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CRANIOFACIAL ADAPTATIONS FOLLOWING TONGUE VOLUME REDUCTION SURGERY: A SYSTEMATIC REVIEW

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ABSTRACT

AIM: To systematically investigate the available literature regarding craniofacial adaptations after tongue volume reduction surgery and critically evaluate the quality of existing evidence.

MATERIALS AND METHOD: A search without restrictions for published and unpublished literature and hand searching was performed. Data on craniofacial adaptations in patients of any age having undergone tongue volume reduction surgery were reviewed. Methodological quality was evaluated using the Robins-I tool (Risk of Bias in Non- randomized studies of intervention).

RESULTS: Out of 425 initially identified unique records, only 3 articles which followed patients up to one year post-surgery fulfilled the selection criteria for inclusion in the systematic review. Two studies presented data on various functional characteristics involving the tongue. After tongue volume reduction surgery, no significant differences were noted in the rest position, or during chewing and swallowing. At the same time, minimal influence was noted on oral stereognosis and motor ability. The third study investigating the effect of tongue volume reduction on dentofacial structures after mandibular setback showed that there was no significant difference in the assessed skeletal, hyoid position and airway cephalometric variables at 1 year. Methodological quality assessment identified various flaws in the included studies.

CONCLUSIONS: The present systematic review showed that, overall, no statistically significant differences were noted in terms of tongue function and dentofacial structure adaptation following tongue volume reduction surgery in the medium term. More high quality studies are needed in order to further investigate craniofacial adaptations following this procedure.

DEDICATION

I would like to dedicate this thesis to my beloved parents and wife for their constant support and encouragement.

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: Tariq Alawadhi

Signature:

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1. INTRODUCTION

Tongue position and volume are considered important elements influencing growth, craniofacial biomechanics and morphogenesis (Josell, 1995; Proffit, 1978; Liu et al., 2008a). The effect of tongue volume on craniofacial skeletal growth is essential for objectively evaluating outcomes of different orthodontic treatments and for determining the etiological mechanisms of various types of malocclusion (Liu et al., 2008a). Pressure from the tongue, lips and cheeks can be a major determinant of the dental equilibrium since teeth are positioned between these organs (Proffit, 1978). It has been suggested that the opposing tongue and lip pressures could be the sole determinants of this equilibrium (Proffit, 1978). The classical equilibrium theory suggests that pressure from the tongue at rest is more influential than during function, and that this pressure is crucial in determining teeth positions (Liu et al., 2008b).

Tongue volume is claimed to affect not only tooth position but also the vertical dimension of the face, mandibular arch size, head posture, maxillary expansion and the location of chin and symphysis (Lowe et al., 1985; Cohen and Vig, 1974a; 1974b; 1976; Turner et al., 1997; Tamari et al., 1991, Doual-Bisser et al., 1989). Tamari et al. (1991) demonstrated a positive relationship between mandibular arch size and tongue volume. This study also proved the tongue's expansive effect through its ability to deliver high pressure on the lingual surfaces of the teeth. However, whether or not the pressure from the tongue on the teeth actually changes after tongue reduction is not known (Fröhlich et al., 1993) as limited data is available on the effect that tongue position and volume changes exert on craniofacial growth and dental arch formation. (Liu et al., 2008a).

The aim of the present systematic review was to investigate and critically appraise the currently available literature regarding the craniofacial adaptations of patients subjected to tongue volume reduction surgery.

2. REVIEW OF THE LITERATURE

The tongue is a large muscular organ that comprises four intrinsic and four extrinsic muscles and fills most of the oral cavity (Ye et al., 2010). It has the capability of assuming different shapes without changing its volume (Kier and Smith, 1985). It contributes to various oral functions such as respiration, speech, deglutition and mastication (Ye et al., 2010). Moreover, it is the key oral structure for speech production and swallowing (Perkins and Kent, 1986; Perlman and Christensen, 1997).

2.1. Anatomy of the tongue

The tongue is a muscular organ consisting of a free body in the oral cavity and a fixed base attached to the hyoid bone and extending into the oral cavity and pharynx. The median sulcus lies in the dorsum of the tongue and divides it longitudinally along the midline into right and left halves. The remnants of the embryologic origin of the tongue are located in the specialized zones in the surface mucosa (Hiatt and Leslie, 2000).

The anterior two thirds are separated from the posterior third of the tongue by the terminal sulcus. The circumvallate papillae (vallate papillae) are a row of mushroom shaped papillae located anterior to the terminal sulcus. . They receive the ducts of the von Ebner serous glands and constitute the taste buds. Filiform and fungiform papillae are found in the remaining mucosal surface of the dorsum of the anterior two thirds. On the posterolateral aspect, the foliate papillae are located on the anterior two-thirds; their taste buds degenerate after the first two years of life. Just posterior to the apex of the terminal sulcus lies the foramen cecum. The lingual tonsils are found in the posterior one third of the tongue mucosa (Drake et al., 2009).

The mucosa of the ventral surface of the tongue is smooth and lacks surface papillae. The lingual frenulum attaches the anterior two-thirds of the tongue to the floor of the mouth. The Blandin-Nuhn glands which produce both serous and mucous saliva are found on either side of the frenulum, extending almost to the tip of the tongue. The bilateral deep lingual veins may be observed on either side of the frenulum. Lateral to each vein the plica fimbriate is located; this often exhibits tissue tags along its free edge. The fringes of the plica fimbriata assist the ducts of the Blandin-Nuhn glands to open into the oral cavity. Overlying the bulging sublingual glands, an elevation of the mucous membrane (plica sublingualis) is found on either side of the lingual frenulum. Several small openings comprising the small sublingual ducts (Rivinus ducts) are encountered and a large sublingual duct (Bartholin duct) from the sublingual gland joins the submandibular duct (Wharton's duct) just before its entry into the oral cavity for the delivery of saliva. From the submandibular gland, along the surface of the plica sublingualis, on either side of the lingual frenulum just posterior to the mandibular incisors, the incisive glands may also be found on the floor of the oral cavity (Hiatt and Leslie, 2000).

The sensory innervation of the tongue involves several nerves. The glossopharyngeal nerve (IX) provides the sensory innervation in the posterior third of the tongue for taste and general sensation. The general sensation of the anterior two thirds is supplied by the lingual nerve, which is a branch of the mandibular nerve (V3), while taste sensation is also provided by the facial nerve (VII) via chorda tympani (Hiatt and Leslie, 2000).

2.1.1. Muscles of the tongue

The tongue muscles comprise paired intrinsic and extrinsic lingual muscles. All the muscles of the tongue are innervated by the hypoglossal nerve except for the palatoglossus muscle, which is innervated by the vagus nerve. The intrinsic muscles of the tongue are divided into superior longitudinal, inferior longitudinal, transverse and vertical muscles. They perform different functions in order to have multiple tongue shapes. They work on flattening and rounding its surface, lengthening and shortening it, curling and uncurling its apex and edges. The intrinsic muscles are responsible for the precision movements of the tongue that are required for speaking, eating and swallowing. The extrinsic muscles of the tongue originate from structures outside the tongue comprising the hypoglossus styloglossus, genioglossus and palatoglossus and are inserted into the tongue. They perform the functions of tongue elevation, retraction, depression and protrusion (Drake et al., 2009).

2.1.2. Vessels of the tongue

The major artery of the tongue is the lingual artery. It originates from the external carotid artery of the neck adjacent to the tip of the greater horn of the hyoid bone. It enters the floor of the oral cavity by passing deep to the hyoglossus muscle, and accompanying the muscle through the aperture formed by the margins of the mylohyoid, superior constrictor, and middle constrictor muscles. The lingual artery then travels to the apex of the tongue by progressing forward in the plane between the hyoglossus and genioglossus muscles (Drake et al., 2009).

The tongue is drained by the dorsal lingual and deep lingual veins. On the undersurface of the tongue, the deep lingual veins are seen through the mucosa. They become separated from the arteries posteriorly by the hypoglossus muscles although they accompany the lingual arteries in anterior parts of the tongue. The dorsal lingual vein drains into the internal jugular vein in the neck, similarly to the deep lingual vein

(Drake et al., 2009).

2.2. Development of the tongue

The tongue starts to develop at about the fourth week of gestation. The pharyngeal arches meet in the midline beneath the primitive mouth, and swellings in the floor of the mouth appear due to the local proliferation of the mesenchyme. First, the tuberculum impar develops in the midline in the mandibular process of the first pharyngeal arch and is lined by two other bulges, the lingual swellings. A large mass consisting of the lateral lingual swellings forms the mucous membrane of the anterior two thirds of the tongue. These swellings quickly enlarge and merge with each other and the tuberculum impar (Nanci, 2003).

The hypobranchial eminence forms the root of the tongue, which develops from the mesenchyme of the third pharyngeal arch. It also forms the mucosa covering the root, or posterior third, of the tongue. The tongue periphery separates from the floor of the mouth by the down-growth of ectoderm around it, which subsequently degenerates to form the lingual sulcus and gives mobility to the tongue. The occipital somites form the muscles of the tongue during which they migrate forward into the tongue area, carrying with them their nerve supply, the hypoglossal cranial nerve. The mucosa of the anterior two thirds of the tongue is derived from the first pharyngeal arch, whereas the the mucosa of the posterior third of the tongue is a derivative of the third pharyngeal arch. (Nanci, 2003).

2.3. Physiology of the tongue

The tongue acts as an integral organ in different oral functions. It helps in the process of mastication by mixing and collecting the small food particles with the secretion of saliva to form a bolus. This process helps in swallowing and subsequent digestion. Swallowing is a reflex response triggered by afferent impulses in the trigeminal, glossopharyngeal and vagus nerves. The hypoglossal, facial and trigeminal nerves assist the efferent fibers to pass to the tongue and pharyngeal muscles. The swallowing process starts with collecting the oral contents on the tongue and moving them back into the pharynx. The tongue also aids in the production of speech. The motor cortex gives signals helping to initiate the appropriate movements of the larynx, lips and tongue to produce speech (Barrett et al., 2012).

Another primary function of the tongue concerns taste. Taste is facilitated by taste buds found on the tongue. They come with ovoid bodies. There are around 10000 taste buds measuring 50-70 μm present on the tongue. Four different types of cells are found in the taste bud: darks cells, light cells, intermediate cells and basal cells. The epithelial cells surrounding the taste bud give rise to the basal cells. These cells differentiate into new taste cells, and continuous replacement of the old cells occurs with a half-time of about 10 days. The other three cells are sensory neurons that respond to taste stimuli. Each taste bud has between 50 and 100 taste cells. These cells may represent different stages of the differentiation of developing taste with light cells being the most mature. Microvilli from the apical ends of taste cells project into the taste pore. There are around 50 nerve fibers that innervate each taste bud (Barrett et al., 2012).

The taste buds are found in the walls of tongue papillae. Close to the tip of the tongue, the fungiform papillae are located in a circular distribution, while the circumvallate papillae are found on the back of the tongue in a V shape. The filiform papillae are small conical projections of the mucosa running parallel to central grove of the tongue. The fungiform papillae have taste buds that are located mostly at the tip of papilla. They contain up to five taste buds. The foliate and circumvallate papillae are mostly found along the sides of the tongue and each has up to 100 taste buds. Saliva is secreted into the cleft around the circumvallate and foliate papillae by the von Ebner's glands. These secretions cleanse the mouth to prepare the taste receptors for new stimulants. Thus, a functional complex is formed by the circumvallate papillae and von Ebner's glands that are important in actual taste detection (Barrett et al., 2012).

2.4. Macroglossia

Macroglossia is the term used to define tongue enlargement due to tumor presence/development, muscle hypertrophy or endocrine disorder (Ruff, 1985). It is described in other sources as the protrusion of the tongue beyond the alveolar crest in the resting position (Nathanson, 1948; Murthy and Laing, 1994). It can cause open bite and usually is diagnosed by clinical examination (Worlford and Cottrell, 1996).

2.4.1. Classification of Macroglossia

Regarding etiology, macroglossia may be classified into true, relative and functional (Morgan et al., 1996). True macroglossia is usually associated with pronounced tongue enlargement due to a disease or syndrome (Balakrishnan and Bailey, 1991) while relative macroglossia is difficult to diagnose as the tongue size is only slightly larger when compared to normal (Guimaraes et al., 2008). The functional type of macroglossia occurs when the tongue does not adapt to the oral cavity after a surgical prodecure (Bell and Proffit, 1980)

True and relative macroglossia may both be subdivided into congenital and acquired. The common causes for congenital macroglossia include muscle hypertrophy and lymphangiomas (McManamny and Barnett, 1985; Rizer et al., 1985). It is also associated with some syndromes such as the Down syndrome and the Beckwith-Wiedemann syndrome (Filippi and Mckusick, 1970; Mixter et al., 1993). Acquired factors could include different conditions such as hypothyroidism, acromegaly and amyloeidosis (Guha et al., 2002; Wittmann, 1977; Mardinger et al., 1999).

2.4.2. Assessment of Macroglossia

The Assessment of macroglossia is performed either directly or indirectly using impression material, or through magnetic resonance imaging (Benson et al., 1987). Macroglossia may also be assessed by means of different clinical and cephalometric features, although the presence of these features might not necessarily contribute to the diagnosis (Worlford and Cottrell, 1996).

The clinical signs of macroglossia may include the tongue able to reach the nose tip, flat broad tongue, dental spacing, Class III malocclusion, mandibular protrusion, buccal tipping of posterior teeth and increased transverse width of upper and lower dental arches. Additional indicative clinical characteristics may include anterior open bite, accentuated curve of Spee in the upper dental arch and reverse curve of Spee in the lower dental arch. Obstructive sleep apnea and drooling have also been associated with macroglossia (Worlford and Cottrell, 1996).

A lateral cephalometric radiograph is used to assess tongue size. The contour of the tongue is traced and the cephalometric points are marked in order to use them for measurements and comparisons (Athanasiou et al., 1995). Cephalometric features associated with marcroglossia are increased mandibular plane angle, dentoalveolar protrusion and increased gonial angle (Friede and Figueroa, 1985).

2.4.3. Complications of Macroglossia

Macroglossia may lead to disruption of physiologic functions including breathing, mastication and phonation, consequently being associated with dentoskeletal deformities and instability following orthodontic or orthognathic surgical treatment (Wolford and Cottrell, 1996). An increased tongue volume might be associated with obstruction of the airway and lead to hypoxia episodes (Bell et al., 1988). Moreover, macroglossia has been associated with functional disturbances of the swallowing mechanism (Lindsay, 1955). To compensate for the interference of the enlarged tongue with normal muscular coordination in swallowing, atypical parts of the organ press against the neighboring tissues, and especially the teeth, with increased force (Lindsay, 1955). This tongue pressure during swallowing was believed to contribute to changes in the axial inclination of individual teeth and the shape of the dental arches (Sheppard, 1953; Tulley, 1956). In addition, aberrant masticatory function might lead to temporomandibular joint disorders, whereas abnormal position and size of the tongue may exert a negative impact on articulation (Margar-Bacal et al., 1987).

According to Schwab et al. (2003) the size of the and tongue is important in the development of obstructive sleep apnea. OSA has been reported in patients with conditions associated with macroglossia (Mezon et al., 1980, perks et al., 1980). The significance of macroglossia in OSA is demonstrated by the strong prevalence of OSA in patients with macroglossia as a primary or secondary condition (e.g., in hypothyroidism, acromegaly, amyloidosis, and Down syndrome) (Hudgel, 1992). Upper airway obstruction may develop in patients with acromegaly due to tongue enlargement while periodic obstruction during sleep has been noticed because the large tongue obliterated the pharyngeal airway (Mezon et al., 1980). According to Lowe et al. (1986a) subjects with OSA demonstrated different craniofacial features that was associated with a long tongue and more severe obstructive sleep apnea was associated with larger tongue and smaller airway volumes. (Lowe et al., 1986b). Tongue enlargement was found to be associated with an increased risk for sleep apnea, but this association lost significance when adjusted for BMI and NC (Schellenberg, 2000). Cephalometric evaluation and computerized tomography (CT) studies have also shown that patients with OSA have enlarged tongues as compared with control subjects (Nelson and Hans, 1997; Lowe, 1990).

The classical equilibrium theory suggests that pressure from the tongue at rest is more influential than during function and the pressure is crucial in determining position of the teeth (Liu et al., 2008b). The pressure from the tongue, lips and cheeks are normally major determinants of the dental equilibrium since teeth are positioned between these organs (Proffit, 1978). It has been suggested that the opposing tongue and lip pressures could be the sole defining factor in the equilibrium (Proffit, 1978). A very large tongue, is thought to constitute an important etiologic factor for dentoskeletal deformities like open bite, bimaxillary protrusion or spacing by exerting an expansive resting pressure on the dental arches or by being interposed between them (Fröhlich et al., 1992; Wolford and Cottrell, 1996). A positive relationship has been observed between the size of the lower dental arch and the volume of the tongue (Tamari et al., 1991). Tongue volume is claimed to affect not only tooth position but also the vertical dimension of the face, mandibular arch size, maxillary expansion and the location of chin and symphysis (Lowe et al., 1985; Cohen and Vig, 1974a; 1974b; 1976; Turner et al., 1997; Tamari et al., 1991, Doual-Bisser et al., 1989). Other complications associated with macroglossia include anterior or posterior cross-bite and protrusion of mandibular incisors (Wolford and Cottrell, 1996; Friede and Figueroa, 1985; Ruff, 1985; Menard et al., 1955; Kawakami et al., 2005; Ruscello et al., 2005).

2.4.4. Treatment of Macroglossia

Marcroglossia treatment depends on its etiology. It is generally managed through the treatment of any systemic disease or condition that causes tongue enalargement while orthodontic treatment, surgery and radiotherapy can also serve as major or adjunctive treatment alternatives. Other types of treatment are more conservative and involve the use of medication and cessation of the parafunctional habits contributing to the problem (Topouzelis et al., 2011).

Tongue volume reduction surgery is the most frequently reported treatment for true macroglossia (Topouzelis et al., 2011). Recognizing the signs and symptoms of macroglossia helps to identify those patients who could benefit from such a procedure in order to improve function, esthetics and treatment stability (Wolford and Cottrell, 1996).

According to Wolford and Cottrell (1996) there are several indications for tongue volume reduction surgery including psychological and speech problems, extremely large tongue mass, and the presence of tooth impressions on the tongue. The decision to proceed with tongue volume reduction surgery depends on the presence of several indications such as the experiencing of functional difficulties (e.g., speech and swallowing problems), or the presence of severe dentoskeletal characteristics such as increased mandibular angle and increased facial height with open bite, all of which may also affect psychological wellbeing (e.g., appearance, involuntary salivation) (Herren et al., 1989; Jung et al., 2014).

Surgical tongue size reduction has been suggested as an adjunctive procedure during mandibular setback surgery in order to prevent respiratory complications. In such cases, it seems logical that when the mandible is set back, the tongue moves also posteriorly and narrows the upper airway. However, physical adaptation of the hyoid, tongue, and cervical musculature are believed to take place in order to prevent airway obstruction and reduce the chance of respiratory problems (Athanasiou et al., 1991; Proffit and Phillips, 2003; Kawakami et al., 2004).

Glossectomy techniques may be classified into two types: the first technique is along the median line, while the second technique is peripheral. Both techniques entail excision of a part of the tissue and subsequent suturing of the excised margins (Gasparini et al., 2002). Depending on the type of excision, there are different sub-types of glossectomy, such as wedge, key-hole, reversed key-hole or W-shaped glossectomy (Siddiqui and Pensler, 1990; Morgan et al., 1996; Harada and Enomoto, 1995).

The complications and potential risks associated with glossectomy can include severe bleeding due to the rich blood supply of the tongue, tongue edema that could cause airway obstruction, lingual nerve and hypoglossal nerve damage that may cause tongue anaesthesia, loss of taste and motor dysfunction of the tongue. In addition, there is a possibility of salivary gland duct injury and scarring which can cause a decrease in tongue mobility, speech difficulty and mastication problems (Egyedi and Obwegeser, 1964; Esser et al., 1974; Kreidler and Rehrmann, 1974; Becker, 1975; Schulz and Sterzik, 1976; Schwenzer et al., 1976).

According to Fröhlich et al. (1992) the effect of glossectomy on tongue pressure on the teeth remains unknown while there is limited evidence on the effect that tongue position and volume changes have on craniofacial growth and dental arch formation (Liu et al., 2008a).

3. AIMS

3.1. Aim of the systematic review

To investigate and critically appraise the currently available literature regarding the craniofacial adaptations in patients subjected to tongue volume reduction surgery.

3.2. Objectives of the systematic review

To retrieve data on the craniofacial function and form adaptations in patients following tongue volume reduction surgery.

3.3. Null hypothesis

There is no difference in the functional and morphological parameters of patients before and after tongue volume reduction surgery.

4. MATERIALS AND METHODS

4.1. Protocol development and registration

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 (CRD42017079878) (Appendix I). In addition, conduct and reporting followed the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011) and the PRISMA statement (Moher et al., 2009), respectively.

4.2. Eligibility criteria

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

4.2.1. Types of study design

Studies included in the present thesis had to be observational studies evaluating changes in the craniofacial structures after the surgical reduction of the tongue. Case reports, case series, studies with less than 10 participants, animal studies and reviews (traditional reviews, systematic reviews and meta-analyses) were not included in the present investigation.

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 II).

4.2.2. Types of participants

The included studies could involve patients of any age and gender. Studies that included patients with clefts, syndromes or congenital anomalies of the craniofacial region, parafunctional habits or temporomandibular disorders were excluded.

4.2.3. Types of interventions

The included studies could involve patients subjected to any type of tongue reduction surgery; as a sole intervention or combined with other procedures.

4.2.4. Types of outcome measures

The studies included in the present review had to provide quantitative data on morphological, postural and functional parameter changes following tongue reduction surgery i.e. oral ability to recognize forms, oral motor ability, skeletal and soft tissue changes, occlusal changes, adaption of upper airway space, mandibular position, tongue pressure on the teeth.

4.3. Information sources and search strategy

The principal investigator (TMA) developed detailed search strategies for each database searched. These were based on the strategy developed for MEDLINE, but revised appropriately for each database taking account of the differences in controlled vocabulary and syntax rules. The following electronic databases were searched (Appendix III): MEDLINE via PubMed, CENTRAL, Cochrane Systematic Reviews, Scopus, Web of Science™ Core Collection, Arab World Research Source, Clinical Trials registry and ProQuest Dissertations & Theses Global database.

No restriction was placed on the language, date or status of publication. In addition, efforts were made to obtain conference proceedings and abstracts where possible and the reference lists of all eligible studies for additional records were searched.

4.4. Study selection

The principal investigator (TMA) and the thesis co-supervisor (EGK) assessed the retrieved records for inclusion independently. They were not blinded to the identity of the authors, their institution, or the results of the research. They obtained and assessed, again independently, the full report of records considered by either reviewer to meet the inclusion criteria. Disagreements were resolved by discussion or consultation with the thesis principal supervisor (AEA). All decisions on study identification were recorded.

4.5. Data collection and data items

The same two persons performed data extraction independently and any disagreements were again resolved by discussion or consultation with the thesis principal supervisor (AEA). Data collection forms were used to record the desired information.

a. Bibliographic details of the study.

b. Details on study design and verification of study eligibility.

c. Participant characteristics (where available number, age, gender).

d. Intervention characteristics (e.g. surgery type, combination with another intervention).

e. Details on outcomes assessed and assessment procedures.

f. Additional information: a prior sample size calculation, measurement reliability assessment.

If clarifications were needed regarding the published data, or additional material was required, then attempts to contact the corresponding authors would be made.

The outcomes relevant to craniofacial changes after tongue reduction surgery retrieved from the studies included in the present review were categorized as follows:

a. Morphological and postural parameters.

b. Functional parameters.

4.6. Risk of bias in individual studies

The principal investigator (TMA) and the thesis co-supervisor (EGK) were to assess the risk of bias in the included studies independently and in duplicate, during the data extraction process, using the ROBINS-I tool (Risk Of Bias In Non-randomised Studies of Interventions) (Sterne et al., 2016). Any disagreements were to be resolved by discussion or consultation with the thesis principal supervisor (AEA). The ROBINS-I tool assessment tool includes the following domains:

a. Bias due to confounding.

b. Bias in selection of participants into the study.

c. Bias in classification of interventions.

d. Bias due to deviations from intended interventions.

e. Bias due to missing data.

f. Bias in measurements of outcomes.

g. Bias in selection of the reported results.

After entering the information reported in each study in the data extraction form, 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 control.

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 of 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 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 to be used to combine data from studies that reported similar measurements in appropriate statistical forms (Der

Simonian and Laird, 1986, Borenstein et al., 2009), since they were expected to differ across studies due to clinical diversity in terms of participant and intervention characteristics.

To identify the presence and extent of between-study heterogeneity, the overlap of 95% CI for the results of individual studies was to be inspected graphically, and Cochrane's test for homogeneity and the I^2 statistic were to be calculated (Higgins and Green, 2011). The results of the I^2 statistic were to be interpreted as follows (Higgins and Greene, 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, 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 deemed possible, exploratory subgroup analyses were planned according to participant and intervention characteristics. Finally, the quality of evidence for the significant differences 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 flowchart of records through the reviewing process is shown in Figure 1. Initially 717 records were identified, and 292 were identified as duplicates, and 384 more were excluded on the basis of their title and abstract. From the 41 records assessed for eligibility, 38 were excluded because they presented case reports, case series and animal studies. Finally, 3 full-text reports were included in the systematic review (Ingervall and Schmoker, 1990; Fröhlich et al., 1993; Kawakami et al., 2004).

5.2. Study characteristics

The general characteristics of the studies included in the present systematic review, as well as sample characteristics, are presented in Tables 1 and 2. They were published between 1990 and 2013 and investigated the effect of tongue volume reduction surgery on a) morphological and postural parameters: maxillomandibular relationships and airway morphology; position of the head, the cervical column, hyoid bone, rest position of the mandible and the tongue (Ingervall and Schmoker, 1990; Kawakami et al., 2004); and b) functional parameters: tongue pressure on the teeth (Fröhlich et al., 1993), oral motor ability and ability to recognize forms (Ingervall and Schmoker, 1990). The mean age of the patients varied from 15 to 21 years, approximately. Ingervall and Schmoker (1990) and Fröhlich et al. (1993) investigated patients before, and approximately 6 and 12 months after, tongue volume reduction surgery, whereas, Kawakami et al. (2004) examined the additive effect of partial glossectomy, before, 1 month and 1 year following mandibular setback.

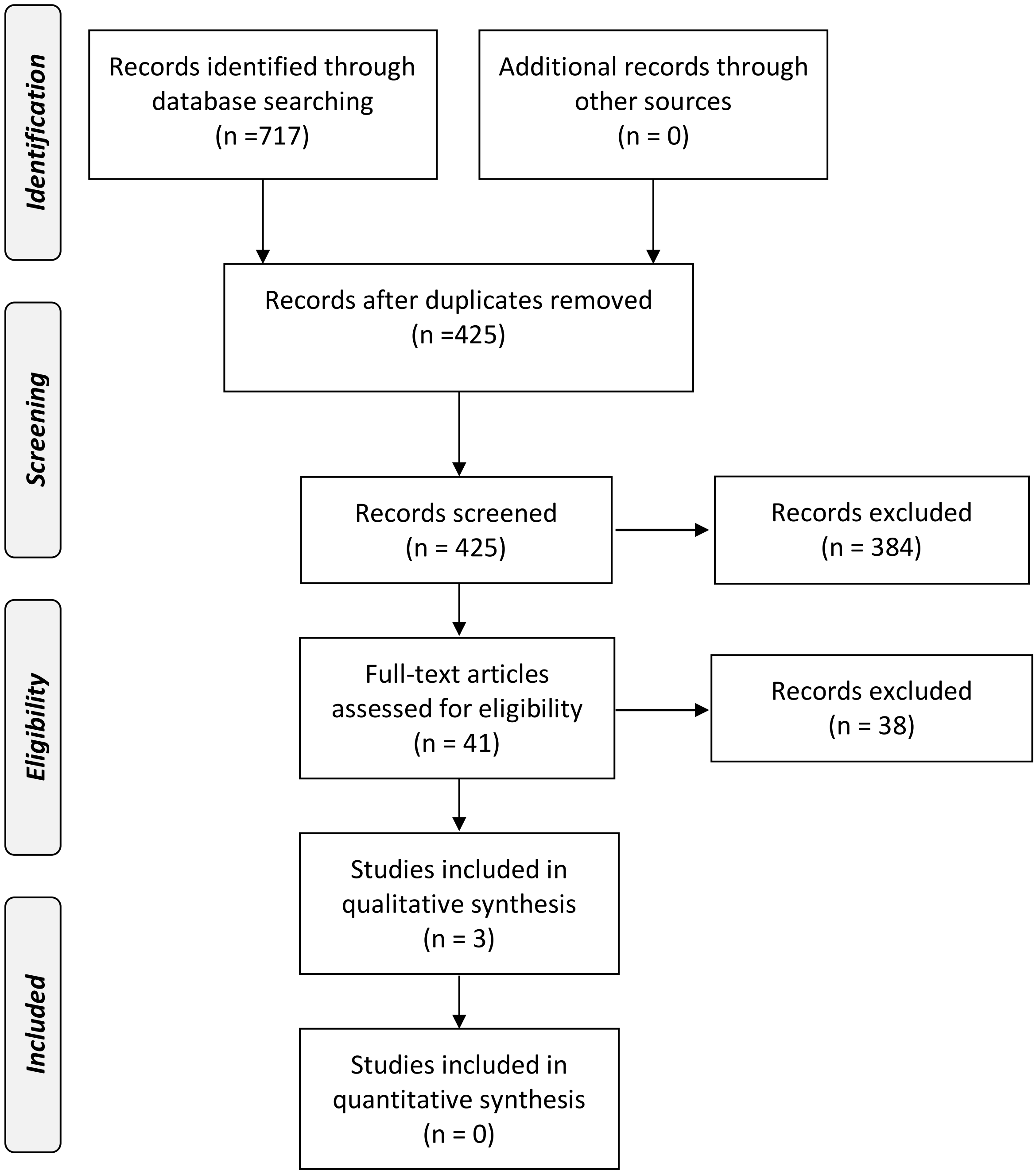

Figure 1. Flowchart of records through the reviewing process.

Table 1. General characteristics of the studies included in the systematic review.

Study	Intervention characteristics	Included outcomes and methods of assessment	Additional information
Ingervall and Schmoker [1990]	**Tongue reduction surgery** According to Schmoker (1985)	**Pre-Op, 3-6 m (median: 5 m) Post-Op; 11-15 m (median: 13 m)** **Oral ability to recognize forms** Subjects asked to try to identify 12 test bodies placed in the mouth, one at a time. Four grades of difficulty were used, each grade comprising three test objects. The time used by the subject for each test body, as well as any misidentification, was noted. **Oral motor ability** Subjects requested to assemble 2 halves of a test piece in the mouth. Four test pieces with increasing degrees of difficulty were used. The time used was recorded. If the subject could not manage to assemble the test piece in 180 seconds, the test was stopped and recorded as a failure. **Cephalometric evaluation of natural position of the head and the cervical column; craniocervical angulation; position of hyoid bone, tongue and mandible** *Natural position of the head:* NSL/VER (º), NL/VER (º), ML/VER (º) Natural position of the cervical column: OPT/HOR(º), CVT/HOR(º) Natural position of the craniocervical angulation: NSL/OPT(º), NSL/CVT(º) Position of the hyoid bone: perpendicular distance between point h and reference lines NSL, NL, ML, RL , CVT Position of the tongue: measurement of perpendicular distance ut-NL, pt-pw Free space and difference in anteroposterior position of the mandible: difference in the distance n-me and ar-pgn (difference between the radiographs in rest position and in the intercuspal position) Profile cephalograms were made with subjects standing upright with head and cervical column in natural position. Three radiographs were taken on each occasion: (1) with the mandible in the rest position; (2) with the mandible in the rest position after the midline of the tongue was coated with radiopaque paste; (3) with the mandible in the intercuspal position with radiopaque paste on the tongue. To obtain the rest position, the subject was asked to swallow and thereafter relax the muscles.	**Power calculations:** No **Method error:** No

BSSO: Bilateral sagittal split ramus osteotomy; Md: Mandibular; Pre-Op: before operation; Post-Op: after operation; SR: semi-rigid; m: month; d: day; y: year; NSL: Nasion-Sella line; VER: True Vertical line; NL: Nasal line; ML: Mandibular line; OPT: Odontoid process tangent; HOR: True Horizontal line; CVT: Cervical verterbra tangent: RL: Ramus line; ut: upper point of the tongue; pt: intersection between the contour of the tongue and upper occlusal line; pw: intersection between the contour of the pharyngeal wall and upper occlusal line; n: Nasion; me: menton; ar: articulare; pgn: prognathion; ANB: angle between point A and B at nasion; FMA: Frankfort mandibular plane angle; D1: The vertical distance between the dorsum of the tongue and posterior nasal spine on a perpendicular line of the Frankfort horizontal plate; D2: The horizontal distance between the posterior pharyngeal wall and the dorsum of the tongue on a line parallel to the palatal plane that runs through the most anterior inferior point on the second vertebra (C2); S-H: The vertical distance between Sella (S) and the most inferior point of the hyoid bone (H). 4) C3-H: Linear distance between H and the most anterior point on the third vertebra (C3); NSH: The angle of S-H to SN plane.

Table 1. General characteristics of the studies included in the systematic review. [Continued]

Study	Intervention characteristics	Included outcomes and methods of assessment	Additional information
Fröhlich et al. [1993]	**Tongue reduction surgery** According to Schmoker (1985)	**First Pre-Op recording 183-1 d (median: 27 d) all subjects; Second Pre-op recording 6-1 d (median: 1 d) 15 subjects;** **First Post-Op recording 155-254 (median: 190 d) 19 subjects; Second Post-op recording 344-484 d (median: 380 d) 17 subjects** **Tongue pressure on teeth** Tongue pressures on lingual surfaces of the teeth were measured: 1. In the interdental space between the maxillary central incisors, 2. In the interdental space between mandibular central incisors, 3. In the interdental space between the mandibular left second premolar and first molar, 4 In the interdental space between the mandibular left second premolar and first molar. Tongue pressure was measured: 1. with the mandible and the tongue in the rest position, 2. during two acts of swallowing water (on command), 3. in the rest position once again, 4. during two acts of swallowing 7 cm^2 of crispbread. Measurements performed with an open cannula embedded in a small custom-made acrylic shield attached to on the lingual surfaces of the teeth. The other end of the cannula was connected via a flexible tube to an extra-oral measuring system. **Electomyographic recordings** Activities of Right anterior temporal muscle and muscles of the floor of the mouth were recorded before and after tongue reduction surgery using electromyographic device, in order to help subjects keep the tongue at rest.	**Power calculations:** No **Method error:** No
Kawakami et al. [2004]	**Group 1:** Md setback BSSO/SR fixation + tongue reduction surgery **Group 2:** Md setback BSSO/SR fixation	**Pre-Op, Post-Op 1 m; Post-Op 1 y** **Skeletal changes:** Overjet, Overbite, ANB, FMA **Hyoid and airway changes:** D1, D2, S-H, C3-H, NSH Measurements on lateral cephalometric radiographs	**Power calculations:** No **Method error:** Yes

BSSO: Bilateral sagittal split ramus osteotomy; Md: Mandibular; Pre-Op: before operation; Post-Op: after operation; SR: semi-rigid; m: month; d: day; y: year; NSL: Nasion-Sella line; VER: True Vertical line; NL: Nasal line; ML: Mandibular line; OPT: Odontoid process tangent; HOR: True Horizontal line; CVT: Cervical verterbra tangent: RL: Ramus line; ut: upper point of the tongue; pt: intersection between the contour of the tongue and upper occlusal line; pw: intersection between the contour of the pharyngeal wall and upper occlusal line; n: Nasion; me: menton; ar: articulare; pgn: prognathion; ANB: angle between point A and B at nasion; FMA: Frankfort mandibular plane angle; D1: The vertical distance between the dorsum of the tongue and posterior nasal spine on a perpendicular line of the Frankfort horizontal plate; D2: The horizontal distance between the posterior pharyngeal wall and the dorsum of the tongue on a line parallel to the palatal plane that runs through the most anterior inferior point on the second vertebra (C2); S-H: The vertical distance between Sella (S) and the most inferior point of the hyoid bone (H). 4) C3-H: Linear distance between H and the most anterior point on the third vertebra (C3); NSH: The angle of S-H to SN plane.

Table 2. Sample characteristics in the studies included in the systematic review.

Study	Inclusion & exclusion criteria	Analyzed sample
Ingervall and Schmoker [1990]	**Inclusion criteria:** All patients referred to a maxillofacial surgeon for tongue reduction with a clinical diagnosis of macroglossia	**27 patients (16 M, 11 F)** **Age at Pre-Op:** 15y8m [range: 9y11m to 22y9m] **Additional features:** lisping, frontal or lateral open bite, bimaxillary protrusion, planned surgical correction of mandibular prognathism
Fröhlich et al. [1993]	**Inclusion criteria:** diagnosis of macroglossia based on discrepancy between tongue size and the size of the oral cavity **Exclusion criteria:** presence of palatal appliance, maxillo-facial surgery	**21 patients (11 M, 10F)** **Age at Pre-op: 15y3m [range: 9y7m-19y5m]** **Additional features**: Angle classification from dental casts: 11 Cl I, 2 Cl II, 8 Cl III 12 Anterior open bite, 7 Posterior open bite. 14 unilateral-bilateral posterior lingual cross bite, 2 anterior cross bite. Spacing anomalies: lack of 2mm or more canine-premolar and incisor region, Mx: spacing in one incisor segment; crowding in four canine-premolar segments. Mn: spacing four canine-premolar segments; crowding two canine premolar segments and one incisor segment. 3 pm extracted in 3 subjects.
Kawakami et al. [2004]	**Inclusion criteria:** patients with mandibular prognathism who received orthodontic treatment before the surgical correction **Exclusion criteria:** 2-jaw surgery and/or craniofacial anomaly such as cleft lip and palate	**40 patients (10 M, 30 F)** **Age at Pre-op: 20.8 years [range: 17y- 37y]**

M: males; m: months; F: females; Pre-Op: before operation; y: years; Ant: Anterior; Post: Posterior; mm: millimeter; Mx: Maxilla; Mn: Mandible; pm: premolar

5.3. Risk of bias within studies

Table 3 presents the summary of findings regarding risk of bias assessment for the three included studies (Ingervall and Schmoker, 1990; Fröhlich et al., 1993; Kawakami et al., 2004). All were considered overall as being at serious risk of bias. More details can be found in Appendix IV.

In general, all studies included in the present review were considered to present serious risk of bias regarding confounding, as important parameters (e.g., gender, age and growth status, type of malocclusion, presence of fixed appliances, tongue volume removed, tongue reduction technique) 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 the assessors were aware of the intervention, or there was no information on blinding or data on measurement reliability or there existed significant concerns regarding the latter (Ingervall and Schmoker, 1990; Fröhlich et al. 1993; Kawakami et al., 2004). Finally, the risk of bias in selection of the reported result was moderate for all the included studies.

Table 3. Summary of the risk of bias assessment.

Domain	**Ingervall and Schmoker, 1990**	**Fröhlich et al., 1993**	**Kawakami et al., 2004**
Bias due to confounding	Serious	Serious	Serious
Bias in selection of participants for the study	Low	Low	Low
Bias in classification of interventions	Low	Low	Low
Bias in measurement of outcomes	Serious	Serious	Serious
Bias in selection of the reported result	Moderate	Moderate	Moderate
Overall	**Serious**	**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. Because of the lack of extensive relevant data, quantitative data synthesis was not possible.

5.4.1. Effect on morphological and postural parameters

Following **tongue volume reduction surgery**, Ingervall and Schmoker (1990) showed significant differences neither in the *position of the head, the cervical column or the hyoid bone*, nor in the *craniocervical angulation* between the pre-surgical and the post-surgical evaluations.

The evaluation of *tongue at the rest position* showed that the distance between the dorsum and the nasal line increased significantly between the pre-surgical and the post-surgical evaluations ($p<0.01$). However, no significant differences were shown during the post-operative follow-up period. Moreover, no significant differences with time were observed on the distance between the posterior part of the tongue and the pharyngeal wall. The distance between the dorsum and the nasal line became greater with increasing age ($p<0.01$), whereas no correlations with gender or excised tongue volume were found.

The *freeway space* decreased significantly between the pre-surgical and the post-surgical evaluations ($p<0.01$), but no significant differences were noted during the post-operative follow-up period. The freeway space decreased with increasing age ($p<0.05$), while no associations with gender or excised tongue volume were noted.

The *anteroposterior position of the mandible in the rest position* did not change significantly between the pre- and the post-operative evaluation.

During the follow-up period after **mandibular setback, accompanied by or without tongue volume reduction surgery**, Kawakami et al. (2004) observed no significant between groups or within group differences in *overjet*, *overbite* and *ANB angle*. Only the *Frankfort-mandibular plane angle* in the group without tongue reduction showed a significant increase during the post-surgical follow-up period ($p<0.05$), indicating a clockwise rotation of the mandibular plane, however, the inter-group difference was not statistically significant.

Moreover, no statistically significant differences between the two groups were noted regarding the *position of the hyoid bone*. Within group evaluation showed that a posterior and downward change was noted in both groups after setback, as S-H and C3-H increased (S-H [mm]: 119.9 ±8.9 to 127.0 ±9.9; C3-H [mm]: 38.7 ±4.6 to 40.7 ±6.1; $p<0.05$) (Kawakami et al., 2004). However, at the 1 year follow-up these measurements did not differ significantly from the preoperative, indicating a tendency toward the original hyoid bone spatial relationships. In the tongue resection group, the NSH angle increased after surgery and remained increased at the 1 year follow-up ($p<0.05$). Again, the inter-group differences were not statistically significant.

Patients subjected to an additional tongue resection showed significantly narrower *airway space at the tongue base* before, and immediately after surgery, compared to the setback only group. No other between groups differences reached statistical significance. In the first group, the airway space at the tongue base did not change between measurements until the 1 year follow-up. On the contrary, subjects not receiving glossectomy showed a marked within group decrease in *airway space at the tongue dorsum and base* at the 1 year evaluation.

5.4.2. Effect on functional parameters

Fröhlich et al. (1993) tested the *tongue pressure on the teeth* at rest, as well as during chewing and swallowing at four sites (maxillary and mandibular incisors and molars) after **surgical tongue volume reduction**. The pressures found during all functions studied exhibited large variability and at rest negative values were recorded in many individuals, particularly in the maxillary incisors.

Resting pressures at the molars decreased significantly from the pre-operative to the 6-month follow-up (maxillary molar median: 3.0 to -0.8 g/cm^2; mandibular molar median: 8.2 to -0.1 g/cm^2), but no difference was noted between the former and the 12-month recordings. Chewing pressure did not change significantly during the observation period. Finally, swallowing pressure at the maxillary incisor decreased significantly from the pre-operative to the 6-month post-operative measurement (median from 128.3 to 107.8 g/cm^2), but was again not significantly different compared to the 12-month follow-up. In general, none of the measurements at 12 months differed significantly from the pre-operative recordings.

No significant correlations were noted for measurements at the same site and the same function between the pre-operative and the 12-month follow-up. Moreover, no significant correlations were observed between the volume, weight, length or width of the removed part of the tongue and the change of the pressures recorded before and 12 months after the operation.

Surgical tongue volume reduction exerted a minor effect on patients' *ability to recognize forms* (Ingervall and Schmoker, 1990). A significant increase in the time used for the identification was observed only for the test bodies of level 3, for which the time was longer at the final evaluation than the initial ($p<0.05$). With regard to the number of misidentifications, the effect was somewhat greater. In two out of the four levels of difficulty, an increase in the number of misidentifications after surgery was noted. The number of misidentifications of level 1 test bodies increased significantly (p<0.001) between the pre-surgical and the post-surgical evaluations. However, no significant differences were shown during the post-operative follow-up period. In contrast, the number of misidentifications of the test bodies of level 2 showed an increase, not only between the pre- and the post-surgical evaluations (p<0.01), but also during follow-up period after the intervention (p<0.05). The number of misidentifications at difficulty levels 2 and 3 was not influenced by gender, age, or volume of the excised part of the tongue. However, for level 1 test bodies, misidentifications were found to be more frequent in boys, older patients, and those from whom a smaller tongue volume had been removed (p<0.05). In general, moderate to strong correlations between the performance at the initial and the final evaluation were noted.

Moreover, tongue volume reduction surgery exerted a minor effect on patients' overall *oral motor ability*, between the baseline and the final evaluation (Ingervall and Schmoker, 1990). The only significant difference between measurements of the number of failures to assemble the test pieces was for level of difficulty 2. Initially, an increase was noted between the pre- and the post-surgical evaluations (p<0.05), followed by a decreased during follow-up period after the intervention (p<0.05).

5.5. Risk of bias across studies and additional analyses

As 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, 2011). Overall, the quality of evidence was considered at best as low (Table 4).

Table 4. Quality of available evidence.

Quality assessment						Subjects	Effect	Quality
Studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**		**Absolute Mean (95% CI)**	
Distance between tongue dorsum and the nasal line [mm | comparison before and 12 months after the operation]								
1	Serious[1]	Not serious	Not serious	Serious[2]	No	27	Median **2.6 mm greater** ***p*<0.01**	⊕⊕◯◯ **LOW**
Freeway space [mm | comparison before and 12 months after the operation]								
1	Serious[1]	Not serious	Not serious	Serious[2]	No	27	Median **0.7 mm less** ***p*<0.01**	⊕⊕◯◯ **LOW**
Ability to recognise forms | level 3 test bodies | time [secs | comparison before and 12 months after the operation]								
1	Serious[1]	Not serious	Serious[3]	Serious[2]	No	27	Median **3.2 secs higher** ***p*<0.01**	⊕⊕⊕◯ **VERY LOW**
Ability to recognise forms | level 1 test bodies| misidentifications [number | comparison before and 12 months after the operation]								
1	Serious[1]	Not serious	Serious[3]	Serious[2]	No	27	Mean **1.44 higher** ***p*<0.01**	⊕⊕⊕◯ **VERY LOW**
Ability to recognise forms | level 2 test bodies| misidentifications [number | comparison before and 12 months after the operation]								
1	Serious[1]	Not serious	Serious[3]	Serious[2]	No	27	Mean **1.52 higher** ***p*<0.01**	⊕⊕⊕◯ **VERY LOW**

CI: Confidence interval
[1] Studies were considered as being of serious risk of bias. [2] The results are based only on one study. [3]The results are based only on one level of difficulty.

6. DISCUSSION

6.1. Summary of evidence

Despite clinical reasoning that tongue volume influences not only the position of the maxillary and mandibular dentition, but also the posture of the mandible and the vertical height of the face (Liu et al., 2008a), there is limited information about the effects of altering tongue volume on craniofacial growth and dental arch formation (Fröhlich et al., 1992; Liu et al., 2008a). Based on the data provided in the present systematic review, overall, no significant differences were noted in the medium term, in terms of dentofacial structure adaptation and tongue function following tongue volume reduction surgery; thus, the null hypothesis can be rejected. Moreover, the concerns raised during quality assessment of the available evidence provide insights regarding confidence in the observed estimates.

From the initially identified records, only three full-text studies evaluating the changes resulting from the tongue volume reduction surgery were included in this systematic review, reflecting the scarcity of relevant research. The consequent lack of extensive data is rather surprising since tongue volume and position have been considered to be critical factors affecting craniofacial growth, and tongue volume reduction surgery is the most frequently reported treatment for true macroglossia (Topouzelis et al., 2011; Ye et al., 2013; Lowe et al., 1985; Cohen and Vig, 1976, 1974a; 1974b; Turner et al., 1997; Tamari et al., 1991, Doual-Bisser et al., 1989).

Based on the information retrieved in the present review, no significant effects on *morphological and postural parameters*, like the position of the head, the cervical column and the hyoid bone, or the craniocervical angulation, were noted after tongue volume reduction (Ingerval and Schmoker, 1990). However, the operation resulted in the tongue filling the oral cavity to a lesser extent than before the intervention, this possibly being the reason for the decrease in the freeway space noted. Liu et al. (2008a) employing a young animal model, observed that a surgical decrease in tongue volume slows craniofacial skeletal growth, especially in the mandibular symphysis regions, and anterior dental arch expansion during periods of accelerated growth. In addition, decreases in bone mineral density and content were noted, especially in the anterior mandibular region.

Furthermore, when tongue volume reduction surgery was applied as an adjunct to mandibular setback, a significant effect on occlusal and skeletal relationships, together with the position of the hyoid bone and the tongue posture was not noted at the 12-month evaluation in either experimental group (Kawakami et al., 2004). Although it would seem logical that when the mandible is set back, the tongue would also move posteriorly and narrow the upper airway; in fact, physical adaptation of the hyoid, tongue, and cervical musculature may occur in order to prevent airway obstruction and thus reduce the chance of respiratory problems (Athanasiou et al., 1991; Proffit and Phillips, 2003; Kawakami et al., 2004). The small effect of tongue reduction on mandibular relapse supports the idea that large tongue volume is not inherent in patients with mandibular prognathism (Yoo et al., 1996) and that adjunctive tongue resection is rarely necessary in the mandibular prognathism patients without the existence of a disproportionate tongue size (Wickwire et al., 1972; Proffit and Phillips, 2003; Kawakami et al., 2004). Moreover, the methodology used may account for the observed results. According to Haskell et al. (2009), the use of lateral cephalometric radiography limited the accuracy of airway measurement as the two-dimensional (2D) images only allowed an anteroposterior dimension measurement in sagittal plane, and failed to provide a full-scaled view of the upper airway. Cone beam computed tomography (CBCT) is an acceptable technique for 3D volumetric depiction and morphological evaluation of the upper airway by allowing a 3D registration of pre- and post-treatment data through identification of specific structures in the cranial base (Haskell et al. 2009).

Regarding *functional parameters* such as the tongue pressure on teeth at rest and during chewing and swallowing, great variability was noted, corroborating previous investigations in young adults (Fröhlich et al., 1991; 1992). No recording was significantly different from the pre-operative recordings 12 months after surgery (Fröhlich et al., 1993). Liu et al. (2008b) showed in an animal study that immediately after tongue volume reduction surgery the overall magnitude of bone surface and suture loading during masticatory function decreased, and the strain orientation changed. However, this effect was less pronounced in the posterior mandible and palate and no strain change was found at the mandibular lingual symphysis. A later follow-up study on tongue pressures during chewing, performed after 4 weeks of healing following tongue reduction surgery, showed elevated strain, particularly on the mandible (Ye et al., 2013). These findings are in contradiction to the hypothesis that lower loads would be exerted on the anterior oral cavity during function (Ye et al., 2013). This could be explained by tongue tissue restructuring processes and healing effects in conjunction with alterations in contraction modes and lingual kinematics during the post-surgical period (Chen et al., 2016; Perkins et al., 2008; Ye et al., 2010). The classical equilibrium theory assumes that pressure from the tongue is critical in determining tooth position and that resting pressure is more influential than functional pressures such as those developing during mastication (Proffit, 1978). It is possible that the significant mass reduction in the anterior tongue results in diminishing resting loads on the anterior oral cavity (Ye et al., 2013) and negative effects on craniofacial growth and bone mineral density (Liu et al., 2008b).

Finally, surgical tongue volume reduction exerted a minor effect on patients' ability to recognize forms and oral motor ability (Ingervall and Schmoker, 1990). Although a learning effect persisting over a long period of time has been reported in subjects non-subjected to glossectomy (Landt, 1983; Landt et al., 1979) that was not observed in the population under investigation. This finding could possibly be ascribed to the fact that more patients wore fixed orthodontic appliances after surgery and the increased repetitions of the tests in the previous investigations. In general, individuals performing well before the operation continued to do so later, corroborating previous longitudinal observations in a young adult population (Land et al., 1979). It is possible that partial tongue reduction does not significantly affect overall oral proprioception, which, except for the tongue mucosa, is associated with receptors in the temporomandibular joints, the teeth, as well as the palatal and the gingival mucosa (Ingervall and Schmoker, 1990).

Overall, the quality of evidence included in the retrieved studies regarding the statistically significant differences at the longest follow-up was considered at best as low, based on the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach (Guyatt et al., 2011). Apart from concerns regarding the precision of the observed estimates and directness of the evidence, in general, all studies were considered to present serious risk of bias, as confounding parameters were not always appropriately controlled. The risk of bias in the measurement of outcomes was considered serious since either the assessors were aware of the intervention, or there was no information on blinding or data on measurement reliability, or significant concerns existed regarding the latter (Ingervall and Schmoker, 1990; Fröhlich et al. 1993; Kawakami et al., 2004).

6.2. Strengths and limitations

The strengths of the present review include using a methodology following well-established guidelines. To our knowledge, there has been no other systematic review conducted on craniofacial changes after tongue volume reduction.

Moreover, the search strategy employed in the present review was both exhaustive, covering electronic, manual, and gray literature material up to May 2017, and comprehensive including every available study investigating craniofacial changes after tongue volume reduction, 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 all performed in duplicate, and any disagreement was resolved by discussion or consultation until a final consensus was achieved.

There are also some limitations to the present review; these arise 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 at best as low. Apart from the general scarcity of relevant information, resulting in subsequent problems regarding the precision of the effect estimates, and indirectness of the available data, varying confounding parameters were not appropriately controlled for and two studies lacked a control group. Furthermore, exploratory subgroup analyses and analyses for "small-study effects" and publication bias (Higgins and Green, 2011), could not be carried out, even though they were incorporated as possibilities according to the review protocol. Finally, the lack of appropriate tools to measure specific parameters following tongue reduction surgery, e.g. CBCT for airway measurements may account for the observed results.

6.3. Recommendations for future research

As the overall quality of the relevant available evidence was considered at best low, and the effect of tongue volume reduction on craniofacial structures and tongue function are still not determined, further research is warranted in order to elucidate the consequences of the altered oral environment on craniofacial growth, development and function, especially in growing subjects.

It has been suggested that well-designed and properly executed Randomized Control Trials provide the best evidence, with a decreased risk of bias on the efficacy of health care interventions (Altman et al., 2001; Oxford Centre for Evidence-based Medicine, 2009). Since random allocation of subjects might be unethical under certain situations, it would be advisable to conduct at least well-controlled prospective non-randomized studies that are comparable to well-performed randomized studies (Sterne et al., 2016). Particular importance should be placed on possible ways to control bias due to confounding and bias in the measurement of outcomes. Moreover, long term evaluation of outcomes would be valuable concerning a variety of malocclusions and clinical situations such as open-bite cases and tongue thrust. Also, using more advanced tools for assessment of different parameters like CBCT scan could be beneficial to assess different hard and soft tissues possible adaptations and airway volume changes in three dimensions (3D) following tongue reduction surgery. Finally, it would be of great interest to further investigate the effect of the different surgical techniques, as well as the effect on other outcomes including speech, taste and sensitivity.

7. CONCLUSIONS

Based on the data provided in the present systematic review, overall, no significant differences were noted in the medium term, in terms of dentofacial structure adaptation and tongue function, following tongue volume reduction surgery. The concerns raised during quality assessment of the available evidence provide insights regarding confidence in the observed estimates. Further research is warranted in order to elucidate the consequences of the altered environment on craniofacial growth, development and function, especially in growing subjects.

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APPENDICES

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

Review question(s)

To investigate current data on craniofacial adaptations after tongue volume reduction surgery and to critically evaluate the quality of 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

The trials to be included should be observational studies evaluating craniofacial adaptations after tongue volume reduction surgery.

Condition or domain being studied

Macroglossia

Participants/ population

Subjects of any age and gender with macroglossia.

Intervention(s), exposure(s)

Tongue volume reduction surgery.

Comparator(s)/ control

No treatment (if applicable).

Outcome(s)

Primary outcomes

Outcomes relevant to craniofacial adaptations (cephalometric variables, tongue position, tongue pressure, etc).

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 (TA 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 (TMA and EGK) using the using the ROBINS-I tool (Risk Of Bias In Non-randomised 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.

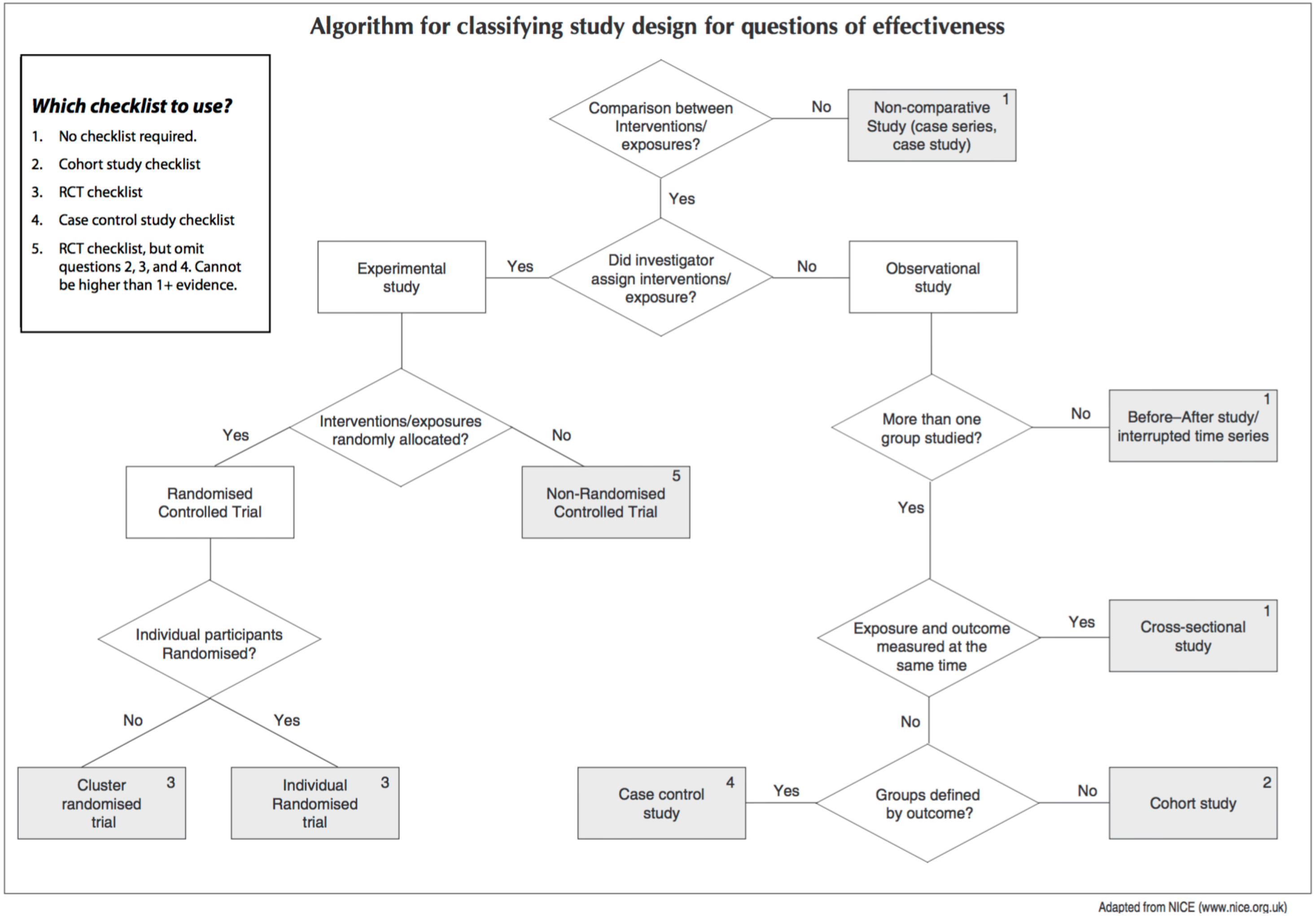
Analysis of subgroups or subsets

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 16th, 2017].

Database	Search strategy
PubMed http://www.ncbi.nlm.nih.gov/pubmed	(((((tongue) AND reduc*)) OR glossectomy)) AND (("fixed appliance" OR orthodon* OR "fixed orthodontic" OR bracket* OR multibracket))
Cochrane Central Register of Controlled Trials http://onlinelibrary.wiley.com/cochranelibrary/search	((tongue AND reduc*) OR glossectomy) AND ("fixed appliance" OR orthodon* OR "fixed orthodontic" OR bracket* OR multibracket) in Title, Abstract, Keywords in Trials'
Cochrane Database of Systematic Reviews http://0-ovidsp.tx.ovid.com.amclb.iii.com/sp-3.16.0b/ovidweb.cgi	orthodon* {Including Limited Related Terms}
Scopus https://www.scopus.com/search/form.url?zone=TopNavBar&origin=searchbasic	TITLE-ABS-KEY (((tongue AND reduc*) OR glossectomy) AND ("fixed appliance" OR orthodon* OR "fixed orthodontic" OR bracket* OR multibracket))
Web of Science™ http://apps.webofknowledge.com/	TOPIC: (((tongue AND reduc*) OR glossectomy) AND ("fixed appliance" OR orthodon* OR "fixed orthodontic" OR bracket* OR multibracket)) Timespan: All years. Search language=Auto
Arab World Research Source http://0-web.a.ebscohost.com.amclb.iii.com/ehost/search/advanced?sid=ff64c697-1ea0-41dc-9afe-961bc654cd05%40sessionmgr4002&vid=0&hid=4114	((tongue AND reduc*) OR glossectomy) AND ("fixed appliance" OR orthodon* OR "fixed orthodontic" OR bracket* OR multibracket)
ClinicalTrials.gov http://clinicaltrials.gov/	(orthodontic OR orthodontics) AND ((tongue AND reduction) OR glossectomy)
ProQuest Dissertations and Theses Global http://search.proquest.com/dissertations	ti(((tongue AND reduc*) OR glossectomy) AND ("fixed appliance" OR orthodon* OR "fixed orthodontic" OR bracket* OR multibracket)) OR ab(((tongue AND reduc*) OR glossectomy) AND ("fixed appliance" OR orthodon* OR "fixed orthodontic" OR bracket* OR multibracket))

Appendix IV. Details of risk of bias assessment. [Domains examined: 1: Bias due to confounding 2: Bias in selection of participants, 3: Bias in classification of intervention, 4: Bias due to deviations from intended interventions, 5: Bias due to missing data, 6: Bias in measurement of outcomes, 7: Bias in selection of the reported result]

Study	Rating		Reasons for rating
(Ingervall and Schmoker, 1990)	**1.**	Serious	Important parameters (like malocclusion and growth) were not controlled.
	2.	Low	No reason to believe that the selection of the participants was biased.
	3.	Low	It is clearly mentioned that all participants received tongue reduction surgery.
	4.	Not applicable	Not applicable
	5.	Not applicable	Not applicable
	6.	Serious	The outcome was assessed by assessors aware of the intervention received
	7.	Moderate	The outcome measurements and analyses are consistent with an *a priori* plan.
Frohlich et al., 1993	**1.**	Serious	Important parameters (like gender, age, growth, malocclusion, presence of fixed appliances space anomalies etc.) were not controlled.
	2.	Low	No reason to believe that the selection of the participants was biased.
	3.	Low	It is clearly mentioned that all participants received tongue reduction surgery.
	4.	Not applicable	Not applicable
	5.	Not applicable	Not applicable
	6.	Serious	The outcome was assessed by assessors aware of the intervention received. Concerns about measurement variability.
	7.	Moderate	The outcome measurements and analyses are consistent with an *a priori* plan.
Kawakami et al., 2004	**1.**	Serious	Important parameters (like gender, age, growth, malocclusion, volume of the removed tongue, tongue reduction technique, etc.) were not controlled.
	2.	Low	No reason to believe that the selection of the participants was biased.
	3.	Low	Two groups: one group with tongue reduction + mandibular setback and the other group mandibular setback without tongue reduction.
	4.	Not applicable	Not applicable.
	5.	Not applicable	Not applicable.
	6.	Serious	No reference to blinding of the assessors in the study or assessment of measurement reliability.
	7.	Moderate	The outcome measurements and analyses are consistent with an *a priori* plan.