search without any restrictions for published and unpublished literature and hand searching was conducted. Data on the relation between soft and hard tissue sagittal changes in patients with cleft lip and palate of any age having undergone any maxillary osteotomies for the correction of maxillary hypoplasia were reviewed and divided in 2 categories: (1) ratios between soft and hard tissue changes and (2) correlations between soft and hard tissue changes. Methodological quality was evaluated according to Cochrane Collaboration guidelines and the random effects method for meta-analysis was used to combine data across studies.

**RESULTS**: Out of the 1054 initially identified unique records only 3 articles fulfilled the selection criteria for inclusion in the systematic review. The correlations between soft and hard tissue changes varied considerably from -0.44 to 0.95 and the ratios in the horizontal and vertical plane varied between 0.33 to 0.57 and 0.12 to 0.48 respectively, depending on the specific points considered and the time of assessment. Methodological quality assessment identified various drawbacks in the included studies.

**CONCLUSIONS:** Based on the present systematic review and meta-analysis, evidence-based conclusions on the relation between soft and hard tissue changes following maxillary osteotomies in cleft lip and palate patients are difficult to draw. High statistically significant correlations were noted at the longest follow-up available only in the stomion superius horizontal and labrale superious vertical response to upper incisor tip movement. More studies of high quality are needed in order to produce results robust enough to be used as a clinical aid during prediction in cleft lip/palate patients.

## DEDICATION

First and foremost, Thanking My Almighty God, for His blessings and love. With great gratitude, I would like to dedicate this thesis to, my dearest parents, my beloved husband and my loving children, who have always stood by my side.

## DECLARATION

I declare that all the content of the thesis is my own work. There is no conflict of interest with any other entity or organization.

Name: Nisha Varughese

Signature:

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## 1. INTRODUCTION

Clefts may affect the lip, alveolar ridge and palate and cause esthetic, functional and consequent psychosocial disorders problems for the affected individuals (Freitas et al., 2012). Cleft lip and palate is the most frequent congenital facial abnormality, with a ratio of 1 in every 700 births (Mossey et al., 2003). Cleft lip and palate has a multifactorial etiology and both genetic and environmental factors are implicated in their pathogenesis (Murray et al., 2002). Patients with these deformities may often have associated problems including otologic disease; speech and language problems, such as delayed onset of speech, articulation disorders, and velopharyngeal incompetence or insufficiency; together with dental deformities that can involve malocclusion and missing, malformed, or supernumerary teeth; facial growth deficiencies; and psychosocial issues.

A significant proportion of patients (25–60%) born with complete unilateral cleft lip and palate require maxillary advancement to correct midface retrusion and improve their esthetic facial proportions (Panula et al., 1993). The orthognathic surgeries commonly used to correct the maxillary hypoplasia are maxillary advancement with Le Fort I osteotomy, mandibular setback by bilateral sagittal split ramus osteotomy, or a combination of both.

The aim of this thesis was to systematically investigate the available literature regarding the relation between soft and hard tissue sagittal changes after maxillary Le Fort I osteotomy, in cleft lip and palate patients that could be used as an aid in cephalometric prediction.

## 2. REVIEW OF THE LITERATURE

Cleft lip and palate is an embryonic malformation characterized by the deficiency and displacement of soft tissues and underlying bony and cartilaginous structures in the lip, nasal sill, and soft and hard palates. These defects occur between the 6$^{th}$ and the 12$^{th}$ week of fetal development, which is concomitant with the morphogenesis of the upper lip and the palate. The failure of to fuse of the frontonasal and maxillary processes gives rise to the cleft of the primary palate which includes the lip, alveolar process, and the hard palate anterior to the incisive foramen. This results in a unilateral or bilateral cleft in a typical location between the premaxilla and the lateral maxilla while failure of the fusion of the palatal shelves results in clefts of secondary palate.

The embryologic development of the lip and palate serves as a basis for a number of cleft classification systems. Cleft lip is classified as unilateral or bilateral, and its extent may be classified as complete or incomplete. Palatal clefts also are described as being unilateral or bilateral, and their extent may also be classified as complete or incomplete. Dahl et al. (1970) divided clefts into four groups: Cleft lip, cleft palate, and unilateral cleft lip and palate and bilateral cleft lip and palate. Elnassry et al. (2007), on the other hand, divided cleft lip and palate patients into seven classes: Class I: unilateral cleft lip; Class II: unilateral cleft lip and alveolus; Class III: bilateral cleft lip and alveolus; Class IV: unilateral complete cleft lip and palate; Class V: bilateral complete cleft lip and palate; Class VI: cleft hard palate; Class VII: bifid uvula. However, the system devised by Kernahan and Stark (1958), classification and diagram, is the most commonly used worldwide. The respective diagram helps in identifying which anatomic segment is involved, but not how severely it is affected.

## 2.1. Epidemiology

Unilateral cleft lip and palate is the commonest single type of cleft, accounting for about 30– 35% of cases with submucous, with other clefts accounting for the rest (Hagberg et al., 1997). Around 20-25 % represents the proportion of isolated cleft lip and cleft palate cases, while bilateral cleft lip and palate is the rarest deformity at 10%. Cleft lip and palate occurs as non- syndromic, isolated malformation in around 70% of cases, while cleft palate is non-syndromic in half of the cases (Jones et al., 1988; Marazita et al., 2002). In general, girls are more likely to be affected by cleft palate, at a ratio of 1:2, and boys show an increased prevalence of cleft lip and palate when compared to girls 2:1 (Tolarova and Cervenka et al., 1998; Saal et al., 2002; Moosey et al., 2009). Left-sided cleft predominates over right sided cleft in a 2:1 ratio in unilateral cleft lip and palate (Dewinter et al., 2003).

The incidence of cleft lip and palate is 1 in every 500 to 1000 births worldwide and varies according to the geographic location, ethnicity, and socioeconomic status (Murray et al., 2002, Cox et al., 2004). Cleft lip occurs in 1 out of 1000 live births in the United States, while cleft palate deformity occurs in 1 out of 2000 live births. Cleft lip deformities have the highest incidence among Native Americans (3.6 in 1000 births), Asians (2.1 in 1000), and Caucasians (1 in 1000), with the lowest incidence among Afro-Americans (0.41 in 1000). However, the incidence of cleft palate is 0.5 in 1000 live births and does not differ among ethnic groups (Strong et al., 2001).

## 2.2. Etiology

Cleft lip and palate has a multifactorial etiology and genetic, with environmental factors being implicated in their pathogenesis (Murray et al., 2002). Many clefts run in families, and these may be non-syndromic or syndromic occurrences.

For non-syndromic clefts, the risk of unaffected parents already having a cleft lip and/or palate child having another affected child is 4%. Similarly, if one parent is affected by a non-syndromic cleft lip and/or palate, the risk of having an affected child is 4% (Curtis et al., 1961; Goodacre and Swan et al., 2011). Moreover, in twins, a 60% concordance rate in monozygotic twins and 10% in dizygotic twins is seen (Grosen et al., 2010). Cases of isolated cleft palate also have shown a familial clustering effect. Genetic factors are thought to contribute to the development of the non-syndromic disorder, as the risk of recurrence of CLP within a family is approximately 28-40- fold greater than for the general population (Rajabian and Sherkat et al., 2000; Aldhorae et al., 2014).

Over 90% of isolated cleft palate cases are non-syndromic, however, more than 300 syndromes are associated with cleft lip with or without cleft palate, such as: Oculoauriculovertebral spectrum, Treacher-Collins syndrome, oral-facial-digital syndrome, the Pierre Robin sequence, Stickler syndrome, van der Woude syndrome (Gorlin et al., 2001). The commonest syndrome associated with cleft lip and palate is the van der Woude syndrome (Dixon et al., 2011), while the most frequent syndrome associated with cleft palate is 22q11 deletion syndrome (Fullman and Boyer et al., 2012).

Whole–exome sequencing has been successful recently in identifying the causative genetic variants for Mendelian traits such as syndromic cleft lip and palate. However, identification of complex and heterogenous traits in non-syndromic cleft lip and palate have yet to be successful

(Dixon et al., 2011). Through the understanding of various syndromes, many genes have been identified which may contribute to non-syndromic cleft lip and palate but, the cause cannot be attributed just to an isolated gene as various genetic factors (e.g. MSX1, IRF-6, SATB2, TGFβ3, TBX22) have been identified across populations. The localization of contributory genetic sequences is still ongoing, with the evaluation of candidate genes, including transforming growth factor alpha (TGF-a) which has been shown to be associated with non-syndromic cleft lip with or without cleft palate (Kaartinen et al., 1995).

Environmental factors such as smoking, corticosteroids, or phenytoin (Hanson et al., 1989) seem to have a contributory role in the onset of the malformation. Smoking during pregnancy has shown to have a dose–response relationship with orofacial clefting (Little et al., 2004) the habit has also been shown to have a contribution of 4% to cleft lip and/or palate (Honein et al., 2007). Alcohol consumption during pregnancy also increases the risk of isolated cleft palate (Goodacre and Swan et al.,2011). While other maternal risk factors include the use of steroids, anticonvulsants (phenobarbital and phenytoin), retinoids, diabetes and nutritional deficiencies (zinc, folic acid and vitamin A) (Lorente and Miller et al., 1978; Park-Wyllie et al., 2000).

### 2.3. Detrimental effects of clefts of lip and palate

Affected children suffer a range of medical problems including feeding difficulties at birth due to problems with the oral seal, swallowing and nasal regurgitation, hearing difficulties due to frequent infections, and problems with speech due to nasal escape and articulation problems. These cleft defects have a long term, adverse influence on the health and social integration of the affected individuals because, even though they can be surgically repaired early in childhood, the residual deformity due to scarring and abnormal facial development results in continuing functional and psychosocial problems (Wong et al., 1998; Hunt et al., 2005).

Feeding and nutrition difficulties are frequently present in cleft lip and palate cases (Badwal et al., 2003). Problems with food intake may adversely affect nutritional status in the early life of children with cleft lip and palate or cleft palate leading to lighter and shorter infants compared to unaffected ones (Avedian et al., 1980; Duncan et al., 1983; Becker et al., 1998). Although some research has indicated that children with clefts attain their expected weight and height by about 2 years of age (Lee et al., 1997) other studies have reported delayed skeletal maturity in boys with clefts over a period ranging from 6 to 20 years (Jensen et al., 1983). Additional developmental delays have been observed in tests regarding cognition, comprehension and expressive language abilities (Jocelyn et al., 1996), as well as fine motor and gross motor skills (Neimanet al., 1997).

Ninety percent of children younger than 2 years of age with an unrepaired cleft have an effusion of the middle ear. The persistence of an effusion in young children leads to variable levels of hearing loss with hearing loss during early childhood potentially leading to difficulties in speech and language development. In general, children with cleft lip and palate are at a higher risk for speech / language problems including difficulties with conversational skills due to the anatomical and structural differences in the oral mechanism (Peterson-Falzone et al., 1995). Velopharyngeal dysfunction can result in many effects on speech and resonance. Young children with cleft palate and serous otitis media have increased risk of conductive hearing loss and the associated delay in speech and language development (Fria et al., 1987). Moreover, there is also some evidence to suggest that there may be a decrease in the measured cognitive abilities of young children with cleft lip and palate as compared with their typical peers (although their IQs still remain within the normal range (Leslie et al.,1996).

Facial esthetics are compromised due to missing, malformed or supernumerary teeth. There may also be problems that are skeletal in nature including a constricted maxillary arch or a deficient or retruded maxilla resulting in a Class III malocclusion. It has been reported that individuals born with clefts have a higher incidence of abnormal crown morphology, hypodontia, supernumerary teeth, and taurodontism (Menezes and Vieira et al., 2008; Küchler et al., 2011). In addition, previous reports have related higher frequencies of dental anomalies as the severity of the cleft increases (Eerens et al., 2001; Slayton et al., 2003; Aizenbud et al., 2005). Facial appearance and speech outcomes may also affect psychological functioning (Millard et al., 2001).

### 2.4. Treatment protocols for cleft lip and palate patients

Treatment of children with cleft lip and palate involves an interdisciplinary approach. The team usually comprises a diverse group of clinicians, including otolaryngologists, plastic surgeons, pediatric dentists, orthodontists, occupational therapists, pediatricians, speech therapists, audiologists, social workers, geneticists, psychologists, and feeding specialists / nutritionists. Each team member provides specific expertise in areas needed for the treatment of children born with a cleft. The cleft team also addresses the needs of both the patient and the accompanying family members. Parents are provided with counseling, genetic information as needed, and verbal and written instructions regarding care plans. In this manner, it is possible to provide long-term follow-up through the entire child's development and achieve all of the following treatment goals: normalized facial esthetics, integrity of the primary and secondary palate, normal speech and hearing, airway patency, Class I occlusion with normal masticatory function, good dental and periodontal health and normal psychosocial development.

The most widely accepted treatment modalities in the management of unilateral cleft lip and palate are listed in Table 1, based on chronologic age, and Table 2, based on the development of the dentition and the maxillofacial skeleton.

**Table 1.** Treatment modalities in the management of unilateral cleft lip and palate which are often based on chronologic age (adapted from Pedro 2012).

| Timing | Procedure |
|---|---|
| After 16 weeks of pregnancy | Cleft lip diagnosis by ultrasound images (the palate is more difficult to acquire) |
| Prenatal | Discussion with a craniofacial surgeon. Consultation with a geneticist. |
| Neonatal | If the child has cleft palate, specialized nipples and bottles are necessary to improve feeding after birth |
| 12 weeks of age | Cleft lip repair |
| 6–12 months of age | Cleft palate one-stage repair with intravelar veloplasty |
| 5 years | Secondary rhinoplasty |

**Table 2.** Treatment modalities in the management of unilateral cleft lip and palate which are often based on dentofacial development (adapted from Pedro 2012).

| Timing | Procedure |
|---|---|
| Prior to cleft lip repair | Pre-surgical infant orthopedics |
| Primary dentition | Orthodontic treatment for maxillary expansion |
| Early mixed dentition | Orthodontic treatment for maxillary expansion and maxillary protraction |
| Before late mixed dentition | Secondary alveolar bone graft with cancellous bone from iliac crest |
| Permanent dentition | Orthodontic treatment for dental arches alignment |
| After end of maxillofacial growth | Orthognathic surgery for maxillary advancement |
| After orthognathic surgery | Postsurgical orthodontics for closure of residual spaces and occlusion final adjustments. Replacement of missing teeth by a prosthodontist |

## 2.5 Orthognathic surgery

Cleft lip and palate patients are born with a challenging deformity that requires multiple surgical interventions to achieve functional and esthetic harmony. During infancy and early childhood, surgical soft tissue repair of cleft lip and palate is implemented to improve function and facial appearance. These early surgical interventions, together with the congenital defects affect the physiological development of the skeleton and the soft tissue but cause growth retardation of mid-facial complex (Adlam et al., 1989; Witzel et al., 1989; Hochban et al., 1993). Normal growth of the upper jaw is affected and thus the child grows into a skeletal Class III due to maxillary hypoplasia.

Midface retrusion secondary to maxillary hypoplasia is a common finding in patients with cleft lip and palate. Clinically, the midface deficiency manifests as a concave facial profile, wide alar base, acute nasolabial angle and inverted nasal tip. Intraoral findings include anterior and posterior crossbite, malocclusion, accentuated curve of Spee, multiple missing teeth, residual cleft and oronasal communication.

Maxillary hypoplasia leading to a Class III skeletal relationship is a common developmental problem affecting patients with cleft lip and palate (Ross et al., 1987; Linton et al., 1998). Through a long term multi-centered longitudinal cephalometric study of the facial growth and development of patients with a repaired unilateral cleft lip and palate, it has been shown that around 25% of patients with cleft lip and palate will require orthognathic maxillary advancement surgery for successful correction (Ross et al., 1987). Maxillary advancement can be performed as a one piece Le Fort I osteotomy in patients with maxillary hypoplasia (Obwegeser et al., 1973; Houston et al., 1989; Ayliffe et al., 1995). Single piece Le Fort I osteotomies allow sagittal, vertical and rotational control of the maxilla.

Le Fort I osteotomy for the correction of maxillary hypoplasia in a cleft palate patient is reported to have been first performed by Axhausen in 1939, but the operation was improved by Schuchardt. In 1967, Hogeman and Wilmar considered the long term stability of the maxilla in patients presenting with cleft lip and palate when maxillary advancement by Le Fort I osteotomy was performed. Gilles and Rowe were the first to complete a maxillary osteotomy in a cleft patient in 1954. Obwegeser modified the Le-Fort I osteotomy in the 1960s. Bell, in 1975, confirmed the vascularity of a down fractured Le Fort I osteotomy through an experimental animal study and popularized its use, in 1974. The complications associated with the Le-Fort I osteotomy were reported by Wilmar. Posnick and Tompson, in 1992, described modifications of the Le Fort I osteotomy for the management of residual deformities in unilateral cleft lip and palate patients. In case of the collapse of the lesser segment, or when there is an edentulous area around the grafted cleft, segmental osteotomies may be carried out to restore the dental arch (Stoelinga et al., 1990). Posnick and Thompson in 1995, 1997, 1998 classified their patients based on the type of cleft and modified the standard Le Fort I osteotomy according to the cleft type; namely unilateral cleft lip and palate and bilateral cleft lip and palate.

*2.5.1 Unilateral cleft lip and palate*

A significant proportion of patients (25–60%) born with a complete unilateral cleft lip and palate require maxillary advancement to correct midface retrusion and improve esthetic facial proportions (Rachmiel et al., 2007; Panula et al., 1993; Ross et al., 1987). Varying frequencies (22% to 48.5%) of Le Fort I osteotomies in these patients have been reported (Rosenstein et al., 1991; Cohen et al., 1995; DeLuke et al.; 1997, Mølsted et al., 2005; Good et al., 2007; Daskalogiannakis and Mehta et al., 2009; Heliovaara and Rautio et al., 2011; Voshol et al., 2012).

In a study of the prevalence of the Le Fort I osteotomy by Mulliken and colleagues in cleft lip and palate patients treated at the Boston Children's Hospital, 48% of their repaired UCLP patients required orthognathic surgery. Similarly, 59.4 % of referred UCLP patients and 48.3% of their complete UCLP patients at the Hospital for Sick Children (Toronto, Canada) required orthognathic surgery (Daskalogiannakis and Mehta et al., 2009) According to Good et al. (2007), the higher frequency of Le Fort I procedures (47.4% in cleft lip and palate patients) in their unit may reflect their preference for operative correction for all patients with poor midfacial esthetics, irrespective of their occlusal relationships.

In UCLP, complications with maxillary osteotomy have been reported in the literature. (Lanigan et al., 1995). Hugo Obwegeser has made many significant contributions to cleft skeletal reconstruction (Drommer et al., 1986; Obwegeser et al., 1966;, 1967; 1969; 1971; 2007; Obwegeser et al., 1985). He succeeded in achieving maxillary cleft advancement to the preferred location without the need for a compromised mandibular setback approach. By the late 1960s cleft maxillary advancement of up to 20 mm had been comfortably achieved by Obwegeser as he gained experience. He realized that the key step in advancing the jaw, whether cleft or non- cleft, was the adequate mobilization of the down fractured maxilla. Demonstration of the blood supply to maxillary segments in animal studies by Bell confirmed the success of the Obwegeser approach. (Bell and Levy et al., 1971; Bell et al., 1975; Dodson et al., 1994; Dodson and Neuenschwander et al., 1997). Obwegeser's techniques for Le Fort I osteotomy for the treatment of UCLP deformity was refined by Posnick in the mid-1980s (Braun et al., 1992; Posnick et al., 1991a; 1991b; 1996; Posnick et al., 1994; Posnick and Tompson et al., 1992).

### *2.5.2 Bilateral cleft lip and palate*

76.5 % of teenagers with repaired BCLP required maxillary advancement, as reported by Mulliken and colleagues (Good et al., 2007). In addition, 65.1 % of BCLP patients required, or underwent, orthognathic surgery, and 79 % of referred BCLP patients, after cleft repair had been carried out, were found to require orthognathic surgery (Daskalogiannakis and Mehta, et al., 2009). A Class III skeletal malocclusion requiring orthognathic correction was present in 17 of 19 consecutive patients followed up to age of 18 (89.5%), in a consecutive group of BCLP patients monitored by David and co-workers from birth to maturity in the Cleft Craniofacial Unit in Adelaide, Australia (David et al., 2006)

Correction of jaw disharmony by surgery in BCLP patients dates back to Steinkamm's description of attempted surgical interventions in 1938 (Steinkamm et al., 1938). Incomplete descriptions of surgical techniques and possible complications with maxillary osteotomy in patients with BCLP can be found in the early literature.(Gillies and Rowe et al., 1954; Gillies and Millard et al., 1957; Fitzpatrick et al., 1977; Sinn et al., 1980; Jackson et al., 1978; Poole et al., 1986; Ward-Booth et al., 1984). Hugo Obwegeser has made important contributions to cleft skeletal reconstruction (Drommer et al., 1986; Obwegeser, 1966; 1967; 1969; 1971; 2007; Obwegeser et al. 1985. The complications associated with the Le Fort I osteotomy in BCLP patients were reported by Wilmar in 1974. (Willmar et al., 1974) The safety of the segmental Le Fort I osteotomy in BCLP patients was clarified by Posnick in the mid-1980s. (Posnick et al., 1996; 2000; Posnick and Tompson,et al., 1993; Posnick et al., 1994). The modified Le Fort I osteotomy (in three segments) should be used for BCLP patients presenting with a 'three segment' maxillary deformity. A standard Le Fort I down fracture is carried out for BCLP adolescent presenting with an intact (successfully grafted) alveolar ridge on both sides.

### *2.5.3 Isolated cleft palate*

Maxillary hypoplasia resulting in malocclusion, unresponsive to either traditional or compensatory orthodontic maneuvers alone, was reported in at least 20 % of Caucasians with ICP who underwent repair by Ross (Abyholm et al., 1981). A combination of factors, including the intrinsic primary cleft defect, secondary hypoplasia due to the surgical repair in infancy, and functional factors (eg; effects of masticatory muscles, respiratory pattern, mandibular rest posture can results in a high incidence of maxillomandibular deficiency for an individual born with ICP. (Canady et al., 1997) The usual reconstructive procedure to be considered is a standard Le Fort I maxillaryosteotomy for isolated cleft palate. Bell and others validated that Obwegeser's Le Fort I technique allowed adequate blood supply for satisfactory routine bone healing without aseptic necrosis or dental injury.

### *2.5.4 Lateral cephalometric radiographic prediction*

Improved facial harmony and a balanced profile are the goals of orthognathic surgery for both the cleft patient and the surgical/orthodontic team. However, predictions of facial esthetic changes are especially difficult in cleft lip and palate patients. The accurate prediction of hard and soft tissue changes is essential in orthognathic surgery. The soft tissue profile may not directly reflect the changes in the underlying skeletal structure during surgical-orthodontic treatment. Strong associations between some parts of the soft tissue with changes in the underlying skeletal structures are seen, but changes in other parts have tended to be more independent of the changes in the skeletal structure. A frequently used guide to the expected soft tissue changes after surgery is expressed simply as the 1:1 correspondence ratio for a specific bone to soft tissue change.

Repositioning of the maxilla changes both the esthetics and functioning of the nose and lips. The soft tissues of the nose, lips and mid face are subject to dimensional changes after maxillary osteotomies. The prediction of the postsurgical soft tissue changes is a crucial part of the pre-surgical treatment planning process. The ability of the surgeon to plan accurately the post-operative change relies on an ability to correlate the soft tissue response to the underlying hard tissue osseous movements Soft tissue movements occurring in conjunction with underlying skeletal tissue movement render a satisfactory functional and aesthetic outcome in cleft lip and palate patients. The relationship between hard and soft tissue movement needs to be understood to obtain predictable results from treatment.

The current methods for the objective evaluation of hard and soft tissue profile changes are unsatisfactory as they make the face conform to a specific predetermined standard. As the current state of prediction techniques are deemed imprecise, the need for valid treatment simulations are imperative (Nurminen et., 1999; Chew et.al., 2008). The traditional methods of the manual acetate tracing “cut and paste” prediction technique (Wolford et al., 1985; Profitt et al., 2003) have been replaced by newer computer assisted software prediction programs employed to select hard to soft tissue ratios (Harradine et al., 1985; Walker et al., 1991). These prediction programs are based on algorithms, assumptions on linearity, and the mean ratios of osseous to soft tissue alterations originating from investigations of variable accuracy. The comparison of the manual to the computerized technique have shown that the hand drawn technique is more accurate in soft tissue prediction for maxillary surgery (Charlotte et al., 2004). Cephalometric prediction in orthognathic surgery can be performed manually, or by computer using several currently available software programs, either alone, or in combination with video images. In addition, three-dimensional prediction methods are also available (Kolokitha and Topouzelis et al., 2011).

Manual prediction is based on presumed changes (Wolford et al., 1985; Proffit et al., 2003), whereas computer programs rely on databases derived from studies with reported mean ratios of soft to hard tissue movements providing an idea of how much a certain soft tissue landmark will move in relation to the respective movement of a hard tissue landmark (Kolokitha and Chatzistavrou et al., 2012). Consequently, the accuracy of the simulation relies on the validity and accuracy of the ratios in the individual database (Eckhardt and Cunningham et al., 2004; Chew et al., 2008).

Furthermore, the manual and most of the computer methods usually presuppose that the soft tissue response is linear, regardless of the amount and direction of skeletal repositioning (Wolford et al., 1985; Proffit et al., 2003; Smith et al., 2004). Not only has the validity of this assumption been questioned (Chew et al., 2008), but also, little consistency has been seen across studies on the values of specific ratios. For example, regarding pogonion soft tissue to pogonion reported ratios after mandibular setback surgery implemented alone exhibit a range from 59% (Enacar et al., 1999) to 104% (Mobarak et al., 2001). In addition, the relevant observations have not been summarized quantitatively; thus their usefulness for clinical practice remains uncertain.

A significant number of studies have calculated the ratios of soft to hard tissue change with Le Fort I osteotomies, however the relevant data on cleft lip and palate patients are sparse. The knowledge of how soft tissue moves in relation to hard tissue may provide better profile predictions, which could potentially improve communication between patients and clinicians.

# 3. AIM

## 3.1. Aim of the systematic review

To investigate the available literature regarding the relation between soft and hard tissue changes after maxillary advancement in cleft lip and palate patients that could be used as an aid in cephalometric prediction.

## 3.2. Objectives of the systematic review

To retrieve data on (1) ratios between soft and hard tissue changes and (2) correlations between soft and hard tissue changes before and after maxillary advancement in cleft lip and palate patients.

## 3.3. Null Hypothesis

There is no significant correlation between soft and hard tissue changes before and after maxillary advancement surgery in cleft lip and palate patients.

# 4. MATERIALS AND METHODS

## 4.1. Protocol Development

The present review was based on a specific protocol developed and piloted following the guidelines outlined in the PRISMA-P statement (Shamseer et al., 2015) and registered in PROSPERO (CRD42017079896) (Appendix I). In addition, conduct and reporting followed the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green et al., 2011) and the PRISMA statement (Moher et al., 2009), respectively.

## 4.2. Selection criteria applied for the review

The selection criteria for the domains of study design, participant characteristics, types of interventions and principal outcome measures applied for the review were as follows:

### *4.2.1. Types of study design*

Studies included in the present thesis were prospective and retrospective clinical trials investigating the relation between soft tissue and osseous changes in patients with cleft lip and palate patients who underwent maxillary surgery. Animal studies, opinion articles, case reports, studies involving less than 10 subjects, reviews, systematic review and meta analyses were excluded.

The type of study design was assessed using the algorithm available from SIGN (Scottish Intercollegiate Guidelines Network, available from http://www.sign.ac.uk (Appendix III).

*4.2.2. Types of participants*

The included studies involved patients of any age with non-syndromic cleft lip and palate of any type. No restrictions were placed on the ethnic origin or age of the patients. Studies involving patients with compromised medical history were excluded.

*4.2.3. Types of interventions*

The included studies included non-syndromic cleft lip and palate patients who underwent Le Fort I surgery, in one piece or in segments. Studies involving other types of Le Fort procedures, distraction osteogenesis or a combination with mandibular or other procedures were excluded.

*4.2.4. Outcome measures*

Correlation coefficients and/or ratios (together with the respective standard deviations or other measures used to quantify the amount of dispersion of a set of data values) between soft tissue changes and osseous surgical relocation, measured from conventional cephalometric points (Viteporn and Athanasiou et al., 1995). Studies not providing information on the dispersion of the data were excluded. The measurements must have been made at pre- and post-surgery and at specified time points, as common sense and research data suggest that decreases in soft tissue swelling continuously occur during the first year after surgery (Van der Vlis et al., 2014).

**4.3. Information sources and search strategy**

The author (NV) developed detailed search strategies for each database searched. They were based on the search strategy developed for MEDLINE but revised appropriately for each database to take into account of differences in controlled vocabulary and syntax rules. The following electronic databases were searched) (Appendix III) Pubmed, Scopus, ISI Web of Science, Cochrane Central register of Controlled Trials, Cochrane database of Systematic Reviews and Arab World research source. Unpublished literature was searched on Clinical Trials gov and Pro-Quest Dissertation and Theses global.

The search attempted to identify all relevant studies irrespective of language and date of publication, as well as publication status. The reference lists of all eligible studies were hand searched for additional studies. Where additional information was needed, the authors were contacted.

### 4.4. Study selection

The author (NV) and thesis co-supervisor (EGK) assessed the retrieved records for inclusion independently. They were not blinded to the identity of the authors, their institution or results of the search. They assessed independently the publications considered by either reviewer to meet inclusion criteria. Disagreements were resolved by discussion or consultation with thesis supervisor (AEA). A record of all decisions on study identification was kept.

### 4.5. Data collection and data items

The same reviewers performed data extraction independently and any disagreements were again resolved by discussion or consultation with the thesis supervisor (AEA). Data collection forms were used to record the desired information, such as bibliographic details, details of study design, verification of study eligibility, participants' characteristics, inclusion and exclusion criteria, intervention characteristics, outcomes assessed and details on assessment procedures. Where possible, the terms used for each cephalometric point were changed to follow the Viteporn and Athanasiou (1995) terminology. For ratios between soft tissue changes and osseous surgical relocations, the mean values together with the respective standard deviations or other measures used to quantify the amount of dispersion of a set of data values were extracted to enable a meta-analysis to be performed. If clarifications of the published data or additional material was needed, then the corresponding authors were to be contacted.

The outcomes relevant to the relation between soft tissue and osseous changes in patients with cleft lip and palate patients who underwent Le Fort I maxillary advancement surgery were then divided into two categories:

**a.** Correlation coefficients between soft and hard tissue changes.

**b.** Ratios between soft and hard tissue changes.

The retrieved data were divided into assessments made up to 6 months after surgery, 6 to 12 months included, and more than 12 months following the operation (Van der Vlis et al., 2014).

### 4.6. Risk of bias in individual studies

The author (NV) and thesis co supervisor (EGK) performed assessments of risk of bias in included studies independently and in duplicate during the data extraction process using the The Cochrane Collaboration’s Risk of Bias assessment tool for Randomized Clinical Trials (Higgins and Greens, 2011) and Robins-I tool (Risk of Bias in Non- randomized studies of intervention) (Sterne et al., 2016), according to study design. Any disagreements were to be resolved by discussion or consultation with the thesis principal supervisor (AEA).

The Risk of Bias for Randomized Clinical Trials assessment tool includes the following domains (Higgins and Green et al., 2011):

a. Random sequence generation (selection bias).

b. Allocation concealment (selection bias).

c. Blinding of participants and personnel (performance bias).

d. Blinding of outcome assessors (detection bias).

e. Incomplete outcome data (attrition bias).

f. Selective outcome reporting (reporting bias).

g. Other sources of bias.

After entering the information reported in each study into the data extraction form, every domain would receive a judgment of low, high or unclear risk of bias (indicating either lack of sufficient information to make a judgment or uncertainty over the risk of bias) (Higgins and Green et al., 2011).

Subsequently, studies were to be judged as being of low, unclear or high risk of bias.

a. Low risk of bias (plausible bias unlikely to seriously alter the results)

b. Unclear risk of bias (bias that raises some doubt about the results)

c. High risk of bias (bias that seriously weakens confidence in the results)

The Robins-I tool assessment tool examines the following domains (Sterne et al., 2016):

a. Bias due to confounding.

b. Bias in selection of participants in the study.

c. Bias in the classification of interventions.

d. Bias due to deviation from intended interventions.

e. Bias due to missing data.

f. Bias due to measurement of outcomes.

g. Bias in selection of reported results.

After entering in the data extraction from the information reported in each study, every domain would receive a judgment of either low, moderate, serious or critical risk of bias or the label “no information” (indicating no information on which to base a judgment about risk of bias for this domain) (Sterne et al., 2016).

Subsequently, studies were to be judged as being of low, moderate, serious or critical risk of bias (Sterne et al., 2016).

a. Low risk of bias: The study is comparable to a well performed randomized controlled trial.

b. Moderate risk of bias: The study provides sound evidence for a non-randomized study but cannot be considered to be a well performed randomized trial.

c. Serious risk of bias: The study has some important problems.

d. Critical risk of bias: The study is too problematic to provide any useful evidence and should not be included in any synthesis.

e. No information: There is no information on which to base a judgment about risk of bias.

### 4.7. Summary measures and synthesis of results

In situations where the retrieved data used different variables measuring the same concept on different scales with a high degree of correlation, the effects of the interventions were planned to be expressed as standardized values (i.e. the Standardized Mean Difference (SMD) together with the relevant 95% Confidence Interval (CI)), in order to enable quantitative synthesis (Deeks et al., 2001). In cases where, in a particular comparison, the same variable was recorded, the intervention effect was planned to be expressed as the Weighted Mean Difference (WMD) together with the 95% CI.

The random effects method for meta-analysis was used to combine correlation coefficients and ratios across studies (Der Simonion and Laird et al., 1986, Borenstein et al., 2007), since they were expected to differ across studies due to clinical diversity in terms of participants (i.e. race/ethnicity, gender, lip morphology) and intervention characteristics (i.e. exact surgical procedure and fixation). The statistically significant correlation coefficients were interpreted as very high positive (or negative) correlation (±0.90 to ± 1.00), high positive (or negative) correlation (±0.70 to ±0.90), moderate positive (or negative) correlation (±0.50 to ±0.70), low positive (or negative) correlation (±0.30 to ±0.50) and negligible correlation (±0.30 to 0.00) (Hinkle et al., 2003).

To identify the presence and extent of between–study heterogeneity, the overlap of the 95 % CI for the results of individual studies was inspected graphically, and Cochrane's test for homogeneity and the $I^2$ static were calculated (Higgins and Green et al., 2011). The results of the $I^2$ statistic were to be interpreted as follows (Higgins and Greene et al., 2011):

- $I^2$ from 0% to 40%: heterogeneity might not be important;
- $I^2$ from 30% to 60%: may represent moderate heterogeneity;
- $I^2$ from 50% to 90%: may represent substantial heterogeneity;
- $I^2$ from 75% to 100%: considerable heterogeneity.

All analyses were to be carried out with Comprehensive Meta-analysis software 2.2.046(©2007 Biostat Inc.). Significance (a) was set at 0.05, except for 0.10 used for the heterogeneity tests (Ioannidis et al., 2008).

### 4.8. Risk of bias across studies and additional analyses

If a sufficient number of trials were identified, analyses were planned for "small-study effects" and publication bias (Higgins and Green, 2011). If possible, exploratory subgroup analyses were planned. Finally, the quality of evidence for outcomes at the longest follow-up was assessed based on the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach (Guyatt et al., 2011).

## 5. Results

### 5.1. Study selection

The flow of records through the reviewing process is shown in Figure 1. Among the 1054 articles initially identified, 81 records were excluded as duplicates. From the 973 articles that remained, 949 were excluded on the basis of full text reports for various reasons and after attempts, to contact the authors for clarifications or additional unpublished data: no correlation coefficients and/or ratios between soft tissue changes and osseous surgical relocation presented no hard tissue or soft tissue measurements (15), unreported follow up period (10), inadequate statistical data (30), combination of Le Fort I maxillary advancement with other kinds of interventions (279), review articles (25), case reports (152), (<10 patients) (5) irrelevant investigations (433).

Finally, 3 full text reports were included in the meta-analysis (Al-Waheidi et al., 1998; Chua and Cheung et al., 2012; Susarla et al., 2015).

### 5.2. Study characteristics

The characteristics of the studies included in the meta-analyses as well as the sample characteristics are presented in Tables 3 and 4. They were published between 1998 and 2015 and analyzed data from 62 cleft lip and palate patients who underwent maxillary Le Fort I osteotomy. Two of the included studies were retrospective before and after comparisons (Al-Waheidi et al., 1998; Susarla et al., 2015) whereas the third involved a Randomized Clinical Trial performing a comparison between surgical relocation and distraction osteogenesis after Le Fort I osteotomy

(Chua and Cheung, 2012). From the latter, only the data involving the surgical relocation group were used.

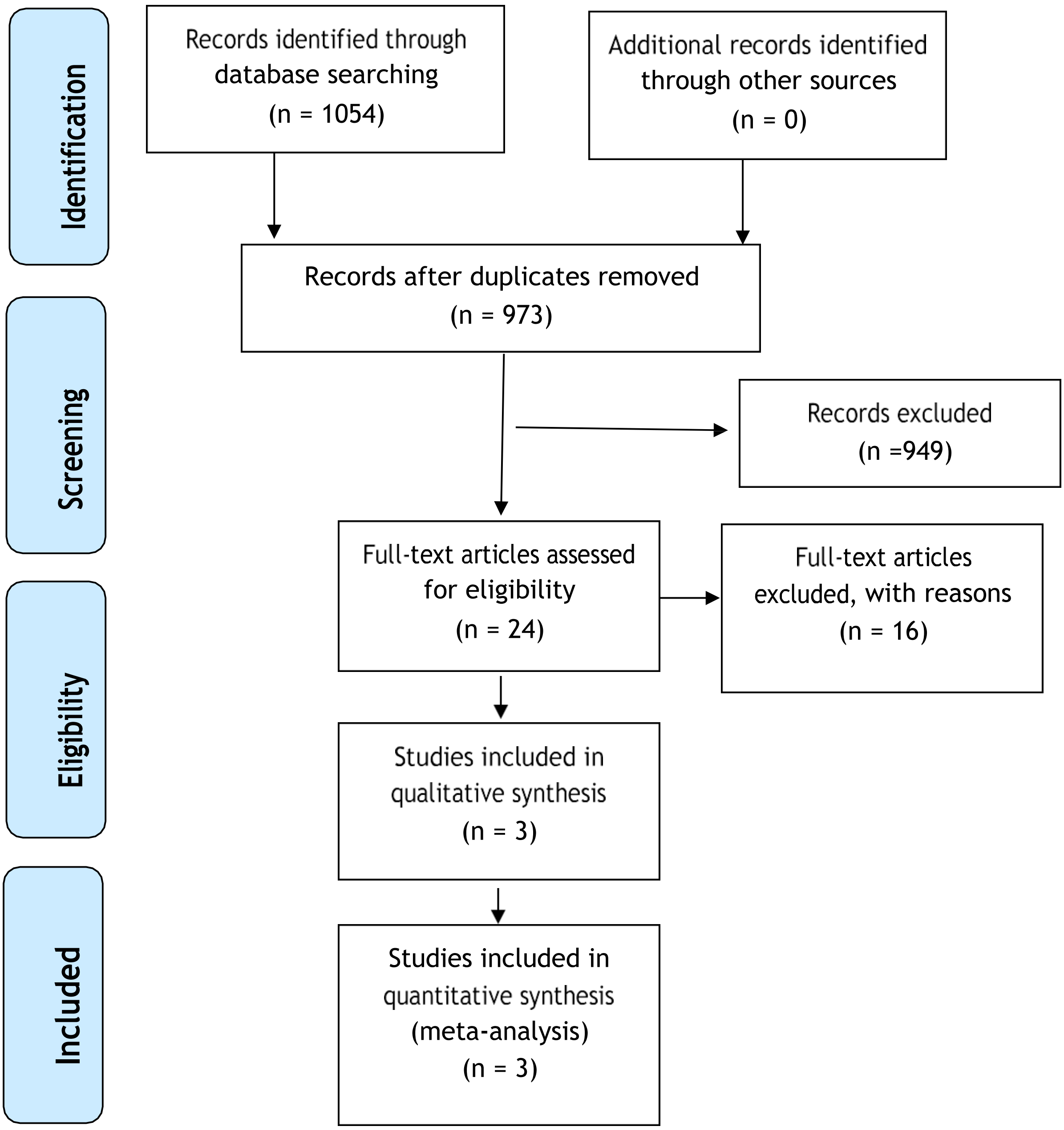


**Figure 1.** Flowchart of records through the reviewing process**.**

Measurements were made on cephalometric radiographs taken in centric occlusion with lips in repose in two studies (Al-Waheidi et al., 1998; Chua and Cheung et al., 2012) whereas Susarla and co-workers (2015) used cephalometric and 3D volumetric data. Measurements were provided for the period up to 6 months after surgery in two papers (Chua and Cheung et al., 2012; Susarla et al., 2015), for the period between 6 and 12 months post-operatively in Al-Waheidi et al. (1998) and Chua and Cheung et al (2012) publications and, finally, for the follow-up exceeding 1 year in the paper by Chua and Cheung et al (2012).

**Table 3.** General characteristics of the studies included in the systematic review.

| Study | Intervention characteristics | Included outcomes and methods of assessment |
|---|---|---|
| **Al-Waheidi et al. [1998]**<br>UK<br>BAC | Le Fort I osteotomy | **[1] Correlations coefficients:**<br>Horizontal and vertical changes: Pn/Isi, Sn/Isi, Sls/Isi, Ls/Isi, Sts-Isi<br>**[2] Ratios:**<br>Horizontal and vertical changes: Pn/Isi, Sn/Isi, Sls/Isi, Ls/Isi, Sts-Isi<br><br>**Cephalograms taken with lips in repose and teeth in occlusion.**<br>*Pre-Surgery:* Not specified; *Post- surgery:* not less than 6 months after surgery<br>The magnification factor was recorded for each radiograph, and all measurements were adjusted appropriately by the computer software. All radiographs were traced on acetate paper. The tracings were digitized using a reflex metrograph, which was linked to a microcomputer for analysis.<br>*Method error assessment:* The same 28 radiographs were re-traced and redigitized after one month by the same examiner. No errors mentioned. |
| **Chua and Cheung [2012]**<br>Hong Kong, PRC<br>RCT | *Group 1:*<br>Le Fort I osteotomy<br>*Group 2:*<br>Le Fort I osteotomy + distraction osteogenesis<br><br>In both groups maxillary segmentalization was done, if necessary according to the dental model surgical plan to fit the occlusion with the mandibular arch. | **[1] Correlations coefficients:**<br>Horizontal and vertical changes: Pn/A, Pn/Isi, Sn/A, Sn/Isi, Ls-A, Ls-Isi, Sts-A, Sts-Isi<br><br>**Cephalograms taken in natural head position and centric occlusion with lips in repose**<br>All the lateral cephalographs were taken using the same orthopantomograph machine<br>*Pre-Surgery:* Shortly before surgery; *Post- surgery:* 6 months, 1 and 2 years<br><br>*Method error assessment:* 40 randomly selected cephalograms from 20 patients were redigitized after one week. Dahlberg's formula; errors less than 1.0 mm. Paired t-test: no significant errors |
| **Susarla et al. [2015]**<br>USA<br>BAC | Le Fort I osteotomy | **[1] Correlations coefficients:**<br>Horizontal changes: Sn/Isi, Ls/Isi, Sts/Isi<br>**[2] Ratios:**<br>Horizontal changes: Sn/Isi, Ls/Isi, Sts/Isi<br>**Cephalograms taken in the fixed position**<br>**3D volumetric data**<br>Pre- and postoperative photographs were superimposed and aligned according to fixed points (bilateral medial canthi and ear-to-cheek junction). Soft tissue and volumetric measurements were obtained using 3D photography (Vectra XT Imaging System, Canfield Scientific, Inc., Fairfield, NJ).<br>*Pre-Surgery:* Not mentioned; *Post- surgery:* 154 ± 88.4 days<br>*Method error assessment:* Not mentioned |

BAC: Before and after comparison; PRC: People's Republic of China; RCT: Randomized Controlled Trial; UK: United Kingdom; USA: United States of America; Pn: Pronasale; Sn: Subnasale; Sls: Superior labial sulcus; Ls: Labrale Superius; Sts: Stomion superius; A: A point; Isi: Incisal edge of maxillary central incisor

**Table 4.** Participant characteristics of the studies included in the systematic review.

| Study | Inclusion and exclusion criteria | Analyzed sample |
|---|---|---|
| **Al-Waheidi et al. [1998]**<br>UK<br>BAC | **Inclusion criteria:** Cleft lip and palate patients who underwent Le Fort I maxillary advancement surgery; consecutively treated; adequate records<br>**Exclusion criteria:** not mentioned | 28 patients<br>10 F; age: 19 ±3.5 y<br>18 M; age: 22.15 ±4.4 y |
| **Chua and Cheung [2012]**<br>Hong Kong, PRC<br>RCT | **Inclusion criteria:** Cleft lip and palate patients requiring advancement of more than 4 mm and less than 10 mm. 16 years or older with complete bony fusion of radial epiphysis confirmed by hand wrist radiography<br>**Exclusion criteria:** syndromes, systemic diseases | 23 patients<br>11 F<br>12 M |
| **Susarla et al. [2015]**<br>USA<br>BAC | **Inclusion criteria:** Cleft lip and palate patients who underwent Le Fort I maxillary advancement surgery; patients treated by the same operator over a 24-month period.<br>**Exclusion criteria:** syndromes, systemic diseases, incomplete records | 11 patients<br>age:17.9 ±1.3 y<br>7 M<br>4 F |

BAC: Before and after comparison; F: Females; M: Males; PRC: People's Republic of China; RCT: Randomized Controlled Trial; UK: United Kingdom; USA: United States of America

### 5.3. Risk of bias assessment

Tables 5 and 6 presents the summary of the findings of the risk of bias assessment for the included randomized study using The Cochrane Collaboration's Risk of Bias assessment tool for Randomized Controlled Trials (Higgins and Green et al., 2011) and for the non-randomised study using the Robins-I tool.

The randomized clinical trial (Chua and Cheung et al., 2012) was considered overall to be of unclear risk of bias. No specific information was available for the domains of allocation concealment, blinding of outcome assessment and other potential threats to validity (Table 5).

**Table 5.** Summary of the risk of bias assessment for the Randomized Clinical Trials (Higgins and Green et al., 2011).

| Domain | Chua and Cheung, 2012 |
|---|---|
| Random sequence generation | Low |
| Allocation concealment | Unclear |
| Blinding of participants and personnel | Low |
| Blinding of outcome assessment | Unclear |
| Incomplete outcome data | Low |
| Selective outcome reporting | Low |
| Other potential threats to validity | Unclear |
| **Summary** | **Unclear** |

The other two non-randomised studies (Al-Waheidi et al., 1998; Susarla et al., 2015) were considered to be of serious overall risk of bias (Table 6). Both studies were considered to present serious risk of bias regarding confounding, as important parameters (like gender, age, type of the defect, amount and direction of surgical movement, lip thickness, surgical technique, etc.) were not always appropriately controlled. In contrast, the risk of bias in selection of participants and classification of interventions was found to be low. The risk of bias in the measurement of outcomes was considered serious as either there was no information on blinding or data on measurement reliability. Finally, the risk of bias in selection of the reported result was moderate for all the included studies.

**Table 6.** Summary of the risk of bias assessment for the non-randomized studies (Sterne et al., 2016).

| Domain | Al- Waheidi et al., 1998 | Susarla et al., 2015 |
|---|---|---|
| Bias due to confounding | Serious | Serious |
| Bias in selection of participants for the study | Low | Low |
| Bias in classification of interventions | Low | Low |
| Bias due to deviations from intended intervention | Not Applicable | Not applicable |
| Bias due to missing data | Not Applicable | Not applicable |
| Bias in measurement of outcomes | Serious | Serious |
| Bias in selection of reported results | Moderate | Moderate |
| **Overall** | **Serious** | **Serious** |

## 5.4. Results of individual studies and synthesis of results

The results of the studies included in the present review are presented below.

### *5.4.1. Correlation coefficients between soft tissue and osseous changes*

Three studies presented correlations between horizontal soft and hard tissue changes (Al-Waheidi et al., 1998; Chua and Cheung et al., 2001; Susarla et al., 2015). The results of quantitative synthesis together with raw results, when a summary measure was not possible due to a lack of more data, are presented in Table 7.

Very high significant correlation was seen only at Sts/Isi horizontal movement, at more than 12 months' postoperative follow-up. Moderate significant correlation was seen for Ls/A at the 6 to 12 months postoperative and for Ls/Isi during the first 6 months.

**Table 7.** Correlation coefficients between horizontal soft and hard tissue changes [Correlation coefficient; 95% CI; p-value]

| | Follow-up | | |
|---|---|---|---|
| | **up to 6 months** | **between 6 and 12 months** | **more than 12 months** |
| **Pn/A** | -0.010; -0.420 to 0.404; 0.964 [Chua and Cheung, 2012] | 0.460; 0.059 to 0.733; 0.026 [Chua and Cheung, 2012] | -0.350; -0.666 to 0.073; 0.102 [Chua and Cheung, 2012] |
| **Pn/Isi** | 0.370; -0.050 to 0.679; 0.082 [Chua and Cheung, 2012] | 0.362; 0.020 to 0.628; 0.038 [Chua and Cheung, 2012; Al-Waheidi et al., 1998] | -0.210; -0.573 to 0.221; 0.340 [Chua and Cheung, 2012] |
| **Sn/A** | 0.100; -0.326 to 0.492; 0.654 [Chua and Cheung, 2012] | 0.100; -0.326 to 0.492; 0.654 [Chua and Cheung, 2012] | -0.030; -0.437 to 0.387; 0.893 [Chua and Cheung, 2012] |
| **Sn/Isi** | 0.390; -0.026 to 0.691; 0.066 [Chua and Cheung, 2012] | 0.148; -0.327 to 0.563; 0.550 [Chua and Cheung, 2012; Al-Waheidi et al., 1998] | 0.120; -0.307 to 0.507; 0.590 [Chua and Cheung, 2012] |
| **Sls/Isi** | NR | 0.440; 0.080 to 0.698; 0.018 [Al-Waheidi et al., 1998] | NR |
| **Ls/A** | 0.330; -0.095 to 0.653; 0.125 [Chua and Cheung, 2012] | **0.680**; 0.372 to 0.853; 0.000 [Chua and Cheung, 2012] | -0.080; -0.476 to 0.344; 0.720 [Chua and Cheung, 2012] |
| **Ls/Isi** | **0.541**; 0.116 to 0.798; 0.015 [Chua and Cheung, 2012; Susarla et al.,2015] | 0.276; -0.022 to 0.529; 0.069 [Chua and Cheung, 2012; Al-Waheidi et al., 1998] | 0.160; -0.270 to 0.537; 0.470 [Chua and Cheung, 2012] |
| **Sts/A** | 0.220; -0.211 to 0.580; 0.317 [Chua and Cheung, 2012] | 0.220; -0.231 to 0.566; 0.365 [Chua and Cheung, 2012] | 0.100; -0.326 to 0.492; 0.654 [Chua and Cheung, 2012] |
| **Sts/Isi** | 0.587; -0.586 to 0.965; 0.327 [Chua and Cheung, 2012; Susarla et al.,2015] | 0.803; -0.298 to 0.987; 0.125 [Chua and Cheung, 2012; Al-Waheidi et al., 1998] | **0.950**; 0.884 to 0.979; 0.000 [Chua and Cheung, 2012] |

Pn: Pronasale; Sn: Subnasale; Sls: Superior labial sulcus; LS: Labrale superious; A: A point; Isi: Maxillary incisor tip; Sts: Stomion superius; moderate to very high statistically significant corellations in bold.

Two studies presented correlation coefficients between vertical soft and hard tissue changes in cleft lip and palate patients treated with maxillary Le Fort I osteotomy surgery (Al-Waheidi et al.,1998; Chua and Cheung et al.,2001). The results of quantitative synthesis together with raw results, when a summary measure was not possible due to a lack of more data, are presented in Table 8.

High significant correlation between soft and hard cephalometric points vertical relocation was observed only for Ls/Isi at the follow-up over than 12 months and moderate significant correlation was observed for Sn/Isi at the less than 6 months' postoperative assessment.

**Table 8.** Correlation coefficients between vertical soft and hard tissue changes [Correlation coefficient; 95% CI; p-value]

| | **Follow-up** | | |
|---|---|---|---|
| | **up to 6 months** | **between 6 and 12 months** | **more than 12 months** |
| **Pn/A** | -0.110; -0.500 to 0.317; 0.621 [Chua and Cheung, 2012] | 0.149; -0.289 to 0.522; 0.529 [Chua and Cheung, 2012] | 0.120; -0.307 to 0.507; 0.590 [Chua and Cheung, 2012] |
| **Pn/Isi** | 0.250; -0.181 to 0.600; 0.253 [Chua and Cheung, 2012] | 0.020; -0.266 to 0.302; 0.893 [Chua and Cheung, 2012; Al-Waheidi et al., 1998] | 0.200; -0.231 to 0.566; 0.365 [Chua and Cheung, 2012] |
| **Sn/A** | -0.090; 0.484 to 0.335; 0.687 [Chua and Cheung, 2012] | 0.110; -0.317 to 0.500; 0.621 [Chua and Cheung, 2012] | 0.110; -0.404 to 0.420; 0.964 [Chua and Cheung, 2012] |
| **Sn/Isi** | **0.550**; 0.178 to 0.784; 0.006 [Chua and Cheung, 2012] | 0.187; -0.149 to 0.484; 0.274 [Chua and Cheung, 2012; Al-Waheidi et al., 1998] | 0.440; 0.034 to 0.721; 0.035 [Chua and Cheung, 2012] |
| **Sls/Isi** | NR | 0.060; -0.320 to 0.424; 0.764 [Al-Waheidi et al., 1998] | NR |
| **Ls/A** | -0.310; -0.640 to 0.117; 0.152 [Chua and Cheung, 2012] | -0.020; -0.429 to 0.395; 0.929 [Chua and Cheung, 2012] | 0.180; -0.251 to 0.551; 0.416 [Chua and Cheung, 2012] |
| **Ls/Isi** | 0.247; -0.118 to 0.553; 0.182 [Chua and Cheung, 2012; Susarla et al.,2015] | 0.298; 0.015 to 0.537; 0.039 [Chua and Cheung, 2012; Al-Waheidi et al., 1998] | **0.720**; -0.438 to 0.873; 0.000 [Chua and Cheung, 2012] |
| **Sts/A** | -0.260; -0.607 to 0.170 p=0.234 [Chua and Cheung, 2012] | -0.050; -0.453 to 0.370; 0.823 [Chua and Cheung, 2012] | -0.440; -0.721 to 0.034; 0.035 [Chua and Cheung, 2012] |
| **Sts/Isi** | 0.358; -0.607 to 0.170; 0.234 [Chua and Cheung, 2012; Susarla et al.,2015] | 0.288; 0.004 to 0.529; 0.047 [Chua and Cheung, 2012; Al-Waheidi et al., 1998] | 0.030; -0.387 to 0.437; 0.893 [Chua and Cheung, 2012] |

Pn: Pronasale; Sn: Subnasale; Sls: Superior labial sulcus; LS: Labrale superious; A: A point; Isi: Maxillary incisor tip; Sts: Stomion superius; moderate to very high statistically significant corellations in bold

### *5.4.1. Ratios between soft tissue and osseous changes*

Two studies included ratios, between horizontal and vertical soft and hard tissue changes in cleft lip and palate patients treated with maxillary Le Fort I osteotomy surgery (Al-Waheidi et al., 1998; Susarla et al., 2015). The results of quantitative synthesis, together with raw results when a summary measure was not possible due to lack of more data, are presented in Table 9.

The horizontal ratios gradually decreased from the time period less than six months post-operatively to time period between six to twelve months.

**Table 9.** Ratios between soft and hard tissue changes in the horizontal and vertical plane.

| | Horizontal changes | | Vertical changes |
|---|---|---|---|
| | **Less than six months** | **Six to twelve months** | **Six to twelve months** |
| **Pn/Isi** | NR | 0.330; 0.207 to 0.453 [Al-Waheidi et al., 1998] | 0.120; -0.076 to 0.316 [Al-Waheidi et al., 1998] |
| **Sn/Isi** | 0.900; 0.610 to 1.190 [Susarla et al., 2015] | 0.330; 0.173 to 0.487 [Al-Waheidi et al., 1998] | 0.100; -0.116 to 0.316 [Al-Waheidi et al., 1998] |
| **Sls/Isi** | NR | 0.520; -0.304 to 0.736 [Al-Waheidi et al., 1998] | 0.190; -0.084 to 0.464 [Al-Waheidi et al., 1998] |
| **Ls/Isi** | 0.970; 0.170 to 1.230 [Susarla et al., 2015] | 0.570; 0.296 to 0.844 [Al-Waheidi et al., 1998] | 0.440; -0.224 to 0.656 [Al-Waheidi et al., 1998] |
| **Sts/Isi** | NR | 0.520; -0.304 to 0.736 [Al-Waheidi et al., 1998] | 0.480; 0.245 to 0.715 [Al-Waheidi et al., 1998] |

Sn: Subnasale; Sls: Superior labial sulcus; LS: Labrale superious; A: A point; Isi: Maxillary incisor tip; Sts: Stomion superius

### 5.5. Risk of bias across studies and additional analyses

Because it was not possible to retrieve a sufficient number of trials, we were not able to conduct analyses for "small-study effects" and publication bias (Higgins and Green et al., 2011).

Overall, the quality of evidence was considered at as low due to the scarcity of the retrieved data and the associated imprecision of the observed effects, together with concerns regarding the risk of bias.

# 6. DISCUSSION

## 6.1. Summary of evidence

Although improved facial harmony and a balanced profile are the goals of orthognathic surgery for both the cleft patient and the surgical/orthodontic team, predictions of aesthetic changes are difficult. As numerous factors may contribute to the variability of soft to hard tissue response following Le Fort I maxillary osteotomy, high statistically significant correlation was noted at the longest follow-up available (more than 1 year) only in the stomion superius horizontal and labrale superious vertical response to upper incisor tip movement. The ratios between soft and hard tissue changes in the horizontal and vertical plane ranged from 0.33 to 0.57 and 0.12 to 0.48 respectively, at follow-ups from 6 to 12 months. In this context, the soft to hard tissue movement ratios reported provide an initial guide that could be potentially useful in the clinical setting, bearing in mind the small number of the eligible trials, their heterogeneity with regard to participants, interventions, implementation, and statistics, as well as the results of the risk of bias assessment.

From the initially identified records, only three full-text studies evaluating the relation between soft and hard tissue changes following maxillary osteotomies in cleft lip and palate patients were included in this systematic review, reflecting the scarcity of relevant research. The consequent lack of extensive data is rather surprising as the ability of the surgeon to plan accurately for the post-operative change relies on the ability to correlate the soft tissue response to the underlying hard tissue osseous movements. Only small amounts of scientific data have been consistent across studies and most studies arrived at associations and values that are not summarized quantitatively to produce ratios useful in clinical practice.

Although still being a subject of debate (Chew et al., 2008), the simulation of orthognathic surgery outcomes by manual and most software programs assumes linearity in the soft tissue response to skeletal movement i.e. a fixed ratio regardless of the amount and direction of skeletal repositioning (Profitt et al., 2003; Smith et al., 2004). This relationship can be verified by investigating the correlation coefficients indicative of the strength of the linear association between osseous and soft tissue alterations. Correlation coefficients may take a range of values from -1 to +1. A correlation coefficient of 0 indicates that no linear association exists between the measured variables. The closer the correlation coefficient is to ± 1, regardless of the direction, the stronger the existing association, indicating a more linear, direct or inversely direct relationship between the two variables; meaning that knowledge of one variable can provide enough information to predict the other.

Prediction of soft tissue response is uncertain and only partially predictable in maxillary compared to mandible surgeries (Wermker et al., 2014). Postoperative esthetic evaluations of patients, who have undergone orthognathic surgery have placed more emphasis on the lips and less on the nose or chin (Burcal et al., 1987). Based on the retrieved data, high statistically significant correlation of stomion superius to upper incisor tip horizontal movement at the longest follow up was noted and moderate correlations of labrale superius to A point and upper incisor tip at earlier assessments. Hui et al. (1994) compared soft tissue changes in nose and lip profiles following maxillary osteotomies in 25 patients with unilateral cleft lip and palate and 25 non-cleft patients. A highly significant correlation was seen in the horizontal lip response in the cleft group, greater than in non-cleft patients, something potentially attributable to the presence of scar tissue which is firmer and the forward push of the underlying maxilla causing smaller lateral displacement of tissues. Moreover, a high correlation for labrale superius and horizontal maxillary advancement greater than 4 mm in UCLP patients was reported by Ewing et al. (1993). However, the above-mentioned studies also included mandibular surgeries and were therefore excluded from the present investigation. In non-cleft patients, moderate to high correlations of Ls and Sts to upper incisor tip have also been reported (Dann et al., 1976; Shuing et al., 1998; Chew et al., 2005; McCollum et al., 2009; Leila et al., 2015).

Moreover, no moderate or significant correlations were found between hard tissue and nose movement. This is in agreement with previous studies by Epker (1986) and Rosen et al. (1988), showing that the nasal tip does not increase proportionally with the horizontal advancement of the maxilla in non-cleft patients, and that the repositioning of these structures is not statistically correlated. The subnasale response to the hard tissue change has also been shown to be unpredictable in previous reports of non-cleft patients (Mansour et al., 1983; Carlotti et al., 1986; Rosen et al. 1988).

Regarding vertical relocation, a high correlation between labrale superius and upper incisor tip was observed at the longest follow-up available. This finding seems to agree with the data of Leila et al. (2015) in non-cleft patients. Low levels of correlation were noted for the rest of the relocations considered, corroborating previous investigations in cleft and not-affected individuals (Dann et al., 1976; Schendel et al., 1976; Mansour et al., 1983; Kerr et al., 1998; Hui et al., 1994; Lin et al., 1995; Shuing et al., 1998; Chew et al., 2005). It has been suggested that horizontal movement is more conducive to assessment and prediction than vertical repositioning. Muscle attachments of the incisive and mental slips of orbicularis oris in the midline region and the overlying connective tissue are tightly bound to underlying osseous tissue, providing a possible explanation for the high correlation of the horizontal gradient in the movement of the upper lip and the observation that soft tissues follow hard tissues more closely, predictably and proportionately (Soncul et al., 2004).

Furthermore, a moderate correlation between subnasale to upper incisor tip vertical movements was noted, in the immediate post-operative period. Most researchers suggest that the nose profile attains its definitive form, after the transient edema and swelling subsides, which is at least 6 months following surgery; thus, interpretation of soft tissue changes is reliable only after this period (Friehofer et al., 1976; 1977; Radney et al., 1981, Stella et al., 1989). The response of the subnasale after surgery has also shown a low correlation to the hard tissue change in previous reports in non-cleft individuals (Radney et al., 1981; Mansour et al., 1983; Bundagaard et al., 1986; Carlotti et al., 1986; Rosen et al., 1988; Jensen et al., 1992; Shiung et al., 1998).

The soft to hard tissue ratios of maxillary surgeries places emphasis on the Ls landmark (vermilion border of upper lip) for correct placement of the upper lip. Facial soft tissue static and dynamic evaluation is not only based on nose and lip balance but should include the relation of upper lip to the maxillary incisors (San Miguel et al., 2014). Data from studies on cleft patients that also included mandibular surgeries, or very few patients, and were therefore excluded from the present investigation, have shown a variation in response (Freihofer et al., 1976; Araujo et al., 1978; Ewing et al, 1993;Hui et al., 1994). Cleft lip/palate patients appear to display a lower Ls:Isi horizontal ratio compared to normal patients, with a mean of 0.54 and range from 0.29-0.66, very close to the ratio reported by the Al-Waheidi and co-workers study included in the present investigation (Freihofer et al., 1976). Other studies have reported large variations; ratios of soft to hard tissue advancement at Ls:Isi ranged from 0.4:1 to 1:1 (Dann et al., 1976; Araujo et al., 1978; Mansour et al., 1983; Carlotti et al., 1986; Rosen et al., 1988;

O'Reily et al., 1989; Jensen et al., 1992). In cleft patients; but after a combination of maxillary and mandibular procedures, Araujo et al. (1978) reported a ratio of 0.29:1, while Hui et al., 1994 and Ewing et al., 1993 found the ratio to be 0.66:1. The latter investigators observed that ratios for maxillary advancements of less than 4 mm increased to 0.74:1. In non-cleft patients, the ratios of Ls:Isi ranged from 0.4:1 to 0.95:1 after Le Fort I maxillary advancement (Carlotti et al., 1986; Radney et al., 1981;Bell et al., 1981; Araujo et al., 1978). This ratio ranged from 0.4:1 and 0.80:1 (0.57:1 mean) if a nasal cinch suture and V-Y lip plasty was performed (Rosen et al., 1998; Del Santo et al., 2004) while the ratio ranged from 0.56:1 to 0.78:1, if V-Y plasty alone, without a cinch was performed (Rosenberg et al., 2002; McCollum et al., 2009). The differences between cleft and non-cleft group responses has been attributed to more retruded soft tissue position preoperatively, secondary scarring, maxillary hypoplasia and cleft contracture (Hui et al., 1994).

The horizontal ratio of Sts to maxillary incisor tip was found to be 0.61:1, and, as mentioned previously, was found to be highly statistically correlated. Hui et al. (1994) reported a ratio of 0.76:1 in cleft patients after a combination of maxillary and other osteotomies. In non-cleft patients, ratios ranging from -0.12:1 to -0.33:1 have been reported after Le Fort I advancement (Bundguard et al., 1986; Van Butsele et al., 1995; Rosenberg et al., 2002; McCollum et al., 2009; Leila et al., 2015), ratios that were much lower than those in cleft patients. This ratio has been suggested to be affected by the type of suturing, as in the case of a decrease after a V-Y suturing had been performed (McCollum et al., 2009).

Nasal base Sn horizontal soft to hard tissue ratio to upper incisor tip was noted to be 0.33:1. The three studies that examined subnasale changes in cleft individuals after a combination of surgical procedures in the maxilla and the mandible related them to the

A point and reported ratios 0.57:1, 0.63:1,0.55:1 respectively (Freihofer et al., 1977; Ewing et al., 1993; Hui et al., 1994). A large variability has been observed with ratios of Sn:A ranging from 0.06 :1 to 0.86:1, in non-cleft patients. (Engel et al., 1979; Mansour et al., 1983; Rosen et al., 1988; Rosenberg et al., 2002; McCollum et al., 2009). These ratios were found to vary according to type of suturing, V-Y plasty and cases where no suturing was done. A continued remodeling of the underlying bone, possibly explained the drop in ratio of Sn/Isi to from 0.90 at less than 6 months to 0.33 at 6- 12 months postoperatively (Ewing and Ross et al., 1993).

The ratio of the superior labial sulcus to the horizontal movement of the upper incisor tip was 0.52:1. Studies of non-cleft patients found ranges of 0.17 to 1.0 for Sls:Isi following Le Fort I maxillary advancements. (O'Reily et al., 1989; Lines et al., 1974; Bell et al., 1981). In the study by Hack et al. (1991), the vertical ratio of Sls:Isi was 0.72:1 at five years post-operatively.

In the present investigation, the vertical ratios were for: Pn:Isi at 0.12:1, Sn:Isi at 0.10:1, Sls:Isi at 0.19:1, Ls:Isi at 0.44:1, St:Isi at 0.48:1 at 6 to 12 months post- operatively. Overall, they were found to be less pronounced compared to the horizontal ratios. The vertical lip to hard tissue movement ratio was about one third in non-cleft patients in previous studies of non-cleft individuals (Radney et al., 1981; Bundgaard et al.,1986; Rosen et al.,1988). Marked variations in vertical analyses could be due to the surgical technique used (San Miguel et al., 2014; Santos et al., 2012). Thus, the vertical ratios have been suggested to be of less clinical use than the horizontal ones (Kerr et al., 1998).

The variability of the soft-hard tissue ratios could be related to the accuracy of cephalometric assessment of soft tissue changes. Method related factors, such as anatomic complexity and superimposition of hard and soft tissues, density and sharpness of image; the observers experience in locating a landmark and precise definition and location of a landmark have also been implicated (Trpkova et al., 1997).

Moreover, parameters related to surgery like the magnitude of skeletal repositioning could also be important. Freihofer et al. (1977) and Stella et al. (1989) have reported different ratios for varying advancements. Variation has also been associated with suturing V-Y or nasal cinch suture. V-Y lip closure increases the Ls: Isi ratio only slightly, while cinch suture increases the ratio at a 0.80:1 value (Collins and Epker, et al., 1982). Finally, the surgeon's level of skill, experience and other differences in surgical techniques, could constitute important factors that influence the soft to hard tissue response (Heliovaara et al., 2001).

There is lack of data concerning, patient related factors, like age, gender and race; things that should be considered when predicting changes,. Gender differences between male and female responses have not been analyzed or reported in maxillary advancement (Kolokitha and Chatzistavrou et al., 2012). Similar ratios were found by Hui et al. (1994) in Japanese and Caucasian populations. Individual tissue reaction to surgery and healing capacity are further important factors that influence the ratios, but are difficult parameters to measure (Heliovaara et al., 2001). Significant differences in soft tissue responses can be seen in different types of cleft lip and palate (bilateral cleft lip and palate, unilateral cleft lip and palate or isolated cleft palate) due to differences in soft tissue thickness, lip thickness, lip length, lip posture, residualdefects and scarring from previous surgeries, differences in growth and morphology present pre-operatively (Heliovaara et al., 2001). In particular, the variability of the-operative soft tissue thickness has been mentioned by various researchers (Freihofer et al., 1976; Stella et al., 1989; McCoullum et al., 2009). Thinner lips followed bone movements better than thicker lips (Freihofer et al., 1977; Stella et al., 1989; McCoullum et al., 2009).

Summarizing the available evidence, the overall quality of evidence was considered as low, due to the scarcity of the retrieved data and the associated imprecision of the observed effects, together with concerns regarding the risk of bias.

### 6.2 Strengths and limitations

The strengths of the present systematic review include the pre-defined protocol, the extensive literature search, and the strict methodology implemented during every stage of the review according to well established guidelines. (Higgins et al., 2011, Liberati et al., 2009). The search strategy employed was both exhaustive, covering electronic, manual, and gray literature material, and comprehensive including every available study on hard and soft tissue changes after Le Fort I maxillary osteotomies in cleft lip and palate patients, irrespective of language, date and status of publication. Every effort to decrease bias in the methodology employed was made. Screening, verification of eligibility, abstraction of information, assessment of risk of bias and of the quality of evidence were performed in duplicate, and any disagreement was resolved by discussion or consultation with the thesis supervisor until a final consensus was achieved. Finally, the random effects model was employed during exploratory quantitative data synthesis (Lau et al., 1997).

There are also some limitations to the present review, arising mainly from the nature and the characteristics of the data retrieved during the review process which resulted in the assessment of the level of available evidence as, at best, low. The scarcity of relevant high-quality studies with evidence-based information precluded meta-analytic procedures for most outcomes. Even in cases where such an approach was attempted, such quantitative syntheses can only be regarded as exploratory until additional research becomes available. However, current concepts support that data from even as few as two studies can be combined, provided that these can be meaningfully pooled (Ryan et al., 2013), as all other summarizing techniques are less transparent and/or are less likely to be valid (Valentine et al., 2010). Furthermore, exploratory subgroup analyses and analyses for "small-study effects" and publication bias (Higgins and Green et al., 2011), could not be carried out even though they were incorporated as possibilities according to the review protocol.

Another limitation relates to the tools used for measuring changes. In two of the included studies, soft tissue measurements were carried out on cephalograms, while the third study employed superimposed three-dimensional photographs. Studies have shown the higher accuracy of three-dimensional data elaboration compared to traditional two-dimensional methods (Chang et al., 2015, Lin et al., 2015). Tissue shape, defects and asymmetries in CLP patients, head rotation, as well as magnification errors, are all factors affecting two-dimensional measurement accuracy. Three- dimensional analysis provides important information in complex CL/P cases involving facial asymmetry, especially yaw and midline adjustments that are regularly missed in two-dimensional methods (Lonic et al., 2016).

Variations in patients follow up for postoperative assessments and cephalometric imaging constitutes another area of concern. Many of the retrieved studies include soft tissue evaluations performed at less than 12 months postoperatively, though research data suggests a decrease in soft tissue swelling still occurring between 6 and 12 months after surgery (Van der Vlis et al., 2014) and that after the first year, soft tissue changes are minimal (Bailey et al., 2007) In other cases, the results required for meta analyses were not reported properly. Studies had to be excluded if the standard deviation of change ratios or other alternative statistics were absent.

Differences in soft tissue thickness, initial dysmorphology, growth and function between patients could possibly affect the soft tissue changes after maxillary repositioning and were not accounted for in any of the studies. Previous surgeries and scarring and residual defects posed another limitation both preoperatively as well as postoperatively (Heliovaara et al., 2001). Other limitations included the number of surgeons, their skill levels and experience, the magnitude of skeletal repositioning, surgical technique and suturing, patient age, gender and race.

### 6.3. Recommendations for future research

Based on the results of the present study, large degree of variability is observed regarding soft tissue response to changes in the underlying hard tissue movements, thus making prediction planning difficult. More good quality prospective studies with large samples are required to narrow the confidence limits of predictability of soft tissue changes and enable the surgeon to plan more precisely. Moreover, studies have to be conducted on the effect and control of the numerous confounding factors affecting soft tissue response. Evaluation of the same variables and consistency in the time periods for post-operative assessment would help in more precise prediction planning and achieving more accurately defined correlations and ratios. Optimally, soft tissue to hard tissue changes for UCLP, BCLP, and ICP have to be investigated separately. Finally, the use of three-dimensional analyses for surgical prediction are recommended (Chang et al., 2017).

## 7. CONCLUSIONS

Based on the present systematic review and meta-analysis, evidence-based conclusions on the relation between soft and hard tissue changes following maxillary osteotomies in cleft lip and palate patients are difficult to draw. High statistically significant correlations were noted at the longest follow-up available only in the stomion superius horizontal and labrale superious vertical response to upper incisor tip movement. More studies of high quality are needed in order to produce results robust enough to be used as a clinical aid during the prediction of the effects of osteotomies in cleft lip/palate patients.

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**Appendix I.** Systematic review protocol used for registration with international prospective register of systematic reviews (PROSPERO).

**Review question**(s)

To investigate current data on the relation between soft tissue and skeletal changes after maxillary advancement surgery in cleft-lip and palate patients and to critically evaluate the quality of the available evidence.

**Searches**

Comprehensive electronic database searches will be undertaken without language restriction in the following databases:

MEDLINE via PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Scopus (www.scopus.com), Web of Science™ Core Collection (http://apps.webofknowledge.com/), Arab World Research Source (http://0-web.a.ebscohost.com.amclb.iii.com) and ProQuest Dissertations & Theses Global database.

Efforts will be made to obtain conference proceedings and abstracts where possible. Authors will be contacted to identify unpublished or ongoing clinical trials and to clarify methodology and data as necessary. Reference lists of included studies will be screened for additional relevant research.

**Types of study to be included**

Clinical trials investigating the relation between soft tissue and osseous changes in patients with cleft-lip and palate following maxillary advancement surgery

**Condition or domain being studied**

Cleft-lip and palate

**Participants/ population**

Patients of any age, gender and race with cleft-lip and palate.

**Intervention(s), exposure(**s)

Maxillary advancement surgery

**Comparator(s)/ control**

Soft and hard craniofacial configuration before treatment

**Outcome(s)**

**Primary outcomes**

Correlation coefficients and/or ratios (together with the respective standard deviations or other measures used to quantify the amount of dispersion of a set of data values) between soft tissue changes and osseous surgical relocation, measured from conventional cephalometric points at pre- and post-surgery cephalograms.

**Data extraction, (selection and coding)**

All assessments including titles and/or abstract screening, full text evaluation, and extraction of data will be performed independently and in duplicate by two investigators (NV and EGK). The investigators will not be blinded to the authors or the results of the research. Disagreements will be resolved by discussion and consultation with a third author where necessary (AEA).

**Risk of bias (quality) assessment**

Assessment of risk of bias will be performed independently and in duplicate by two investigators (NV and EGK) using the using the ROBINS-I tool (Risk Of Bias In Non-randomized Studies of Interventions). Disagreements will be resolved by discussion and consultation with a third author where necessary (AEA).

**Strategy for data synthesis**

In situations where the retrieved data use different variables measuring the same concept on different scales with a high degree of correlation, the effects of the interventions are planned to be expressed as standardized values (i.e. the Standardized Mean Difference (SMD) together with the relevant 95% Confidence Interval (CI)), in order to enable quantitative synthesis. In cases where in a particular comparison the same variable is recorded, the intervention effect is planned to be expressed as the Weighted Mean Difference (WMD) together with the 95% CI. The random effects method for meta-analysis is to be used to combine data from studies that report similar measurements in appropriate statistical forms, since they are expected to differ across studies due to clinical diversity in terms of participant and intervention characteristics. Heterogeneity will be assessed using both the Chi-squared test and the I-squared statistic. If an adequate number of trials are identified, we will carry out analyses for "small-study effects" and publication bias.

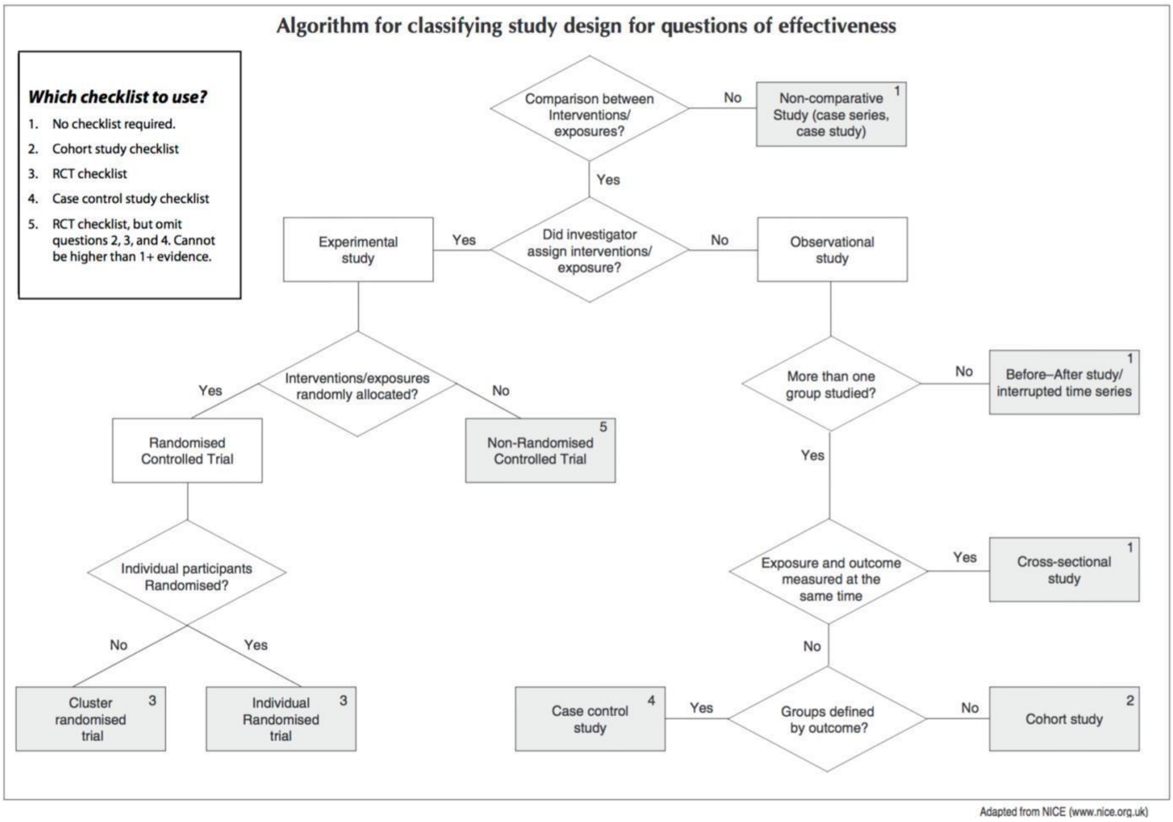
**Analysis of subgroups or subsets**

If the necessary data are available, subgroup analysis will be performed.

Dissemination plans

Peer-reviewed orthodontic journal

**Appendix II**. Scottish Intercollegiate Guidelines Network (SIGN) algorithm for classifying study design for questions of effectiveness.



**Appendix III**. Strategy for database search [until May 5th, 2017].

| Database | Search strategy | Hits |
|---|---|---|
| PubMed | (maxilla OR maxillary OR Le Fort) AND (advancement OR impaction OR intrusion OR (superior repositioning) OR downgrafting OR ( inferior repositioning) OR (expansion) OR widening OR SARPE OR (surgically assisted) OR (surgically-assisted) OR distract*) AND ((cleft lip) OR (cleft-lip) OR (cleft lip and palate) OR (cleft-lip and palate) OR (alveolar cleft*)) NOT (animals NOT humans) | 614 |
| Cochrane Central Register of Controlled Trials | (maxilla OR maxillary OR Le Fort) AND (advancement OR impaction OR intrusion OR (superior repositioning) OR downgrafting OR (inferior repositioning) O R (expansion) OR widening OR SARPE OR (surgically assisted) OR (surgically-assisted) OR distract*) AND ((cleft lip) OR (cleft-lip) OR (cleft lip and palate) OR (cleft-lip and palate) OR (alveolar cleft*))<br>in Title, Abstract, Keywords in Trials' | 24 |
| Cochrane Database of Systematic Reviews | ((cleft lip) OR (cleft-lip) OR (cleft lip and palate) OR (cleft-lip and palate) OR (alveolar cleft*)) {Including Limited Related Terms} | 11 |
| Scopus | TITLE-ABS-KEY ( ( maxilla OR maxillary OR le AND fort ) AND ( ( cleft AND lip ) OR ( cleft-lip ) OR ( cleft AND lip AND palate ) OR ( cleft-lip AND palate ) OR ( alveolar AND cleft* ) ) ) AND ( LIMIT-TO ( SUBJAREA , "DENT" ) ) | 167 |
| Web of Science™ | TOPIC: ((maxilla OR maxillary OR Le Fort) AND (advancement OR impaction OR intrusion OR (superior repositioning) OR downgrafting OR (inferior repositioning) OR (expansion) OR widening OR SARPE OR (surgically assisted) OR (surgically-assisted) OR distract*) AND ((cleft lip) OR (cleft-lip) OR (cleft lip and palate) OR (cleft-lip and palate) OR (alveolar cleft*)))<br>Timespan: All years.<br>Search language=Auto | 722 |
| Arab World Research Source | (maxilla OR maxillary OR Le Fort) AND (advancement OR impaction OR intrusion OR (superior repositioning) OR downgrafting OR (inferior repositioning) OR (expansion) OR widening OR SARPE OR (surgically assisted) OR (surgically-assisted) OR distract*) AND ((cleft lip) OR (cleft-lip) OR (cleft lip and palate) OR (cleft-lip and palate) OR (alveolar cleft*)) | 6 |
| ClinicalTrials.gov<br>http://clinicaltrials.gov/ | ((cleft lip) OR (cleft-lip) OR (cleft lip and palate) OR (cleft-lip and palate) OR (alveolar cleft*)) | 70 |
| ProQuest Dissertations and Theses Global<br>http://search.proquest.com/dissertations | ti((maxilla OR maxillary OR Le Fort) AND (advancement OR impaction OR intrusion OR (superior repositioning) OR downgrafting OR (inferior repositioning) OR (expansion) OR widening OR SARPE OR (surgically assisted) OR (surgically-assisted) OR distract*) AND ((cleft lip) OR (cleft-lip) OR (cleft lip and palate) OR (cleft-lip and palate) OR (alveolar cleft*)) ) OR ab((maxilla OR maxillary OR Le Fort) AND (advancement OR impaction OR intrusion OR (superior repositioning) OR downgrafting OR (inferior repositioning) OR (expansion) OR widening OR SARPE OR (surgically assisted) OR (surgically -assisted) OR distract*) AND ((cleft lip) OR (cleft-lip) OR (cleft lip and palate) OR (cleft-lip and palate) OR (alveolar cleft*)) ) | 8 |