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The status of cephalometry in the prediction of non-CPAP treatment outcome in obstructive sleep apnea patients: a literature review

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Conflicts of interest

The authors report no conflict of interest with respect to the topic of the manuscript.

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Summary

Obstructive sleep apnea syndrome (OSAS) is the most common sleep disordered breathing disorder (SDB) in adults and is characterized by a recurrent partial or complete collapse of the upper airway during sleep. This can be caused by many factors, sometimes interacting, such as skeletal malformations, soft tissue crowding, respiratory instability and the various effects of aging, obesity and gender that dictate craniofacial and upper airway anatomy. Research has demonstrated that the majority of patients exhibit at least one anatomical component such as retrognathia or a narrow posterior airway space that predisposes to the development of OSAS.

Within the predisposing elements for OSAS many seem to point to anatomical characteristics. A standardized and relatively simple radiologic technique to evaluate anatomical craniofacial relationships is cephalometry. This has been used already for a long time in orthodontics, but is now gradually being introduced in OSAS treatment to envisage optimal treatment selection as well as to predict treatment outcomes.

The purpose of the present review is to evaluate the contribution of cephalometry in the prediction of outcomes from OSAS treatments that depend on the upper airway morphology in their mechanisms of action such as oral appliances that advance the mandible as well as various surgical methods. In addition, an overview of imaging modalities and methods that currently are being used in cephalometric analysis in OSAS patients is provided.

The findings indicate that isolated cephalometric parameters cannot be used to reliably predict treatment outcomes from mandibular advancement devices and surgical methods for OSAS. Extreme or outlying values of cephalometric parameters may rather be used as contra-indicators or ‘red flags’ instead of predictors.

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Keywords

Sleep disordered breathing; obstructive sleep apnea syndrome; cephalometry; prediction; therapy outcome; oral appliance; mandibular advancement device; uvulopalatopharyngoplasty; multi-level salvage surgery; maxillo-mandibular advancement

Abbreviations

AHI	apnea hypopnea index
AI	apnea index
BMI	body mass index
CBCT	cone beam computed tomography
CPAP	continuous positive airway pressure
CT	computed tomography
EBM	evidence based medicine
ESS	Epworth sleepiness scale
F	female
HB	hyoid bone
H-UPPP	Han-uvulopalatopharyngoplasty
M	male
MCP	maximal comfortable protrusion
MDA	mean disease alleviation
MLS	multi-level salvage surgery
MMA	maxillo-mandibular advancement
MP	maximal protrusion
MRI	magnetic Resonance Imaging
n	sample size
NS	not specified
OA	oral appliance
OAm	oral appliance of the type that advances the mandible
OAt	oral appliance of the type that stabilizes the tongue
OSAS	obstructive sleep apnea syndrome
PAS	posterior airway space
PG	polygraphy
PPP	palatopharyngoplasty

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PSG	polysomnography
RDI	respiratory disturbance index
SDB	sleep disordered breathing
Subj.	subjective
UPPP	uvulopalatopharyngoplasty
VO	vertical opening
Z-PPP	zetapalatopharyngoplasty

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1. Introduction

Sleep-disordered breathing (SDB) comprises a spectrum of disorders characterized by abnormalities of the respiratory pattern during sleep [1, 2]. Obstructive sleep apnea syndrome (OSAS) is the most common SDB disorder with an estimated prevalence in the United States of America of 10% among 30-39 year old men, 17% among 50-70 year old men, 3% among 30-49 year old women and 9% among 50-70 year old women [3]. OSAS is characterized by a recurrent partial or complete collapse of the upper airway during sleep. The ensuing hypoxaemia triggers an arousal causing fragmentation of the patient's sleep attributing to the excessive daytime sleepiness being one of the cardinal symptoms of OSAS [4]. Untreated OSAS leads to cardiovascular disease, neurocognitive deficits and depression [5-7]. Such symptoms may render a patient incapable of e.g. driving and can have a serious negative impact on social relationships, work performance and accidents, as well as on quality of life [8-10].

The increased frequency of the upper airway collapsing can be caused by many factors, acting either alone or in concert, such as skeletal malformations, soft tissue crowding, respiratory instability and the various effects of aging, obesity and gender that dictate craniofacial and upper airway anatomy [11]. The relative contribution of each individual factor to the clinical expression of OSAS is highly patient dependent [12]. Extensive research has demonstrated that the majority of patients exhibit at least one anatomical component such as retrognathia or a narrow posterior airway space that predisposes to the development of OSAS [11, 13].

OSAS treatment ranges from non-invasive continuous positive airway pressure (CPAP) or oral appliances (OA) that advance the mandible (OAm), to surgery such as uvulopalatopharyngoplasty (UPPP), maxillo-mandibular advancement (MMA) or multi-level salvage surgery (MLS). Currently, titratable, custom-made OAm therapy is recommended [14-17]. OA that advance the tongue (OAt) are not included in this review, because of lack of evidence that supports this therapy [16]. Individual treatment selection often is a slow cascade process of consecutive trial and error. The ability to predict treatment outcome in individual patients could therefore not only avoid long periods before treatment is successful, but could also reduce the amount of consumed health care resources per patient [18].

Within the predisposing elements many seem to point to anatomical characteristics. A standardized and relatively simple radiologic technique to evaluate anatomical craniofacial relationships is cephalometry. It has been used already for a long time in orthodontics, but it is now gradually being introduced in OSAS treatment to envisage optimal treatment selection as well as to predict treatment outcome [13, 19, 20].

The purpose of the present review is to evaluate the potential contribution of cephalometry to the prediction of outcomes from the primary non-CPAP treatment alternatives in adults and to provide an overview of the imaging modalities and methods that are currently being used in cephalometric analysis in OSAS patients.

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2. Methods

2.1 Database search

A systematic online search was carried out starting with the database 'PubMed' between February 26th and March 27th, 2014. The medical subject headings (MeSH) 'obstructive sleep apnea' and 'cephalometry' or a combination of the search keywords 'obstructive sleep apnea' and 'cephalometric' or 'mandibular advancement' or 'oral appliance' or 'uvulopalatopharyngoplasty' or 'multilevel surgery' or 'maxillomandibular advancement' were applied (Figure 1): 1909 potential relevant publications were retrieved. Based on study of the titles and abstracts, initially 37 full papers were selected for OAm therapy, 19 full papers for UPPP surgery, nine full papers for MLS surgery and 12 full papers for MMA surgery.

Exploring the reference list of each full paper yielded four additional papers, one for OAm therapy, two for UPPP and one for MLS, extending the search beyond the initial PubMed database MeSH-based strategy.

After each full paper was studied, 15 papers were excluded based on the exclusion criteria specified in Figure 1, yielding a total of 66 papers that were selected.

All of the papers described case series and were categorized as evidence based medicine (EBM) level 4, except the EBM level 1 meta-analysis published by Holty and Guilleminault in 2010 [21].

[FIGURE 1]

2.2 Definitions of cephalometric variables

Due to the large variety of names and definitions used in the literature for the description of cephalometric variables, similar definitions were grouped. A list of abbreviations and corresponding definitions as used in the present review is given in Table 1.

[TABLE 1]

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3. Results

3.1 Imaging modalities and methods currently used for cephalometric analysis

3.1.1 Cephalometric radiographs

Cephalometric analysis in SDB patients is predominantly performed on lateral x-ray images recorded with the patient in a standardized upright position. The patient may be oriented with the Frankfort plane horizontal to the floor or with the head in its natural position [22-24], which might influence some measurements. Such cephalograms are relatively inexpensive, fast and easy to record and are often readily available in a clinical dental environment. Cephalograms recorded in this manner generate reproducible results but they do not represent the conditions during sleep since they are made with the patient awake and in and in an upright position [25].

Cephalograms recorded with the patient awake in a supine position aim to provide a more realistic anatomical image of the airway and craniofacial structures that closely resembles the physiology seen during sleep [26]. The effect of gravity has indeed been shown to influence some upper airway dimensions and cephalometric measurements such as the length and width of the uvula, the position of the hyoid bone and the general shape of the upper airway [27, 28]. The added value of supine cephalograms, however, has been a subject of debate for several years: it is for instance more laborious, time consuming, and thus less practical for larger groups of patients [25, 29]. Additionally, the supine position is not standardized and does not resemble the predominant sleeping position in every patient [29]. Moreover, Martin et al. [30] suggested that OSAS patients actively maintain their upper airway size in the supine position in order to prevent upper airway collapse while they are awake. Acquiring a radiologic image of the collapsibility of the upper airway might therefore be unfeasible as long as the patients are awake [30-32].

Other limitations of lateral cephalometric radiographs include difficulties in the identification of cephalometric landmarks [33], geometric distortions, superimposition of structures and missing data due to a 2D analysis of 3D structures [13]: a cephalometric analysis based on a 2D radiograph does not take into account the contribution of the transversal structures or any compensatory changes that may occur in these structures during the manifestation of SDB [26]. Studies have shown that some transversal structures such as the lateral pharyngeal walls that are not visible on cephalograms possibly play a role in the development of OSAS. For instance, the airway in SDB patients is shown to be typically circular or elliptical with its long axis in the sagittal plane, in contrast to healthy individuals who generally have the long axis in the lateral direction [34]. A 2D cephalogram will consequently overestimate the true airway size in OSAS subjects but underestimates the available airway space in normal subjects [26]. Some studies have investigated whether the recording of antero-posterior cephalograms could partially overcome this limitation [13, 35, 36]. According to these studies, the velopharyngeal width and maxillary bone proportions measured on antero-posterior cephalograms were significantly different between SDB patients and healthy subjects [13, 35]. Combining lateral and antero-posterior cephalograms could thus possibly provide an easy and inexpensive solution to improve the evaluation of craniofacial and upper airway anatomy in SDB patients [13, 35]. The multitude of potentially predictive cephalometric parameters reported in the literature for non-CPAP therapy however underlines the complexity and patient specific multi-factorial nature of OSAS. [33].

However, acquiring x-ray images imposes a health risk by exposing the patient to ionizing radiation. Cephalometric radiology emits approximately 5-10 μSV of radiation per image, which is the equivalent of less than 1 day of naturally occurring background radiation [37-39]. Although the radiation dose is relatively low, accumulation through multiple exposure times needs to be avoided in order to minimize the potential adverse health effects [37].

3.1.2 Fluoroscopy

Fluoroscopy is another imaging technique that has been used to perform cephalometric measurements in SDB patients [40]. The technique can produce lateral and transversal images as well as dynamic images of the craniofacial and upper airway anatomy [41]. More importantly, fluoroscopic images can be recorded during natural or drug induced sleep [40, 42]. However it shares several limitations with cephalometric radiographs, including 2D analysis of 3D structures and exposure to ionizing radiation. The effective radiation dose of videofluoroscopy is approximately 25 μSV per minute, which is the equivalent of four days of natural background radiation [41]. Consequently, the accumulated health risk will greatly depend on the duration of the examination protocol.

3.1.3 Computed tomography

3D images of craniofacial and upper airway anatomy for cephalometric analysis can be obtained with X-ray computed tomography (CT). Compared to a cephalogram, CT scanning significantly improves soft tissue contrast and allows precise measurements of cross-sectional areas at different levels as well as 3D reconstruction and volumetric assessment. Fast scanning times and relatively quiet scanning conditions even allow a dynamic assessment of the airway during a respiratory cycle as well as measurements during natural sleep [43]. Conventional CT however exposes the patient to a high level of ionizing radiation: multi slice CT generates up to 1.2 mSV per image or the equivalent of 6 months of natural background radiation. In addition, the area that will be exposed may contain radiation-sensitive organs eg the thyroid and salivary glands in the head and neck region [39]. Currently, conventional CT for cephalometric evaluation of SDB patients is therefore often replaced by cone beam CT (CBCT). CBCT devices do generate significantly less ionizing radiation per image. The effective dose of one maxillofacial image ranges between 68 μSV and 368 μSV, which is the equivalent of 1.5 to 8 weeks of natural background radiation [44]. Additionally, CBCT devices are compact, less expensive and thus more readily available in a clinical environment or a dental practice, but the quality of CBCT image is significantly lower for soft tissues. As long as radiation exposure is higher than that of a conventional cephalogram, CBCT will probably not find its way into routine clinical practice for cephalometric analysis.

3.1.4 Magnetic Resonance Imaging

3D images of the upper airways can be acquired without generating ionizing radiation using magnetic resonance imaging (MRI). MRI offers additional advantages such as excellent soft tissue contrast and the possibility to acquire multiple images with various contrast characteristics without health consequences for the patient [43]. Although most MRI sequences currently used for cephalometric analysis are originally designed to visualize soft tissues, new sequences are being developed to enhance the applicability of MRI for cephalometric analysis. For instance, Eley et al.

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recently developed the so-called 'black-bone' sequence which suppresses the signal of water and fat to enable a more accurate differentiation between bone and soft tissues by displaying bone in a dark or black color and soft tissue in a uniformly grey color [45]. The limited availability and long waiting lists, long scanning time and associated cost of MRI technology on the other hand currently prevents clinicians to use MRI as a routine clinical application for SDB patients.

3.2 Cephalometric parameters used in the prediction of treatment outcome

3.2.1 Oral appliances

During sleep oral appliances that advance the mandible (OAm) aim to increase the cross-sectional dimension of the upper airway [16]. In general patients more readily accept OAm therapy compared to CPAP due to the discrete and compact design of the appliance (46). Recent data also indicates that the therapeutic effectiveness or mean disease alleviation (MDA) of OAm therapy might be comparable to that of CPAP, the golden standard treatment for OSAS [17, 46-50]. Still, it is important to select patients for OAm therapy, since persistent respiratory events might cause harm to the individual patient, particularly those with more severe OSAS [51, 52].

An extensive literature search has yielded 31 papers reporting on potential predictive cephalometric parameters for OAm treatment outcome. 28 studies reported on the predictability of baseline parameters and 14 studies discussed the predictability of these variables with an OAm in situ. The details of each paper are summarized in Table 2.

[TABLE 2]

3.2.2 Baseline cephalometric parameters

Seven out of 28 studies were not able to demonstrate any statistically significant baseline predictors for OAm treatment outcome [53-59]. The potentially predictive parameters presented in the remaining 21 studies are classified in the present review in four groups according to the literature outcome (Table 3). The first group called 'reported in >1 study' comprises all the cephalometric parameters that demonstrated a statistically significant contribution to the treatment outcome in more than one study and showed an identical relationship between the parameter and the measure of treatment outcome in all these studies. The second group called ‘conflicting results’ comprises all the cephalometric parameters that demonstrated a statistically significant contribution to the treatment outcome in more than one study but showed an opposite relationship between the parameter and the measure of treatment outcome in at least one other study. The third group called ‘solitary results’ comprises all the cephalometric parameters that demonstrated a statistically significant contribution to the treatment outcome in only one study. The fourth group called ‘not significant’ comprises all the studies that evaluated a specific parameter included in one of the previous 3 groups, but was not able to demonstrate a statistically significant relationship with the treatment outcome.

[TABLE 3]

3.2.3 Cephalometric parameters with OAm in situ

Six out of 14 studies were not able to demonstrate any statistically significant predictor with OAm in situ for OAm treatment outcome [54, 56-58, 60, 61]. The potentially predictive parameters presented in the remaining eight studies were classified into groups as described before (Table 4).

[TABLE 4]

3.2.4 Uvulopalatopharyngoplasty

Uvulopalatopharyngoplasty (UPPP) is one of the most widely performed upper airway surgical procedures used to treat OSAS [62]. UPPP generally encompasses the removal of redundant mucosa, the uvula and/or the tonsils followed by the reshaping of the upper pharynx in order to decrease the collapsibility of the retro-palatal airway. The original UPPP procedure to treat OSAS as described by Fujita et al. has been modified numerous times in order to reduce the morbidity and improve the treatment outcome [63]. The success rate of the procedure has been reported to range between 40% and 60% [64].

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An extensive literature search has yielded 14 papers reporting on potential predictive cephalometric parameters for monotherapy UPPP outcome. The details of each paper are summarized in Table 5.

[TABLE 5]

Four out of 14 studies were not able to demonstrate any statistically significant predictor for monotherapy UPPP outcome [65-68]. The potentially predictive parameters presented in the remaining 10 studies were classified as described before (Table 6).

[TABLE 6]

3.2.5 Multi-level salvage soft tissue surgery

Multi-level salvage surgery (MLS) comprises a combination of UPPP with a variety of other soft tissue surgery procedures such as genioglossus advancement, hyoid suspension, tongue base reduction etc. Lin et al. reported in their meta-analyses a success rate of 66.4% [69]. MLS surgery is currently accepted as a primary or secondary treatment in patients with narrowing at multiple sites and/or levels in the upper airway, particularly if a preceding UPPP monotherapy failed [70].

An extensive literature search has yielded nine papers reporting on potential predictive cephalometric parameters for MLS outcome. The details of each paper are summarized in Table 7.

[TABLE 7]

Two out of nine studies were not able to demonstrate any statistically significant predictor for MLS outcome [71, 72]. The potentially predictive parameters presented in the remaining seven studies were classified as described before (Table 8).

[TABLE 8]

3.2.6 Maxillomandibular advancement

Maxillomandibular advancement (MMA) is a surgical procedure designed to enlarge the upper airway and to reduce its collapsibility by simultaneously advancing the maxilla as well as the

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mandible. Repositioning the jaws will also indirectly advance the soft tissue structures and muscles that are attached to the jaws [73]. The success rate of MMA is approximately 86%, which makes it the most successful surgical procedure for the treatment of OSAS [64, 74]. Furthermore, MMA has even been reported to be equally effective as CPAP in treating OSAS patients [75].

An extensive literature search has yielded 12 papers reporting on potential predictive cephalometric parameters for MMA outcome. The details of each paper are summarized in Table 9.

[TABLE 9]

Six out of 12 studies were not able to demonstrate any statistically significant predictor for MMA outcome [76-81]. The potentially predictive parameters presented in the remaining six studies were classified as described before (Table 10).

[TABLE 10]

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4. Discussion

The present review summarizes to the best of our knowledge all cephalometric variables that have been reported in the literature that allegedly contribute to a favorable treatment outcome with non-CPAP therapies for treatment of OSAS, such as OAm therapy, UPPP, MLS or MMA. This review includes a detailed description and discussion of the imaging modalities and methods used for this cephalometric analysis.

The inconclusive results concerning the use of cephalometric variables to predict the outcome of non-CPAP therapies suggest that these parameters alone probably cannot be used to reliably predict treatment outcome. As a consequence, cephalometry without additional screening methods cannot become a routine procedure yet in the diagnostic work-up of OSAS and the selection of non-CPAP therapy. Nevertheless, combining cephalometric parameters with other patient's characteristics such as polysomnographic, endoscopic and anthropomorphic measurements could still improve the patient selection procedure to some extent [20, 29]: extreme values of the most interesting cephalometric parameters, such as a very long soft palate might be usable as contra-indicators or 'red flags' instead of predictors [82, 83].

The results for OAm therapy, given in Table 3 and 4, suggest that not one parameter has enough compelling evidence to imply that it could reliably predict a favorable non-CPAP treatment outcome. On the other hand, the amount of inconclusive evidence for soft tissue parameters as well as skeletal parameters suggests that it might be interesting to take into account the type of etiology of OSAS in each patient before looking for predictive parameters, as suggested by Woodson and Conley [67].

The results for UPPP warrant a similar conclusion as that described for OAm therapy: there is not one single cephalometric parameter that produces enough evidence to suggest that it could predict a favorable treatment outcome (Table 6). However, some parameters could be underrepresented in the current results because many of the patients included in the studies were already preselected based on e.g. collapse pattern and/or the severity of OSAS. Nevertheless, UPPP treatment is irreversible and

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has a relatively low success rate (40-60%) and thus should be carefully deliberated prior to performing surgery. Currently, UPPP is often part of a multi-phase surgical approach designed to specifically target the site(s) of obstruction and prevent unnecessary surgery in pursuance of minimal postoperative complications [84].

The results for MLS suggest that a small ANB angle with or without a posteriorly positioned mandible might predict a favorable treatment outcome despite the highly heterogeneous treatment protocols used in the papers studied (Table 8). All other cephalometric parameters do not show sufficient convincing evidence.

The results for MMA suggest that a large amount of maxillary advancement probably contributes to a favorable treatment outcome (Table 10). The evidence provided by the meta-analysis of Holty & Guilleminault [21] is very promising due to the large population size despite the multiple studies that did not find a significant result.

There are all kinds of other parameters aside from cephalometry that have been advocated to predict OSAS treatment outcome. Some parameters such as young age, low baseline AHI, low BMI and small neck circumference are shown to be beneficial for most treatment modalities. A second group of parameters such as the site of collapse is used for several treatment modalities though different results contribute to a favorable outcome. A third group of parameters is specifically designed for one type of treatment such as ‘drug induced sleep endoscopy with a simulation bite’ to predict OAm treatment outcome [85]. Another example of this approach is to pursue OAm therapy in order to predict MMA outcome before surgery [86]. The majority of all studies use a combination of several types of parameters. The predictive value of these parameters however is still being investigated or undetermined. Until now, no consensus has yet been reached as to which parameters can reliably predict the treatment outcome and thus should be included in the treatment selection procedures of OSAS patients.

This review has some limitations that need to be considered. The various treatment protocols, sample sizes, inclusion and exclusion criteria, success criteria, ethnicity of the subject population, skeletal class of this population as well as study designs that are reported in the literature, make it very complicated to compare results. This can be attributed to several contributing factors. First, the 'weight' of each parameter contributing to the treatment outcome is highly variable and difficult to estimate on the basis of the published data, because this depends on multiple factors such as the quality and design of the study and the statistical approach that was used. So, each parameter cannot be regarded as equally important. Second, care should be taken when considering the validity of using less conventional cephalometric parameters such as surface area of the maxilla or the ratio inferior airway space/tongue length, because their effect is hard to define due to the limited number of studies that reviewed them. Third, not all authors mentioned clearly the effect of each and every parameter that was verified statistically during the study. As a consequence either the number of insignificant results reported is likely to be incomplete or the contribution of some parameters to the treatment outcome could have easily been overestimated. Fourth, several studies, mainly papers reporting on more invasive treatment modalities, introduced a bias by relying on a preselected patient population. As a consequence, the contribution of the studied parameters to the treatment outcome might be over- or underestimated. Fifth, many authors simply state that either a higher or a lower value for a given parameter contributes to a more favorable treatment outcome without mentioning the range or cut-off value at which the parameter is found to be beneficial. Lastly, most of the papers reviewed show an unequal gender distribution with generally a small proportion of females. It has indeed been found that females are more likely to be successfully treated with oral appliances [87]. So, when females are under proportioned in the study population and given the effect of gender differences on cephalometric measurements [88], skewing of the resulting conclusions could very easily be introduced. All these elements make it complex to compare results and to apply them into daily clinical practice.

To conclude, isolated cephalometric parameters can up till now not be used to reliably predict non-CPAP treatment therapy outcome, regardless of the treatment modality. This conclusion evidently does not question the clinical use of cephalometric values and distances to assess certain anatomical variations or abnormalities. Extreme or outlying values of cephalometric parameters may therefore rather be used as contra-indicators or 'red flags' instead of predictors. Also combining cephalometric assessment with polysomnographic, endoscopic and anthropomorphic measurements could favor patient selection although no consensus can be retrieved from the present literature on this.

Future projects should prospectively study the clinical value of the most promising cephalometric parameters as discussed in this paper e.g. a small ANB angle for MLS and a large maxillary advancement for MMA treatment, combined with other known or likely predictive parameters.

Practice points:

1. Isolated cephalometric variables probably can up till now not be used to reliably predict treatment outcome irrespective of the non-CPAP treatment modality.
2. Extreme or outlying values of cephalometric variables may rather be used as contra-indicators or 'red flags' instead of predictors.
3. The following cephalometric variables might contribute to a favorable treatment outcome for non-CPAP OSAS treatment:

a) Multi-level salvage surgery: small discrepancy between the maxilla and mandibula (ANB angle)

b) Maxillo-mandibular advancement surgery: large maxillary advancement

Research agenda:

1. Investigate the clinical value of the following cephalometric variables:
   a) Multi-level salvage surgery: small discrepancy between the maxilla and mandibula (ANB angle)
   b) Maxillo-mandibular advancement surgery: large maxillary advancement
2. Investigate predictive value of a combination of these cephalometric parameters with other known or likely predictive factors described in the literature.
3. Investigate the predictive value of cephalometric parameters in each type of OSAS etiology separately.

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Figure 1 Overview of the literature search strategy.

Table 1 Overview of the definitions and abbreviations with corresponding full name of the cephalometric parameters mentioned in this review paper.

Table 2 Overview and characteristics of the selected papers regarding potential cephalometric predictors for OAm treatment outcome.

Table 3 Overview of all the statistically significant baseline cephalometric parameters correlated with a favorable OAm treatment outcome and their corresponding references. All measurements were derived from baseline images taken when the patient was awake unless stated otherwise. The following parameters are grouped in one feature: H-Me, HB-C3, H-Gn, H-Rgn, H-Go (relative horizontal position of the hyoid bone); H-MP, HB-ANS, HB-PNS (relative vertical position of the hyoid bone); SNB, SN-Pg (horizontal position of the mandible); Tongue volume, cross-sectional area of the tongue (tongue size). See Table 1 for definitions of abbreviations.

Table 4 Overview of all the statistically significant cephalometric parameters correlated with a favorable OAm treatment outcome and their corresponding references. All measurements were derived from images taken when the patient was awake and wearing an OAm unless stated otherwise. The following parameters are grouped in one feature: H-MP, H-PNS (Vertical position of the hyoid bone); SNB, SN-Pg (horizontal position of the mandible). See Table 1 for definitions of abbreviations.

Table 5 Overview and characteristics of the selected papers regarding potential cephalometric predictors for monotherapy UPPP treatment outcome. See Table 1 for definitions of abbreviations.

Table 6 Overview of all the statistically significant cephalometric parameters correlated with a favorable monotherapy UPPP treatment outcome and their corresponding references. All measurements were derived from baseline images taken when the patient was awake unless stated otherwise. The following parameters are grouped in one feature: H-MP, H-PP, angle H-Me-MP (Vertical position of the hyoid bone). See Table 1 for definitions of abbreviations.

Table 7 Overview and characteristics of all the selected papers regarding potential cephalometric predictors for multi-level salvage surgery outcome. See Table 1 for definitions of abbreviations.

Table 8 Overview of all the statistically significant cephalometric parameters correlated with a favorable multi-level salvage surgery outcome and their corresponding references. All measurements were derived from baseline images taken when the patient was awake unless stated otherwise. The following parameters are represented as one feature: SNA, C3-FM-NP (horizontal position maxilla); SNB, C3-FM-Me (horizontal position mandible); H-MP, posterior edge of the hyoid bone-MP (Vertical position of the hyoid bone). See Table 1 for definitions of abbreviations.

Table 9 Overview and characteristics of all the selected papers regarding potential cephalometric predictors for maxillomandibular advancement surgery outcome. See Table 1 for definitions of abbreviations.

Table 10 Overview of all the statistically significant cephalometric parameters correlated with a favorable MMA surgery outcome and their corresponding references. All measurements were derived from baseline images taken when the patient was awake unless stated otherwise. The following parameters are represented as one feature: maxillary advancement, Δ SNA (maxillary advancement). See Table 1 for definitions of abbreviations.

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Abbreviation	Full name	Definition
AFH	anterior facial height	Distance from nasion to menton.
ANB	discrepancy between the maxilla and mandibula	Angle between the lines point A-nasion and point B-nasion.
ANS	anterior nasal spine	The tip of the median sharp bony process of the palatine bone in the hard palate.
Ar	articulare	The intersection point of the external dorsal contour of mandibular condyle and the temporal bone.
Ba	basion	The lowest point on the anterior border of the foramen magnum.
Ba-SN	cranial base angulation	Angle between basion and anterior cranial base.
Cd	condylion	Most superior point on the condylar head.
Clp	point clp	Top of the posterior clinoid process.
FH	Frankfort horizontal plane	A plane going through the inferior margin of the left orbit and the upper margin of each external auditory meatus.
FM	point FM	Point on DEL C1 at the level of the anterior lacrimal crest.
Gn	gnathion	The most anterior point on the contour of the bony chin symphysis.
Go	gonion	The most inferior, posterior, and lateral point on the external angle of the mandible.
H	hyoidale	Most superior point of the Hyoid bone situated in the anterior midline of the neck between the chin and the thyroid cartilage.
H1	H1 point	Intersection of a line going through the hyoidale and perpendicular to the Frankfurt horizontal plane and a line parallel to the Frankfurt horizontal plane and going through the sphenoidale.
H2	H2 point	Intersection of a line going through the hyoidale and perpendicular to the Frankfurt horizontal plane and the palatal plane.
HYPOXA	cross-sectional area of the hypopharynx	Area outlined by the inferior border of the oropharynx, posterior surface of the epiglottis, line parallel to the palatal plane through point c4 and posterior pharyngeal wall.
IAS or PAS	inferior airway space or posterior airway space	Width of the airway along the extension of a line through gonion and point B.
		Width of the airway along the extension of a line through gonion and menton.
		Width of the airway along the extension of a line through gonion and gnathion.
		Width of the airway on the level of the base of the tongue.
		Minimal width of the airway on the level of the base of the tongue parallel to a line connecting the posterior nasal spine and the anterior nasal spine.
		Minimal width of the airway along a line perpendicular to the posterior pharyngeal wall on the level of the base of the tongue.
		Narrowest width of the airway on the level of the base of the tongue
LAFH	lower anterior facial height	Distance from anterior nasal spine to menton.
		Distance from anterior nasal spine to gonion.
		Distance from anterior nasal spine to gnathion.
		Distance from spina prim to menton.
LPFH	lower posterior facial height	Distance from the posterior nasal spine to the gonion.
M	point M	Junction of the nasofrontal, maxillofrontal and maxillonasal sutures.
mandibular incisor inclination	mandibular incisor inclination	Angle between a line from incisor edge of the lower central incisor to its apex and the mandibular plane.
mandibular jaw	mandibular jaw length	Distance along a straight line between the central incisors to a line connecting the most posterior edges of the most posterior molar of both sides.
		Distance between gonion and gnathion.
		Distance between gonion and menton
		Distance between gonion and point B
mandibular molar eruption	mandibular molar eruption	Distance of a perpendicular line connecting the mandibular plane and the occlusal surface of first mandibular molar.
MAS	middle airway space	Width of the airway between the tip of the soft palate and the posterior pharyngeal wall parallel to the line through gonion and point B.
maxilla	maxillar length	Distance between the condylion and point A. Distance between ANS and PNS
maxillary intermolar distance	maxillary intermolar distance	Distance between the most buccal points of the crowns of the maxillary first molars.
maxillary molar eruption	maxillary molar eruption	Distance of a perpendicular line connecting the Frankfort horizontal plane and the occlusal surface of first maxillary molar.

		Distance of a perpendicular line connecting the palatal plane and the occlusal surface of first maxillary molar.
Me	menton	The most inferior point on the lower border of the bony symphysis.
MP	mandibular plane	Line joining Me and Go, tangent to lower border of the mandible close to the gonial angle and lowest point of the symphysis
N	nasion	The most anterior point of the frontonasal suture.
NP	point NP	Entrance of the nasopalatine canal.
OB	overbite	Vertical overlap of the incisors.
Od	point Od	Tangent point of the posterosuperior part of the odontoid.
OJ	overjet	Horizontal overlap of the incisors.
OP	occlusal plane	Line through the surface of the molars and incisors
OPT	odontoid process tangent	Line joining the most superior posterior edge of cervical vertebra C1 with the most inferior edge point of cervical vertebra C1.
OROPHSURF	surface area of the oropharynx	Surface within the extension of the maxillary plane, the posterior pharyngeal wall, the extension of the occlusal plane and the posterior edge of the soft palate.
OROSURF	oropharynx surface area	Surface within the lines connecting the posterior nasal spine, the posterior pharyngeal wall, the most anterior edge of the hyoid bone and the most anterior edge of the epiglottis.
OROXA	cross-sectional area of the oropharynx	Area outlined by the inferior border of the nasopharynx, the posterior surface of the soft palate, the line parallel to the palatal plane from the tip of the palate to the dorsal surface of the tongue, the posterior inferior surface of the tongue, the line parallel to the tip of the epiglottis and the posterior pharyngeal wall.
PFH	posterior facial height	Distance from sella turcica to gonion.
Pg	pogonion	The most anterior point on the contour of the chin.
Pm	pterygomaxillare	The intersection between the nasal floor and the posterior contour of the maxilla.
PNS	posterior nasal spine	The tip of the posterior spine of the palatine bone in the hard palate.
point A	point A	The deepest midline point between the maxillary alveolar crest and the anterior nasal spine.
point B	point B	The deepest midline point between the mandibular alveolar crest and the most anterior point of the contour of the chin.
PP	palatal plane	Plane through the anterior nasal spine and the posterior nasal spine.
RHINOPHSURF	surface area of the rhinopharynx	Surface within the anterior edge of the cranial base, the posterior pharyngeal wall, the extension of the maxillary plane and the posterior edge of the pterygomaxillary fissure.
S	sella	Center of the sella turcica.
SAAS	superior anterior airway space	Width between the soft palate and the tongue dorsum.
SN	anterior cranial base	Line joining sella and nasion.
SNA	position of the maxilla	Angle between point A and the anterior cranial base.
SNB	position of the mandibula	Angle between point B and the anterior cranial base.
SN-FH	angle between the cranial base and the Frankfort horizontal plane	Angle between the cranial base and the Frankfort horizontal plane.
SN-MP	angle between cranial base and mandibular plane	Angle between cranial base and mandibular plane.
SN-OPT	cranio-cervical angle	Angle between the anterior cranial base and the odontoid process tangent.
SP	soft palate length	Length measured from Pm to the most inferior tip of the soft palate.
		Length measured from PNS to the most inferior tip of the soft palate.
Sp	spina prim	Intersection point of the line connecting ANS-PNS and the line N-Me.
SPAS	superior posterior airway space	Width of the airway behind the soft palate at the level of the midpoint of a line connecting the inferior tip of the soft palate and the posterior nasal spine.
		Narrowest width of the airway behind the soft palate parallel to a line through gonion and point B.
		Narrowest width of the airway behind the soft palate.
		Narrowest width of the airway behind the soft palate parallel to a line connecting the anterior nasal spine and the posterior nasal spine.
		Narrowest width of the airway behind the soft palate along a line perpendicular to the posterior pharyngeal wall.
		Width of the airway behind the soft palate at the level of the most posterior tangent point of the posterior edge of the soft palate.
TB	tongue base	Most posterior part of the tongue.
TH	tongue height	Perpendicular distance from the most superior point of the tongue to the line

		connecting the base of the epiglottis and the tip of the tongue.
TGL	tongue length	Linear distance between the tongue tip and the base of the epiglottis.
UAFH	upper anterior facial height	Distance from nasion to anterior nasal spine.
		Distance from nasion to spina prim.

TABLE 1

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Authors, reference number	N F/M	Imaging modality	Patient orientation	Protrusion	Population Nationality	OAm	Relevant details
Kim YK et al 2014 [89]	86 [10F]	Lateral cephalometric radiograph	Upright standing	60% of MP but < 6.0mm	Korean	Custom-made monobloc [Deep drawn splint]	• Patients who had oropharyngeal surgery were excluded. • 41 Responders, 45 non- responders. • Portable PG monitoring system.
Milano F et al 2013 [90]	23 [3F]	Lateral cephalometric radiograph Dental casts	Upright	Relief subj. symptoms	Italian	Custom-made titratable duobloc [Silensor]	• All patients had an AHI<50. • 14% of the patients exhibited a skeletal class III, 65% a class II and 21% a class I.
Shen HL et al 2012 [91]	52 [4F]	Lateral cephalometric radiograph	Upright	MCP	Taiwanese	Custom-made titratable duobloc [Intraoral Snoring Therapy-device]	• The mean BMI was only 24.8 ± 2.6 kg/m^2. • 29 Responders, 23 non- responders.
Ng AT et al 2012 [20]	72 [17F]	Lateral cephalometric radiograph	Upright seated	MCP	Australian	Custom-made titratable duobloc [SomnoDent MAS]	• The authors used multiple classification criteria for responders and non-responders. • 14% of the population exhibited a skeletal class III.
Mostafiz W et al 2011 [18]	53 [11F]	Lateral cephalometric radiograph Plaster models	Not specified	MCP	Australian	Custom-made titratable duobloc [SomnoDent MAS]	• 9% of the patients exhibited a skeletal class III. • 25 complete, 17 partial and 11 non-responders.
Sutherland K et al 2011 [56]	18 [13F]	MRI [T1-SE]	Supine	75.6% ±12.6 of MP	Australian	Custom-made titratable duobloc [Modified SomnoDent MAS]	• 12 responders, six non- responders.
Lam B et al 2011 [61]	28 [4F]	Lateral cephalometric radiograph	Not specified	MCP	Chinese	Custom-made monobloc	• All patients with AHI ≥ 30. • All subject had some degree of retrognathism. • Large VO.
Chan AS et al 2010 [57]	69 [22F]	MRI [T1-SE]	Supine	MCP	Australian	Custom-made titratable duobloc [Modified SomnoDent MAS]	• 33.3% of the patients exhibited a skeletal class III. • The partial responders were pooled together with the complete responders.
Lee CH et al 2010 [40]	76 [8F]	Lateral cephalometric radiograph Sleep video fluoroscopy	Not specified Supine	60% of MP	Korean	Custom-made monobloc	• 56 Responders, 20 non-responders.
Lee CH et al 2009 [53]	50 [4F]	Lateral cephalometric radiograph	Not specified	60% of MP	Korean	Custom-made monobloc	• Patients with a moderate to severe nasal septum deviation were excluded. • 37 Responders, 13 non-responders.
Doff MH et al 2009 [25]	52 [7F]	Lateral cephalometric radiograph	Upright	AHI<5 or MCP	Dutch	Custom-made titratable duobloc [Thornton adjustable positioned]	• Home PG monitoring system. • 42 Responders, 10 non-responders. • Relative large VO [>10mm].
Poon KH et al 2008 [92]	10 [NS]	Lateral cephalometric radiograph	Upright	75% of MP	Chinese	Custom-made titratable duobloc [Intraoral Snoring Therapy-device]	• Efficacy of the OAm not specified.

Hoekema A et al 2007 [29]	49 [NS]	Lateral cephalometric radiograph	Upright	AHI<5 or MCP	Dutch	Custom-made titratable duobloc [Thornton adjustable positioned]	• 39 Responders, eight non-responders.
Sam K et al 2006 [58]	23 [7F]	CT	Supine	MCP	Chinese	Custom-made monobloc	• Only mild to moderate OSA patients with an ESS≥9. • 14 good responders, nine moderate responders.
Otsuka R et al 2006 [93]	18 [0F]	Lateral cephalometric radiograph	Upright	Relief subj. symptoms or MCP	Canadian	Custom-made titratable duobloc [Klearway]	• Non-responders were matched for gender, age, BMI and severity of OSA.
Horiuchi A et al 2005 [94]	25 [0F]	Lateral cephalometric radiograph	Upright	70-80% of MP	Japanese	Custom-made monobloc [self-cured acrylic resin]	• Split night PSG. • 15 Responders, 10 non-responders. • Only the results of the comparison between responders and non-responders defined by the AHI was included in this review to enable comparison with the other articles.
Tsuiki S et al 2004 [60]	20 [0F]	Lateral cephalometric radiograph	Supine	Relief subj. symptoms or MCP	Canadian	Custom-made titratable duobloc [Klearway]	• 14 Responders, six non-responders.
Endo S et al 2003 [59]	103 [NS]	Lateral cephalometric radiograph	Upright	70% of MCP	Japanese	Custom-made monobloc [Deep drawn splint]	• 65 Responders, 38 non-responders.
Rose E et al 2002 [95]	57 [6F]	Lateral cephalometric radiograph	Upright	Not specified	German	Custom-made monobloc [Karwetzky modified activator]	• Only mild to moderate OSA patients. • Patients with an AHI>30/h were excluded. • Relative large VO. • Success definition was defined depending on the age.
Mehta A et al 2001 [96]	24 [5F]	Lateral cephalometric radiograph	Upright	Relief subj. symptoms or MCP	Australian	Custom-made titratable duobloc	• Limited vertical coverage of the teeth. • Nine responders, six partial responders, nine non-responders.
Liu Y et al 2001 [97]	42 [5F]	Lateral cephalometric radiograph	Not specified	Relief subj. symptoms or MCP	Canadian	Custom-made titratable duobloc [Klearway]	• Patients were classified as good [n=13], moderate [n=25], or poor responders [n=9]. • The poor responders were older + higher BMI. • Only the results of the correlation analysis between the cephalometric parameters and % AHI change were included in this review to enable comparison with the other articles.
Liu Y et al 2000 [32]	16 [4F]	Lateral cephalometric radiograph	Supine	Relief subj. symptoms or MCP	Canadian	Custom-made titratable duobloc [Klearway]	• 11 responders, five non-responders.
Liu Y et al 2000 [98]	22 [4F]	Lateral cephalometric radiograph	Upright seated	75% of MP	Chinese	Custom-made monobloc	• 5 patients had previously a UPPP. • 13 Responders, nine non-responders. • A correlation was only found with the AI not RDI.
Gao XM et al 1999 [99]	11 [3F]	MRI	Supine	Not specified	Chinese	Not specified	• The mean BMI was only 23.9 ± 2.3 kg/m^2. • All patients with AHI≥30/h.
Marklund M et al 1998 [100]	32 [0F]	Lateral cephalometric radiograph	Upright seated	4-6 mm or until relief of snoring	Swedish	Custom-made monobloc	• Calculations were based on the AHI for each sleeping position separately. • Significant differences were only found for the supine AHI. • 20 responders, 10 non-responders according to supine AHI.

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Ferguson KA et al 1997 [55]	19 [NS]	Lateral cephalometric radiograph	Upright	Relief subj. symptoms or MCP	Canadian	Custom-made titratable duobloc [Anterior mandibular positioner]	• 12 Responders, eight non-responders. • Only mild to moderate OSA patients. • Home PG monitoring system.
Menn SJ et al 1996 [54]	23 [1F]	Lateral cephalometric radiograph	Upright seated	MCP	American	Custom-made titratable duobloc [Mandibular repositioning device]	• 16 Responders, seven non-responders.
Mayer G and Meier-Ewert K 1995 [83]	30 [6F]	Lateral cephalometric radiograph	Prone	Not specified	German	Custom-made monobloc [Esmarch appliance]	• Relative large VO. • Patients with an AI <30 or older than 75 years were excluded.
Eveloff SE et al 1994 [101]	19 [3F]	Lateral cephalometric radiograph	Upright standing	Voluntary protrusion distance	American	Custom-made titratable duobloc [Herbst appliance]	• All patients were obese. • 10 patients gained weight during the study (0.5-12.7kg)
Yoshida K 1994 [102]	20 [1F]	Lateral cephalometric radiograph Plaster casts	Not specified	Not specified	German	Custom-made monobloc [Esmarch appliance]	• Relative large VO.
Bonham PE et al 1988 [103]	12 [NS]	Lateral cephalometric radiograph Plaster cast	Upright standing	MCP	American	Custom-made monobloc	• Mean AHI after treatment is high [35.99].

Abbreviations: AHI=apnea hypopnea index, AI=apnea index, BMI=body mass index, CT=computed tomography, ESS=Epworth sleepiness scale, F=number of female participants, M=number of male participants, MCP=maximal comfortable protrusion, MP=maximal protrusion, MRI=magnetic resonance imaging, N=number of participants, NS=not specified, OAm=oral appliance of the type that advances the mandible, OSA=obstructive sleep apnea, PG=polygraphy, PSG=polysomnography, RDI=respiratory disturbance index, Subj.=subjective, VO=vertical opening. See Table 1 for the definitions of the abbreviations used in the present table.

TABLE 2

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Reported in >1 study	Not significant	Conflicting results	Not significant	Solitary results	Not significant
Short SP [20, 40, 83, 91, 102]	[18, 29, 53-55, 89, 90, 93, 94, 101, 103]	Large ANB [29] versus small [59]	[18, 20, 55-57, 89-91, 94, 96, 97]	Large SNA [83]	[18, 20, 29, 54, 56, 57, 59, 90, 91, 93, 94, 96, 100-103]
Narrow IAS [91, 93]	[18, 20, 29, 40, 53-55, 57, 59, 83, 89, 90, 94, 96, 97, 101-103]	Retruded mandible [29, 32, 83, 91] versus non-retruded [59] Wide pharynx is better [96]	[18, 20, 54-57, 89, 90, 93, 94, 96, 100, 102, 103]	Large OB [29] Wide pharynx is better [96]	[20, 61, 90, 91, 93, 94, 97, 101, 102]
Narrow MAS [32, 93]	[18, 29, 32, 55, 59, 83, 93, 94, 97, 102, 103]	Narrow SPAS [97, 103] versus wide [96]	[18, 20, 40, 53, 55, 59, 89, 91, 93, 94]	Short maxilla [18]	[93, 94]
Forward position HB [95, 97]	[18, 29, 55-57, 89-91, 93, 94]	High position HB [59, 90, 101, 102] versus low [95]	[18, 20, 29, 54-57, 61, 89, 91, 93, 94, 96, 103]	Short mandibular jaw [102]	[18, 20, 59, 90, 94, 96, 98]
small OROXA [93, 97]	-	Small SN-MP angle [90, 95, 98, 100] versus large [20, 96]	[29, 91, 93, 94, 103]	Long SN [98]	[20, 29, 94, 96]
Large Ba-SN angle [20, 98]	[29, 56, 57, 94, 96]	Large OJ [29, 61] versus small [97]	[20, 89-91, 93, 94, 101, 102]	Small angle SN-Go-B [83]	[102]
		Short UAFH [18] versus long [29]	[20, 94, 100]	Small MP-FH angle [98]	-
		Large tongue [18] versus small [99]	[59]	Small S-Gn-FH angle [98]	-
		Wide SAAS [103] Versus narrow [97]	-	Short distance ANS-epiglottis [59]	-
				Mandibular incisors inclination towards lips [94]	[18]
				Less erupted mandibular molars [94]	-
				Small maxillary intermolar distance [18]	-
				Less erupted maxillary molars [97]	[94]
				small ratio pharynx length/OROXA [97]	-
				Short LAFH [100]	[18, 20, 29, 56, 57, 89, 94]
				Short LPFH [89]	-
				Large ratio UAFH-LAFH [98]	-
				Large ratio PFH-AFH [95]	[29, 90, 93]
				Short AFH [91]	[18, 20, 29, 93, 100]
				Large maximum protrusion [29]	-
				Long distance point B-C2 [83]	-
				Short distance C4-Gn [93]	-
				Large TH [32]	[18, 20, 55, 59, 89, 91, 93, 97]
				Small ratio MAS/TGL [93]	-
				Large ratio tongue-oral cavity [18]	-
				Short PNS-TB [83]	-

Abbreviations: AFH=anterior facial height, ANB=angle between point A – nasion – point B, ANS=anterior nasal spine, B=Point B, Ba=Basion, C2=second cervical vertebra, C4=fourth cervical vertebra, FH=Frankfort horizontal plane, Gn=Gnathion, Go=Gonion, HB=hyoid bone, IAS=inferior airway space, LAFH=lower anterior facial height, LPFH=lower posterior facial height, MAS=middle airway space, MP=mandibular plane, OB=overbite, OJ=overjet, OROXA=cross-sectional area of the oropharynx, PFH=posterior facial height, PNS=posterior nasal spine, S=Sella, SAAS=superior anterior airway space, SN=anterior cranial base, SNA=angle between sella – nasion – point A, SP=soft palate length, SPAS=superior posterior airway space, TB=tongue base, TGL=tongue length, TH=tongue height, UAFH=upper anterior facial height. See Table 1 for

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the definitions of the abbreviations used in the present table.

TABLE 3

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Reported in >1 study	Not significant	Solitary results	Not significant
High position HB [83, 101]	[57, 58]	Large Δ HB-MP [92]	[25, 54, 61, 101]
Short SP [40, 101]	[83]	Retruded mandible [32]	[57, 58, 83]
		Large horizontal protrusion [94]	[57, 60, 100]
		Wide SPAS [40]	-
		Large Δ MAS [25]	-
		Large Δ airway space at the level of the lower corner of C2 [25]	-
		Large Δ HYPOXA [32]	-
		Large Δ retro-palatal airway volume [99]	-
		Small Δ TH [32]	-
		Small angle of mouth opening [40]	-

Abbreviations: C2=second cervical vertebra, HB=hyoid bone, HYPOXA=cross-sectional area of the hypophrynx, MAS=middle airway space, MP=mandibular plane, SP=soft palate length, SPAS=superior posterior airway space, TH=tongue height, Δ=difference between pretreatment and posttreatment measurement. See Table 1 for the definitions of the abbreviations used in the present table.

TABLE 4

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Authors	N F/M	Imaging modality	Patient orientation	Population Nationality	Relevant details
Liu SR et al 2013 [104]	51 [4F]	Lateral cephalometric radiograph	Upright seated	Chinese	• Patients with a Friedman stage I to II received H-UPP [n=31], patients with a stage II to III + IAS>11 mm received Z-PPP [n=20]. • All patients had an AHI>30/h. • Responders lost significantly more weight than non-responders post-surgery.
Lee CH et al 2010 [105]	69 [NS]	Sleep video- fluoroscopy Lateral cephalometric radiograph	Supine Not specified	Korean	• Patients with nasal septum deviation or turbinate hypertrophy underwent concomitant septoturbinoplasty. • 27 Responders and 42 non-responders.
Yi HL et al 2009 [106]	34 [5F]	Lateral cephalometric radiograph	Not specified	Chinese	• 22 Responders and 12 non-responders. • The authors use the RDI, not the AHI. • All patients had a Friedman stage II o III and a IAS>11mm. • All patients received Z-palatopharyngoplasty.
Millman RP et al 2000 [82]	46 [3F]	Lateral cephalometric radiograph	Upright standing	American	• Patients were unselected. • 16 Responders and 30 non-responders.
Boot H et al 1997 [68]	60 [7F]	Lateral cephalometric radiograph	Upright seated	Dutch	• Desaturation index was used instead of AHI to determine treatment success. • The uvula was shortened but not removed. • 21 Responders and 39 non-responders.
Woodson BT and Conley SF 1997 [67]	43 [NS]	Lateral cephalometric radiograph	Upright seated	American	• Patients were stratified according to skeletal type before analysis of the cephalometric parameters was performed. • 23 Responders and 20 non-responders.
Woodson BT et al 1997 [107]	66 [5F]	Lateral cephalometric radiograph	Upright	American	• 32 Responders and 34 non-responders.
Tsushima Y et al 1997 [108]	24 [2F]	Digital fluoroscopy	Supine	Finnish	• 17 Responders and seven non-responders. • OSAS patients were diagnosed with a static charge sensitive bed, a specialized PG system. • Patients were categorized into 3 grades according to the severity of the OSAS. Patient who shifted to a lower grade after treatment were classified as responders.
Doghramji K et al 1995 [66]	40 [NS]	Lateral cephalometric radiograph	Upright standing	American	• All patients had a collapse (>50%) at the soft palate level during fiberoptic nasopharyngoscopy with Muller maneuver. • 17 Responders and 36 non-responders.
Petri N et al 1994 [109]	30 [2F]	Lateral cephalometric radiograph	Upright	Danish	• Patients were unselected • 12 patient had previously undergone a septoplasty • All sleep studies were performed with a portable. • Small tonsils were left intact. • Success criteria were based on the AI. • 19 Responders and 11 non-responders.
Okamoto M and Fujita S 1993 [110]	62 [7F]	Lateral cephalometric radiograph	Upright Supine	American	• 36 Responders and 26 non-responders.
Ryan CF et al 1990 [111]	60 [4F]	Lateral cephalometric radiograph	Upright seated	Canadian	• Only apneas were recorded, no hypopneas. • 48 Responders and 12 non-responders.
Shepard JW, Jr. and Thawley SE 1989 [65]	23 [0F]	Lateral CT	Supine	American	• Eight responders and 15 non-responders. • The patients were relatively young [52±2y].

Gislason T et al 1988 [112]	34 [3F]	CT	Supine	Swedish	• Patients were unselected • No differentiation was made between obstructive, central and mixed apneas. • 22 Responders and 12 non-responders.
		Lateral cephalometric radiograph	Not specified		

Abbreviations: AI=apnea index, AHI=apnea hypopnea index, CT=computed tomography, F=number of female participants, H-UPPP=Han-uvulopalatopharyngoplasty, IAS=inferior airway space, M=number of male participants, N=number of participants, NS=not specified, OSAS=obstructive sleep apnea syndrome, PG=polygraphy, RDI= respiratory disturbance index, Z-UPPP=etapalatopharyngoplasty. See Table 1 for the definitions of the abbreviations used in the present table.

TABLE 5

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Reported in >1 study	**Not significant**	**Conflicting results**	**Not significant**	**Solitary results**	**Not significant**
High position HB [82, 108, 109]	[66-68, 104, 106, 107, 110-112]	Wide IAS [104] Versus narrow [111]	[66, 68, 82, 106, 108-110, 112]	Long PNS-point A [109]	[110]
				Long mandibular jaw [106]	[104, 108]
				Small angle of mouth opening during sleep [105]	-
				Small SN-OPT [109]	-
				Wide SPAS [105]	[108, 110, 111]
				Wide SPAS during sleep [105]	-
				Wide IAS during sleep [105]	-
				Small ratio IAS – tongue length [111]	-
				Narrow tongue width [112]	-
				Small MP-FH angle [106]	[104, 107]
				Short H1-H [107]	[67, 82]
				Short H2-H [107]	[67, 82]
				Short Ar-Go [107]	[67]
				Short PFH [107]	[67]
				Large PNS-Ba [110]	[67, 107]

Abbreviations: Ar=articulare, Ba=Basion, FH=Frankfort horizontal plane, Go=Gonion, HB=hyoid bone, IAS=inferior airway space, MP=mandibular plane, OPT=odontoid process tangent, PFH=posterior facial height, PNS=posterior nasal spine, SN=anterior cranial base, SPAS=superior posterior airway space. See Table 1 for the definitions of the abbreviations used in the present table.

TABLE 6

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Authors	N F/M	Imaging modality	Patient orientation	Population Nationality	Type of surgery	Relevant details
Zhang J et al 2013 [113]	119 [0F]	Spiral CT	Supine	Chinese	H-UPPP + transpalatal advancement pharyngoplasty	• 74 Responders and 45 non-responders.
Kim SJ et al 2012 [114]	85 [NS]	Lateral cephalometric radiograph	Upright standing	Korean	UPPP + genioglossus advancement	• 35 Responders and 50 non-responders.
Yin SK et al 2007 [115]	18 [0F]	Not specified	Not specified	Chinese	UPPP + genioglossus advancement + Hyoid suspension	• All patients with AHI>40/h. • All patients had multilevel obstruction of the oropharynx and hypopharynx. • It is not clearly mentioned if the imaging modality used to measure the cephalometric parameters was the same for each patient. • 12 Responders and six non-responders. • Responders were significantly younger than non-responders.
Teitelbaum J et al 2007 [116]	33 [NS]	Lateral cephalometric radiograph	Upright sitting	French	UPPP + hyothyrohoidopexy + genioglossus advancement	• Seven responders and 26 non-responders.
Liu SA et al 2005 [71]	44 [0F]	Lateral cephalometric radiograph	Not specified	Taiwanese	UPPP+ genioglossus advancement	• All patients with AHI>40/h. • Patients who previously have been treated surgically were excluded. • Some patients were <18 years. • 23 Responders and 21 non-responders.
Vilaseca I et al 2002 [117]	20 [0F]	Lateral cephalometric radiograph	Upright sitting	Spanish	[Previously failed UPPP] + hyothyropexia [n=9] [Previously failed UPPP] + hyothyropexia + genioglossus advancement [n=11]	• All patients showed multilevel obstruction [oropharynx: SP>40mm + hypopharynx: SNB≤77° + IAS≤10mm] and a post UPPP AHI>20/h. • All patients were <65 years • Mandibular osteotomy with genioglossus advancement was only performed in patients with a mandibular deficiency [SNB<78°]. • Seven responders and 13 non-responders.
De Dieuleveult T et al 2000 [118]	47 [1F]	Lateral cephalometric radiograph MRI [sequence not specified]	Not specified Supine	French	Genioglossus advancement + Hyoid suspension + UPPP [n=22] Tongue base reduction with hypoepiglottoplasty via cervical approach [n=8] + UPPP [n=17]	• All patients with AHI≤30 /h • All patients with SNA≥79° and/or SNB≥77°. • Patients with a tongue surface>27cm2 and a part of the tongue under the edge of the mandible>5cm2 received a tongue base reduction.
Ramirez SG and Loube DI 1996 [72]	12 [0F]	Lateral cephalometric radiograph	Upright sitting	American	UPPP + genioglossus advancement + hyoid suspension [n=4] + tonsillectomy [n=4] + nasal septoplasty [n=2]+ turbinate resection [n=2]	• All patients with BMI≥25. • All patients with SNB≥72°. • Patients with a hypopharyngeal obstruction were excluded. • Patients with AHI≤20/h were excluded.
Riley RW et al 1989 [119]	55 [2F]	Lateral cephalometric radiograph	Upright sitting	American	UPPP + genioglossus advancement + hyoid bone suspension [n=49] Genioglossus advancement + hyoid bone suspension [n=6]	• All patients were morbidly obese. • 37 Responders and 18 non-responders.

Abbreviations: AHI= apnea hypopnea index, CT=computed tomography, F=number of female participants, H-UPPP=Han-uvulopalatopharyngoplasty, IAS=inferior airway space, M=number of male participants, N=number of participants, NS= not specified, SNA=angle between sella – nasion – point A, SNB= angle between sella – nasion – point B, SP=soft palate length UPPP=uvulopalatopharyngoplasty. See Table 1 for the definitions of the abbreviations used in the present table.

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Reported in >1 study	Not significant	Solitary results	Not significant
Small ANB [114, 117]	-	Small SNA [118][a]	[71, 72, 114, 117-119][b]
Non-retruded mandible [114, 119]	[71, 72, 115, 117, 118]	Small maxilla [118][a]	[114, 118][b]
Wide IAS [114, 115]	[71, 72, 116-119]	Small angle MP-FH [114]	[118]
		High position HB [113]	[71, 114-118]
		Short airway [114]	-
		Short LAFH [114]	[118]
		Small angle OP-FH [114]	-
		Large OROSURF [118][b]	[118] [a]
		Wide MAS [114]	-
		Large OROPHSURF [116]	-
		Small RHINOPHSURF [116]	-
		Small angle C1-C3 [118][a]	[118][b]
		Large angle C3-C4 [118][b]	[118][a]

[a] Only the patient population of the study by De Dieuleveult et al[118] that received a genioglossus advancement, Hyoid suspension and UPPP.
[b] Only the patient population of the study by De Dieuleveult et al[118] that received a tongue base reduction with hypoepiglottoplasty via cervical approach with or without UPPP.

Abbreviations: ANB=angle between point A – nasion – point B, FH=Frankfort horizontal plane, HB=hyoid bone, IAS=inferior airway space, LAFH=lower anterior facial height, MAS=middle airway space, MP=mandibular plane, OP=occlusal plane, OROPHSURF=surface area of the oropharynx (other definition then OROSURF), OROSURF=oropharynx surface area, SNA= angle between sella – nasion – point A, UPPP=uvulopalatopharyngoplasty. See Table 1 for the definitions of the abbreviations used in the present table.

TABLE 8

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Authors	N F/M	Imaging modality	Patient orientation	Mean Protrusion	Population Nationality	Type of surgery	Relevant details
Ronchi P et al 2013 [120]	15 [4F]	Lateral cephalometric radiograph	Not specified	Maxilla: 5.2±4.5 mm Mandibula: 9.5±8.7 mm	Italian	MMA+ Genioglossus advancement	• Portable two channel PG monitoring system.
Varghese R et al 2012 [76]	24 [6F]	Lateral cephalometric radiograph	Not specified [natural resting head position]	Maxilla: 9.4±1.3 mm Mandibula: 9.0±2.0 mm	Americans	Primary MMA [n=16] Salvage MMA after soft tissue surgery [n=8]	• None of the patients had significant nasal or palatal obstruction prior to surgery.
Susarla SM et al 2011 [77]	12 [6F]	Lateral cephalometric radiograph	Not specified	Not specified	Americans	MMA [n=2] MMA + genioglossus advancement [n=21]	• All patients had pre-existing maxillary and/or mandibulary retrognathism. • The authors use the RDI, not the AHI. • The post-surgical weight of the patients is not measured.
Holty JE and Guilleminault C 2010 [21]	627 [75F]	Not specified: data pooled from multiple studies	Not specified: data pooled from multiple studies	Maxilla*: 9.3±6.5 mm Mandibula*: 11.3±6.7 mm	Not specified: data pooled from multiple studies	Primary MMA [33%] Salvage MMA after soft tissue surgery [67%]	• Meta-analysis of 22 study populations. • Most patients had maxillary and/or mandibulary insufficiency prior to surgery.
Jones R et al 2010 [81]	20 [3F]	Lateral cephalometric radiograph	Upright	Not specified	Australian	Salvage MMA after soft tissue surgery + chin advancement	• All patients had an AHI≤30 /h • All patients had an obstruction al the level of the oropharynx. • All patients had previously failed sift tissue surgery.
Lye KW et al 2008 [121]	15 [2F]	Lateral cephalometric radiograph	Not specified	Maxilla: 8.6 [3.1-11.0] mm Mandibula: 9.0 [4.9-16.6] mm	Americans	Salvage MMA after geniotomy, UPPP, septoplasty or turbinoplasty [n=12] Primary MMA [n=3]	• All patients failed CPAP treatment prior to surgery.
Teitelbaum J et al 2007 [116]	18 [NS]	Lateral cephalometric radiograph	Upright sitting	Not specified	French	Salvage MMA after soft tissue surgery [n=NS] Primary MMA [n=NS]	• 12 Responders and six non-responders. • Since there was no difference between the parameters of the primary MMA and salvage MMA patients, both groups were combined.
Smatt Y and Ferri J 2005 [80]	18 [3F]	Lateral cephalometric radiograph	Not specified	Maxilla: 5.2±1.8 mm Mandibula: 10.7±2.8 mm	French	MMA + genioplasty, uvuloplasty and glossoplasty	• All patients had maxillary and/or mandibulary insufficiency prior to surgery. • All patients with AHI≥30/h. • 15 Responders and three non-responders.
De Dieuleveult T et al 2000 [118]	26 [1F]	Lateral cephalometric radiograph MRI [sequence not specified]	Not specified Supine	Maxilla**: 7.0 [4-12] mm Mandibula**: 12.0 [8-17] mm	French	Primary MMA	• All patients with AHI≤30 /h • All patients with SNA<79° and/or SNB<77°. • 15 Responders and seven non-responders.

Riley RW et al 2000 [122]	40 [7F]	cephalometric radiograph	Not specified	Maxilla: 7.1±1.3 mm Mandibula: 10.8±2.7 mm	American	MMA + genioglossus advancement + hyoid suspension	• 36 Responders and four non-responders. • The mean RDI= 71.2±27.0/h. • 75% of the patients exhibited mandibular deficiency prior to surgery.
Riley RW et al 1990 [78]	40 [7F]	Not specified	Not specified	Not specified	American	Salvage MMA after various soft tissue surgery procedures.	• All patients had an isolated obstruction at the tongue base level.
Waite PD et al 1989 [79]	23 [2F]	Lateral cephalometric radiograph	Not specified	Maxilla: 7.3±2.6 mm Mandibula: 12.3±3.5 mm	American	MMA+ adjunctive procedures Salvage MMA after UPPP [n=5]	• The authors use the RDI, not the AHI.
* In a subset of 97 patients, the data of the remaining 530 patients is unknown. ** Median not mean							

Abbreviations: AHI=apnea hypopnea index, CPAP=continuous positive airway pressure, F=number of female participants, IAS=inferior airway space, M=number of male participants, MMA=maxillo-mandibular advancement, MRI=magnetic resonance imaging, N=number of participants, NS=not specified, PG= polygraphy, RDI= respiratory disturbance index, SNA=angle between sella – nasion – point A, SNB=angle between sella – nasion – point B, UPPP= uvulopalatopharyngoplasty. See Table 1 for the definitions of the abbreviations used in the present table.

TABLE 9

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Reported in >1 study	Not significant	Solitary results	Not significant
Large maxillary advancement [21, 120-122]	[76, 77, 79, 80]	Narrow minimal IAS [116]	[21, 118, 122]
		Narrow minimal SPAS [116]	-
		Narrow airway below the TB [116]	-
		Large surface area of the maxilla [118]	-

Abbreviations: IAS=inferior airway space, SPAS=superior posterior airway space, TB=tongue base. See Table 1 for the definitions of the abbreviations used in the present table.

TABLE 10

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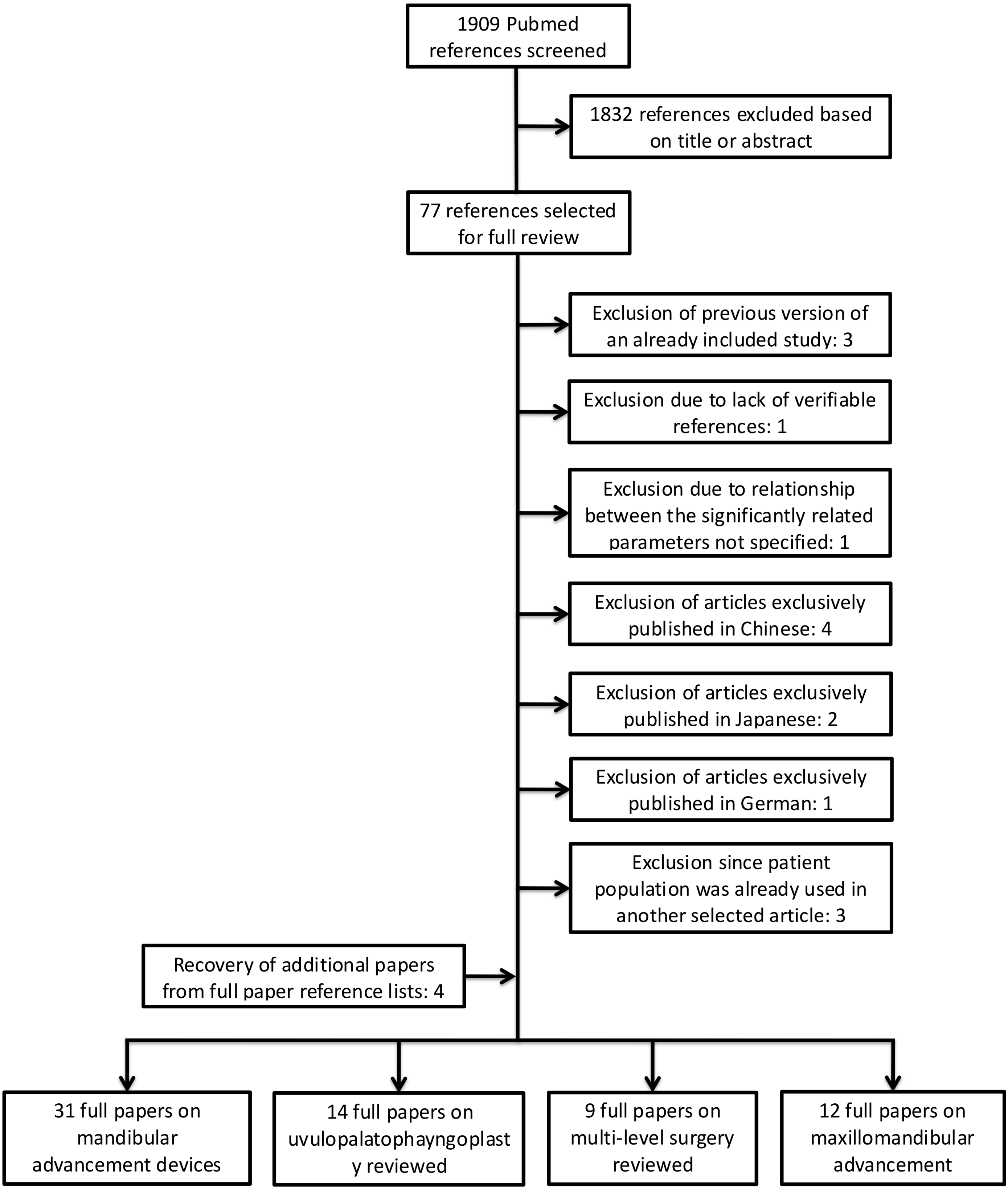
1909 Pubmed references screened
1832 references excluded based on title or abstract
77 references selected for full review
Exclusion of previous version of an already included study: 3
Exclusion due to lack of verifiable references: 1
Exclusion due to relationship between the significantly related parameters not specified: 1
Exclusion of articles exclusively published in Chinese: 4
Exclusion of articles exclusively published in Japanese: 2
Exclusion of articles exclusively published in German: 1
Exclusion since patient population was already used in another selected article: 3
Recovery of additional papers from full paper reference lists: 4
31 full papers on mandibular advancement devices
14 full papers on uvulopalatophayngoplasty reviewed
9 full papers on multi-level surgery reviewed
12 full papers on maxillomandibular advancement

FIGURE 1