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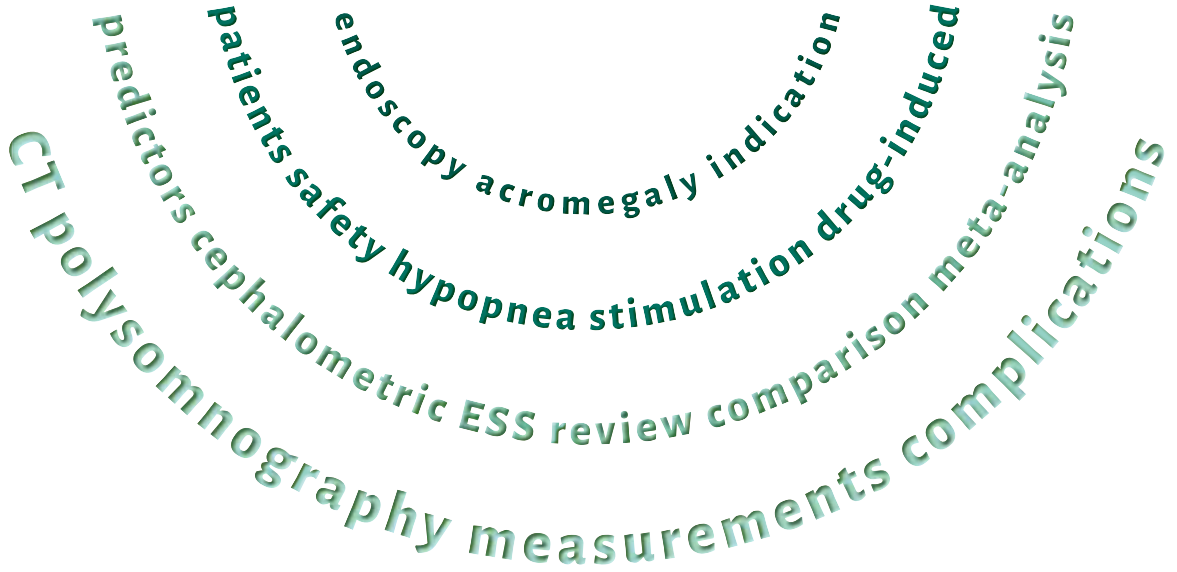

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CHAPTER

General introduction

BACKGROUND

Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder[1]. It is characterized by repetitive episodes of complete or partial upper airway obstruction during sleep, resulting in cessations (apneas) or reductions (hypopneas) in ventilation, with consequent hypoxia, hypercapnia, and/or related arousals[2, 3]. In the third edition of the International Classification of Sleep Disorders (ICSD-3), OSA is categorized into adult OSA and pediatric OSA[1]. In this thesis, we only focus on adult OSA.

OSA has been reported to be present in 9% to 38% of the general adult population: 13% to 33% of men, and 6% to 19% of women[4]. People with OSA may have complaints, such as loud or irregular snoring, daytime sleepiness, nocturia, chocking and gasping in sleep, and morning headache, but many are asymptomatic[2, 3, 5]. When left untreated, OSA can increase the risk of the development of cardiovascular disease, metabolic disease, psychiatric disorders, neurocognitive impairment, and all-cause morbidity[3, 6-9]. Additionally, the impairment in daytime function associated with untreated OSA is also a safety hazard[3, 10]. The adverse consequences of OSA highlight the importance of early diagnosis and effective management of this disorder.

Pathogenesis and risk factors of OSA

OSA is a highly heterogeneous disorder. Currently, four major phenotypic traits are thought to contribute to the pathogenesis of OSA, which include anatomical factors (narrow or collapsible upper airway), impaired pharyngeal dilator muscle function, premature awakening to airway narrowing (a low respiratory arousal threshold), and an oversensitive ventilatory control system (high loop gain)[11-13]. Other factors, like end-expiratory lung volume and redistribution of body fluid, may also play a role[14, 15]. The relative contribution of these traits to OSA pathogenesis varies substantially between patients.

Upper airway anatomy/collapsibility

Although OSA is a multifactorial disorder, a certain level of upper airway anatomical impairment is a prerequisite cause of its development. Studies using different imaging techniques (e.g., computed tomography [CT]) have provided insight into the OSA pathogenesis. Compared to non-OSA control subjects, patients with OSA were found to have a narrower pharyngeal space and a longer upper airway[16, 17]. A

systematic review showed that the most relevant anatomical characteristics of the upper airway that is linked to OSA pathogenesis is a small minimum cross-sectional area[18].

The upper airway consists of a collapsible segment (the pharynx), extending from the hard palate to the larynx. The collapsibility of the pharynx is determined by the difference between the pressure of the surrounding tissue and the stability of pharyngeal wall, which can be quantified by pharyngeal critical closing pressure (Pcrit)[19]. A high Pcrit indicates a high collapsibility of the airway. Upper airway collapse occurs when Pcrit exceeds the intraluminal pressure.

Dilator muscle function

The pharyngeal dilator muscles play a crucial role in maintaining upper airway stability. The largest pharyngeal dilator muscle is the genioglossus muscle, of which the activity is related to respiration, upper airway negative pressure, and arousal state[20]. During wakefulness, for both OSA patients and non-OSA subjects, the activation of pharyngeal dilator muscles is effective to oppose the negative upper airway pressure and hold the airway open. However, during sleep, when basal and compensatory dilator muscle activity cannot counteract the inherently impaired airway anatomy and the negative airway pressure, the upper airway patency cannot maintain in OSA patients[12].

Respiratory arousal threshold

A cortical arousal from sleep during a respiratory event occurs when negative intrathoracic pressure reaches a threshold (i.e., respiratory arousal threshold)[21]. Arousals have been considered crucial to reopen the upper airway following a respiratory event. However, recent evidence suggests that arousals may not be necessary to reopen the airway in many cases. Frequent arousals perpetuate blood-gas disturbances, breathing instability, sleep fragmentation, and subsequent upper airway collapse during sleep. A low respiratory arousal threshold may lead to, or worsen OSA[21, 22].

Ventilatory control system

During sleep, ventilation is primarily governed by the metabolic chemoreflex control system, where the partial pressure of carbon dioxide (P_{CO2}) tightly regulates the ventilatory rate[23, 24]. The sensitivity of the negative feedback system controlling

ventilation is characterized by "loop gain". The "loop gain" is calculated as the ventilatory response/ventilator disturbance ratio[24]. A high loop gain indicates an unstable control system. Individuals with a high loop gain have a larger ventilatory response to a small change in CO_2. This hyperventilation may increase the magnitude of hypocapnia and consequently result in low ventilatory drive with subsequent upper airway collapse[25].

Risk Factors

The risk factors for OSA mainly include obesity, increased age, male gender, family history and genetics, cranial facial anatomy resulting in a narrow airway, nasal congestion, alcohol, and smoking[26, 27]. Postmenopausal women are reported to have a higher risk of OSA than premenopausal women[28]. In addition, some other factors have also been identified as risk factors for OSA, including the use of certain medications (e.g., opioids and benzodiazepines[29]) and endocrine disorders (e.g., hypothyroidism[30], polycystic ovarian syndrome[31], and acromegaly[32]).

Diagnosis of OSA

The diagnosis of OSA is based on clinical presentation and physical examination findings suggestive of the disorder, coupled with the objective demonstration of abnormal breathing during sleep, by means of polysomnographic recording[3, 13, 33].

Clinical assessment

The clinical presentation in people with suspected OSA can vary among individuals. The most common symptoms suggestive of OSA are snoring and excessive daytime sleepiness. Other symptoms include, but are not restricted to, witnessed apneas, nocturnal choking or gasping, insomnia, nocturia, unrefreshed sleep, morning headaches, dry mouth, memory impairment, and fatigue[3, 33].

The physical examination of a patient with suspected OSA should include body mass index, neck circumference, nasal examination, pharyngeal anatomy including the lateral wall, soft palate, uvula, and tongue, facial skeletal characteristics of the maxilla and mandible, and dental status including occlusion[33, 34].

Polysomnography

The "gold standard" for the diagnosis of OSA is full polysomnography (PSG). Multiple physiologic signals are monitored by PSG during sleep, and generally include brain

waves (electroencephalogram), eye movements (electrooculogram), chin muscle activity (chin electromyogram), air flow, thoracic and abdominal movements, blood oxygen levels (oximetry), heart rate and rhythm (electrocardiogram), leg movements (leg electromyogram), body position, and audio recordings[35].

The collected data can be scored according to the American Academy of Sleep Medicine (AASM) scoring manual. Apnea is defined as a decrease of more than 90% in the nasal-oral airflow with a duration of at least 10 seconds. Hypopnea is defined as a decrease of more than 30% in the airflow for at least 10 seconds, combined with an at least 3% oxygen desaturation and/or arousal[36]. The apnea-hypopnea index (AHI) is defined as the number of apneas and hypopneas per hour of sleep. ICSD-3 defines OSA as: 1) an AHI ≥ 5 events/h combined with one or more OSA-related symptoms or associated medical or psychiatric disorders; or 2) an AHI ≥ 15 events/h without OSA-related symptoms or comorbidities[1]. Although some alternative measures of OSA severity, such as hypoxic burden, have been suggested, AHI has been the most widely used measure of OSA severity[37]. Based on the AHI, the severity of OSA is defined as: mild (AHI 5-15 events/h), moderate (AHI 16-30 events/h), and severe (AHI > 30 events/h).

Upper airway assessment

Multiple imaging techniques have been used to assess the upper airway abnormalities, such as lateral cephalogram, CT, magnetic resonance imaging (MRI), traditional nasopharyngoscopy, and drug-induced sleep endoscopy (DISE)[38, 39]. As this thesis involves the reliability of upper airway measurements on CT and the role of DISE in improving patient selection for OSA treatment, only CT and DISE are further introduced below.

Computed tomography CT is a fast, non-invasive, and commonly available technique allowing for assessing the upper airway three-dimensionally (3D). It can provide excellent imaging of the airway and its surrounding soft tissues and bone structure. A specific type of CT, dynamic 3D CT, can be performed to acquire dynamic 3D imaging of the upper airway over the respiration cycle[40]. Radiation exposure is the main downside of CT scanning. CT analysis of the upper airway has helped gain more insight into the OSA pathogenesis.

Drug-induced sleep endoscopy DISE is an endoscopic examination performed during pharmacologically induced sleep in order to identify the site(s), degree(s), and configuration(s) of upper airway collapse. DISE is mainly indicated when continuous positive airway pressure (CPAP; the gold standard of OSA treatment) fails or is not accepted by the patient, and alternative treatment modalities (e.g., upper airway surgery, hypoglossal nerve stimulation [HNS], mandibular advancement device [MAD], or a combination of different therapies) are considered[39]. Absolute contraindications are American Society of Anesthesiologists (ASA) score IV, pregnancy, and allergy to DISE sedative agents[39].

During DISE, different passive maneuvers can be performed with the aim of predicting the response to some specific treatment modalities[41]. A jaw thrust maneuver is a gentle advancement of the mandible up to approximately 5 mm, which may mimic the effect of MAD.

The Velum Oropharynx Tongue base Epiglottis (VOTE) classification is widely used for documenting the DISE findings[42] (**Figure 1**). It involves the four most common sites of collapse in the upper airway: velum, oropharynx, tongue base, and epiglottis. The degree of obstruction at the four sites can be: 0 (up to 50 % of obstruction), 1 (50-75 %), 2 (75-100 %), or X (not visualized). As for the collapse configuration(s), a distinction is made between anteroposterior, lateral, and concentric. The possible level(s), degree(s), and configuration(s) of collapse based on the VOTE classification system are shown in **Table 1**[42].

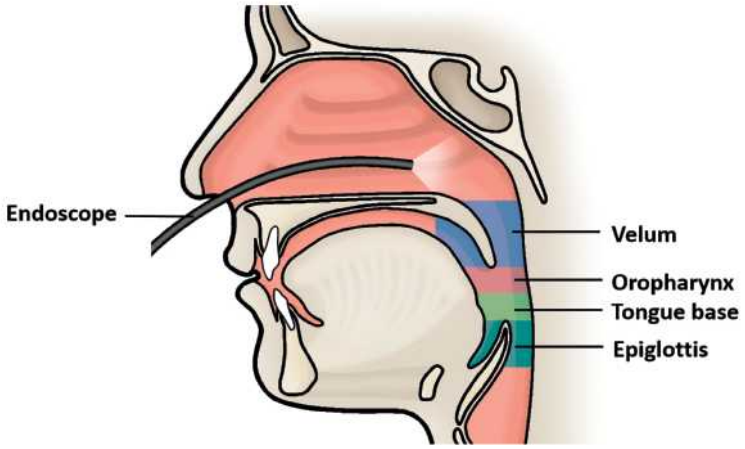

Figure 1. VOTE classification for DISE

Table 1. The VOTE classification[42]

Structure	Degree of obstruction[a]	Configuration[c]		
		AP	Lateral	Concentric
Velum				
Oropharynx[b]				
Tongue base				
Epiglottis				

AP, anteroposterior.

[a] Degree of obstruction: 0 = no obstruction; 1 = partial obstruction; 2 = complete obstruction.

[b] Oropharynx obstruction can be distinguished as related solely to the tonsils or including the lateral walls.

[c] Configuration noted for structures with degree of obstruction > 0.

Management of OSA

The most common treatment options for OSA include behavior therapy, such as weight loss, reducing alcohol and sedative use, and positional therapy; CPAP, which is the current gold standard treatment for especially severe OSA; MAD; and surgical therapy, such as upper airway surgery (single- and multi-level surgery), maxillomandibular advancement (MMA), and hypoglossal nerve stimulation (HNS)[43, 44].

In this thesis, we mainly focus on MMA surgery in the treatment of OSA. Additionally, the clinical efficacy and safety of MMA were compared with those of multilevel surgery (MLS) and HNS. Hence, only MMA, MLS, and HNS are further introduced below.

Maxillomandibular advancement

MMA, also known as bimaxillary advancement surgery, is a form of facial skeletal surgery. It involves a combination of a LeFort I osteotomy of the maxilla and a bilateral sagittal split osteotomy of the mandible to advance the maxillomandibular complex, with or without counterclockwise rotation of the complex[45, 46] (**Figure 2**). It has been suggested that by altering the skeletal framework, MMA can enlarge the entire retropalatal and retrolingual airway and stabilize the pharyngeal dilator muscles, thereby reducing upper airway collapsibility[47, 48]. The reported rate of surgical success of MMA ranges from 65% to 100%[48-50]. A meta-analysis suggested that surgical success of MMA is associated with younger age, lower preoperative weight and AHI, as well as greater degree of maxillary advancement[51].

The most current American Academy of Sleep Medicine (AASM) practice guidelines recommends that "MMA is indicated for surgical treatment of severe OSA in patients who cannot tolerate or who are unwilling to adhere to positive airway pressure therapy, or in whom oral appliances, which are more often appropriate in mild and moderate OSA patients, have been considered and found ineffective or undesirable"[52].

The relative contraindications for MMA mainly include significant medical comorbidities (e.g., severe heart failure), unstable psychological problems, morbid obesity (body mass index [BMI] > 35 kg/m^2), older age, and alcohol and/or drug dependency[53, 54].

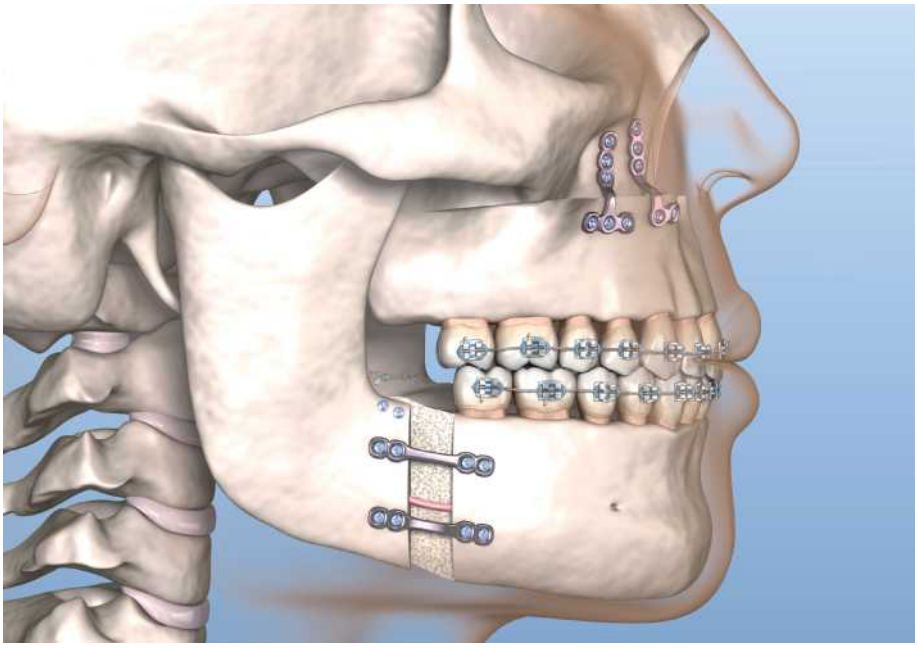

Figure 2. Maxillomandibular advancement surgery. LeFort I osteotomy, maxillary advancement, and rigid fixation; bilateral sagittal split osteotomy, mandibular advancement, and rigid fixation. From *Alex Mit/Shutterstock.com*. Usage with permission.

Multilevel surgery

MLS is a combined procedure (simultaneous surgery) or stepwise multiple operations (staged surgery), which involves velopharyngeal and hypopharyngeal regions. The surgical procedures involved in MLS are heterogeneous. The most commonly performed MLS includes a palatal surgery (e.g., uvulopalatopharyngoplasty [UPPP], expansion sphincter pharyngoplasty [ESP]) as a basic technique, with a second

procedure (e.g., radiofrequency thermotherapy of the tongue base, genioglossus advancement, hyoidthyroidpexia) designed to improve the hypopharynx[55-57]. The surgical success rate of MLS varies amongst studies and ranges from 47.5% to 100%[56-60].

According to the most current AASM practice, "use of multi-level or stepwise surgery (MLS), as a combined procedure or as stepwise multiple operations, is acceptable in patients with narrowing of multiple sites in the upper airway, particularly if they have failed UPPP as a sole treatment"[52].

The relative contraindications for MLS mainly include significant medical or psychiatric comorbidities, morbid obesity (BMI > 35 kg/m^2), and specific anatomical contraindications to the upper airway surgery (e.g., severe retrognathia)[61]. Additionally, a complete concentric collapse of the soft palate (CCCp) and a lateral oropharyngeal collapse during DISE may be negative prognostic factors for MLS[62, 63].

Hypoglossal nerve stimulation

HNS is a novel therapy for patients with moderate to severe OSA[2]. In contrast to traditional surgical approaches for OSA, HNS is a non-anatomical modifying surgery, which involves a surgical procedure for device implantation. HNS device works by electrically stimulating the branches of the hypoglossal nerve that innervate muscles responsible for protruding the tongue and thus maintaining upper airway patency during sleep[64]. Current evidence suggests that HNS therapy can improve upper airway patency not only at retrolingual level but also at retropalatal level[65]. Although it remains to be proven, mechanical palatoglossal coupling may explain the multilevel effect of HNS[66]. Currently, the most commonly used HNS device is Inspire upper airway stimulation (UAS) system (Inspire Medical Systems, Maple Grove, MN, USA). Previous studies have shown that UAS therapy is successful in 50% to 77.8% of the patients[67-69].

HNS therapy is currently indicated for age 22 years or older, moderate to severe OSA (AHI 15 events/h to 65 events/h), and difficulty accepting or adhering to CPAP[64].

This therapy is currently not considered appropriate for > 25% central and mixed apneas of the total AHI, a BMI > 32 kg/m^2, patients who are pregnant or plan to become pregnant, preexisting anatomic variants or neurologic disorders, and patients who require MRI[64]. In addition, CCCp is an absolute contraindication for unilateral HNS therapy[70].

THESIS OUTLINE

Main research questions

- Are there differences in the effects of MMA on respiratory function and facial esthetics between OSA patients with and without anteroposterior maxillomandibular deficiency? (**Chapter 2**)
- Which clinical features are predictive of MMA surgical outcome (response versus non-response) in patients with OSA? (**Chapter 3** and **4**)
- Are there differences in the clinical efficacy and safety between MMA and other multilevel approaches (MLS and UAS) for the treatment of OSA? (**Chapter 5** and **6**)
- What is the degree of the natural intra-individual variation in the upper airway measurements on CT scans at two time points? (**Chapter 7**)

The overall aim of this thesis is to gain further insight into the role of MMA in treating OSA, which may contribute to the optimization of surgical management of OSA.

Thesis chapters

This chapter (**chapter 1**) presents a general introduction, including the background of OSA, upper airway imaging techniques, and surgical therapies for OSA described in this thesis.

Chapter 2 presents a comparison of the MMA outcome between OSA patients with and without anteroposterior maxillomandibular deficiency. More specifically, that study compares the effects of MMA on respiratory function between patients with and without maxillomandibular deficiency based on PSG variables and patient satisfaction in postoperative breathing; and compares the changes in facial esthetics after MMA between both groups based on cephalometric measurements and patient satisfaction in postoperative facial esthetics.

In **chapter 3**, we explore the existence of the predictors of MMA surgical outcome (response versus non-response), from the most commonly available clinical data including patient-related, polysomnographic, cephalometric, and surgical variables.

Chapter 4 focuses on the role of DISE in the prediction of MMA surgical outcome. The tested hypothesis is that the upper airway collapse site(s), configuration(s), and

degree(s) during baseline DISE can predict MMA surgical outcome. Additionally, the value of jaw thrust maneuver during DISE in the prediction of MMA outcome is explored.

Chapter 5 presents a systematic review and meta-analysis, in which the clinical efficacy and safety are compared between MMA and MLS in the treatment of OSA.

In **chapter 6**, a systematic review is presented with the aim to comparatively evaluate the efficacy and safety of MMA and UAS in the treatment of OSA.

In **chapter 7**, we develop and validate a 3D method to characterize the upper airway on CT. Using this method, the natural intra-individual variation in the upper airway measurements on supine CT scans at two different time points (3 to 6 months interval) is quantified.

Chapter 8 reports a patient who was referred for consultation of MMA surgery for severe OSA but was subsequently diagnosed with acromegaly. After transsphenoidal resection of a pituitary adenoma, the patient's OSA was almost completely resolved.

Chapter 9 provides the main findings of the studies included in this thesis, general conclusions, and suggestions for future studies.

Chapter 10 presents a summary of this thesis in English and Dutch.

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CHAPTER 2

Effects of maxillomandibular advancement on respiratory function and facial esthetics in obstructive sleep apnea patients with versus without maxillomandibular deficiency

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ABSTRACT

The aim of this study was to compare the effects of maxillomandibular advancement (MMA) on respiratory function between obstructive sleep apnea (OSA) patients with and without maxillomandibular deficiency, and to compare the changes in facial esthetics after MMA between the two groups. MMA-treated patients who had both baseline and follow-up polysomnography (PSG) data and lateral cephalograms were enrolled in this retrospective study. In addition to PSG and cephalometric data, patient satisfaction with postoperative breathing and facial esthetics, and overall satisfaction with the treatment were assessed. Twenty-one patients were classified as not having maxillomandibular deficiency (without-deficiency group) and 40 patients as having maxillomandibular deficiency (with-deficiency group). The improvements in respiratory parameters (e.g., apnea-hypopnea index) and patient satisfaction with postoperative breathing were comparable in the two groups (P = 0.094-0.713). The changes in facial profile measurements (e.g., nasal prominence, nasolabial angel, and lip positions relative to the true vertical line) and patient satisfaction with postoperative facial esthetics were also comparable in the two groups (P = 0.148-0.983). In conclusion, no significant difference in the effects of MMA on respiratory function and facial esthetics between OSA patients with and without maxillomandibular deficiency was observed.

Keywords: Obstructive sleep apnea; Maxillo-mandibular surgery; Maxillofacial abnormalities; Treatment outcome; Cephalometry

INTRODUCTION

Obstructive sleep apnea (OSA) is increasingly recognized as a public health threat, with a prevalence of 9-38% in the general adult population[1, 2]. Continuous positive airway pressure (CPAP) was introduced in 1981, and since that time it has become the gold standard therapy for moderate to severe OSA[3]. However, the efficacy of CPAP is often hampered by poor compliance and low tolerance, which has prompted the search for alternative treatments[4, 5].

Riley and Powell pioneered the use of maxillomandibular advancement (MMA) for the treatment of OSA in the mid-1980 s, due to the recognition of the aetiology of OSA, which often involves concomitant maxillary and mandibular deficiencies[6]. MMA consists of advancement of the maxillomandibular complex by osteotomies of the maxilla and mandible, thus leading to enlargement of the pharyngeal space and reduction of pharyngeal collapsibility[7, 8].

Since the advancement of both jaws is functionally and esthetically beneficial to patients with maxillomandibular deficiency (maxillary and mandibular retrognathia), MMA has been primarily employed as the first-line treatment for OSA patients with this deficiency[9]. Nevertheless, MMA is also used to treat OSA patients without this deficiency but with other specific indications, for example failure or intolerance of other forms of therapy, or complete concentric collapse at the velum level as observed with drug-induced sleep endoscopy (DISE)[10, 11]. Although MMA is generally thought to be a highly effective surgical therapy for moderate to severe OSA[12, 13], some reported rates of surgical success are not that high[14-16], and there is still room for improvement. Besides, due to the limited evidence on the clinical efficacy of MMA in OSA patients without maxillomandibular deficiency[10, 17], in clinical practice some sleep specialists are of the opinion that MMA should preferably be performed for OSA patients with significant mandibular deficiency. More evidence on the efficacy of MMA in OSA patients without deficiency is therefore needed.

The unacceptable alteration in facial profile following MMA is also of great concern to OSA patients, especially for those without maxillomandibular deficiency, which may dissuade OSA patients from considering MMA as a treatment option[18]. It appears that the esthetic results of MMA in OSA patients without such deficiency have only been evaluated subjectively in two previous studies[10, 17].

Therefore, the objectives of this study were (1) to compare the effects of MMA on respiratory function between OSA patients with and without maxillomandibular deficiency based on respiratory parameters measured by polysomnography (PSG) and patient satisfaction with postoperative breathing, and (2) to compare the changes in facial esthetics after MMA between the two groups based on cephalometric measurements and patient satisfaction with postoperative facial esthetics.

METHODS

This retrospective study was deemed not to be subject to the Medical Research Human Subjects Act by the Medical Ethics Committee of the Amsterdam UMC (location AMC) and a formal approval was therefore waived (Reference number W19_170#19.209).

Participants

Participants were recruited from a consecutive series of patients with OSA undergoing MMA in the Department of Oral and Maxillofacial Surgery, Amsterdam UMC (location AMC), between November 2010 and March 2020. The following inclusion criteria were applied: age ≥ 18 years; presence of OSA diagnosed by PSG preoperatively; CPAP failure or intolerance; patients with a follow-up PSG at least 3 months after MMA; and patients with a preoperative cephalogram and a follow-up cephalogram at least 6 months after MMA. The exclusion criteria were as follows: patients who declined the use of their data for research purposes; edentulous individuals; previous history of LeFort I osteotomy and/or bilateral sagittal split osteotomy (BSSO); and syndromic patients.

All of the patients were classified into one of two groups, based on the maxillofacial skeletal criteria of the Steiner analysis[19]: those without maxillomandibular deficiency (without-deficiency group), i.e. patients with sella–nasion–A-point angle (SNA) > 80.5° and sella–nasion–B-point angle (SNB) > 78.5°; those with maxillomandibular deficiency (with-deficiency group), i.e. patients with SNA ≤ 80.5° and/or SNB ≤ 78.5°.

Polysomnography

All patients included in this study underwent an overnight PSG at baseline and at least 3 months after surgery (mean 5.4 ± 2.8 months). The PSG recordings were scored manually according to the American Academy of Sleep Medicine (AASM)

criteria[20]. The collected PSG parameters included preoperative and postoperative apnea-hypopnea index (AHI), oxygen desaturation index (ODI), and lowest oxygen saturation (LSAT). Based on Sher's criteria, surgical success was defined as a postoperative AHI of less than 20 events/h and at least 50% reduction in AHI following surgery[21]. Surgical cure was defined as a postoperative AHI of less than 5 events/h[22].

Cephalometric measurements

A standard lateral cephalogram was taken before and at least 6 months after surgery (mean 12.8 ± 7.7 months). Each radiograph was taken in centric occlusion and with the lips in relaxed position. All of the cephalograms were traced by one observer using Viewbox 4 software (dHAL Software, Kifissia, Greece). The landmarks and reference planes are shown in **Figure 1**. The variables were classified into hard tissue variables, upper airway variable (**Figure 2**), and soft tissue variables (**Figure 3**). To assess the reliability of the cephalometric analysis, the same observer randomly selected 10 lateral cephalograms and repeated the measurements 1 month later.

Maxillomandibular advancement surgery

All patients underwent a MMA procedure (LeFort I osteotomy of the maxilla and BSSO of the mandible) with or without counterclockwise rotation of the maxillomandibular complex, performed by two dedicated surgeons. Rigid fixation with titanium miniplates and screws was used to stabilize the maxillary and mandibular osteotomies. Additional procedures, including genioplasty and genioglossus advancement, were performed in certain cases. The patients treated during the earlier years of the study period had a two-dimensionally planned operation, using a standard surgical protocol with the goal of 8-10 mm advancement of the maxillomandibular complex. The patients treated later during the study period had a three-dimensionally planned operation, using a personalized surgical protocol. In the personalized protocol, the final position of the bony segments was determined comprehensively by taking into account multiple patient-related factors, i.e. the severity of the OSA, skeletal pattern, dental occlusion, and facial characteristics. In addition, given that scar tissue resulting from prior upper airway surgery could restrict the MMA surgical movement, when patients had received extensive prior airway surgery, the planned degree of advancement was appropriately reduced. Upper airway collapse patterns were also taken into account when preoperative DISE was available. For example, a sufficient degree of mandibular advancement was

planned when there was significant collapse of the tongue base and/or the epiglottis during DISE.

Subjective evaluation

At least 6 months after MMA, a self-assessment questionnaire was mailed to the patients to subjectively evaluate their perceptions of the MMA surgery for OSA. The patients were requested to use an 11-point VAS to separately indicate the level of satisfaction with postoperative breathing, satisfaction with postoperative facial esthetics, and overall satisfaction with the MMA treatment, with 0 representing "not satisfied at all" and 10 representing "completely satisfied".

Statistical analysis

Data were analysed using IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA). Quantitative data were reported as the median and interquartile range (IQR). Categorical data were reported as the frequency and percentage. To determine intra-observer reliability of the cephalometric analysis, the intra-class correlation coefficient (ICC) was determined for the repeated measurements. Normality was tested using the Shapiro-Wilk test. To compare quantitative variables between the without-deficiency and with-deficiency groups, the independent-samples t-test was used when the data were normally distributed and the Mann-Whitney U-test was used when the data were not normally distributed. Differences between the two groups in categorical variables (sex and presence or absence of counterclockwise rotation, genioglossus advancement, and genioplasty) were assessed by $\chi 2$ test or Fisher's exact test as appropriate. For the comparison of the preoperative and postoperative values, the paired-samples t-test was applied in the case of normally distributed data and the Wilcoxon signed-rank test in the case of non-normally distributed data. Spearman correlation analysis was used to assess the correlation between the reduction in AHI and facial esthetics satisfaction score. A P-value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

In total, 104 patients underwent MMA for OSA during the study period. Forty-three patients were excluded from the study for the following reasons: declined the

use of their data for research (n=3), edentulous individuals (n=17), and absence of a preoperative or a follow-up cephalogram (n=23). Therefore, 61 patients were included in this study (78.7% male, 21.3% female; median age 50.0 (IQR 44.0, 58.5) years; median body mass index (BMI) 29.0 (IQR 26.4, 31.3) kg/m^2; median AHI 49.6 (IQR 35.1, 67.4) events/h).

The ICC of the cephalometric analysis ranged from 0.914 to 0.996, indicating excellent intra-observer reliability[23]. According to the skeletal criteria of the Steiner analysis, 21 out of the 61 patients did not have maxillomandibular deficiency preoperatively (median SNA 83.3° (IQR 81.9°, 85.4°), median SNB 79.4° (IQR 78.6°, 82.2°)). Among the 40 patients with maxillary and/or mandibular deficiency (median SNA 79.8° (IQR 76.8°, 81.3°), median SNB 73.3° (IQR 71.6°, 75.9°)), 23 (57.5%) had concomitant maxillary and mandibular deficiency, 16 (40%) had only mandibular deficiency, and one (2.5%) had only maxillary deficiency.

Baseline characteristics of the two study groups, without-deficiency versus with-deficiency

When comparing the baseline characteristics between the without-deficiency and with-deficiency groups, no significant difference was found in the baseline demographic and PSG variables. For baseline soft tissue measurements, a more protrusive position of the upper lip (UL–TVL) (P=0.017), lower lip (LL–TVL) (P<0.001), and soft tissue pogonion (Pog'–TVL) (P<0.001) relative to the true vertical line (TVL) was observed in the without-deficiency group, while a significantly larger facial convexity (P=0.011) was observed in the with-deficiency group. In contrast, the nasal prominence, nasolabial angle, position of the upper lip relative to the E-line (UL–E-line), and position of the lower lip relative to the E-line (LL–E-line) did not differ significantly between the two groups (**Table 1**).

Clinical efficacy of maxillomandibular advancement

The surgical characteristics and airway space in the two study groups are summarized in **Table 2**. The degree of advancement of A-point and B-point did not differ significantly between the two groups, while the degree of advancement of pogonion (Pog) was significantly greater in the with-deficiency group (P=0.046). The increase in posterior airway space (PAS) following MMA did not differ significantly between the two groups (P=0.264) (**Table 2**).

An overview of the preoperative and postoperative PSG values in the two study groups can be found in **Table 3**. A significant reduction in median AHI from 41.6 (IQR 32.1, 62.6) events/h to 11.1 (IQR 6.2, 27.1) events/h in the without-deficiency group ($P<0.001$) and from 52.2 (IQR 35.3, 69.6) events/h to 10.3 (IQR 4.9, 21.9) events/h in the with-deficiency group ($P<0.001$) was observed. There was no significant difference between the two groups in the improvements in AHI, ODI, and LSAT. Surgical success was achieved in 57.1% of the without-deficiency group compared to 67.5% of the with-deficiency group ($P=0.423$), while surgical cure was achieved in 14.3% of the without-deficiency group compared to 27.5% of the with-deficiency group ($P=0.398$).

Change in facial esthetics after maxillomandibular advancement

After MMA, significant decreases in nasal prominence and nasolabial angle, as well as significant increases in UL–TVL, LL–TVL, Pog'–TVL, UL–E-line, and LL–E-line were observed in both groups ($P=0.046$ to $P<0.001$). A significant decrease in facial convexity was found in the with-deficiency group ($P<0.001$), but not in the without-deficiency group ($P=0.070$).

The changes in soft tissue measurements were comparable in the two groups. Postoperatively, UL–TVL ($P=0.002$), LL–TVL ($P<0.001$), and Pog'–TVL ($P<0.001$) were more protrusive in the without-deficiency group than in the with-deficiency group and the facial convexity was significantly lower in the without-deficiency group ($P=0.012$), while the nasal prominence, nasolabial angle, UL–E-line, and LL–E-line were similar in the two groups (**Table 4**).

Subjective assessment of patient satisfaction

Thirty (49.2%) questionnaires were completed and returned: 10 by patients without maxillomandibular deficiency and 20 by patients with deficiency. In the without-deficiency group, the number of patients reporting a satisfaction score ≥7 in terms of postoperative breathing, facial esthetics, and overall satisfaction was six (60%), five (50%), and four (40%), respectively; in the with-deficiency group, it was 10 (50%), 13 (65%), and 11 (55%), respectively. The number of patients in the without-deficiency group reporting a satisfaction score<3 in terms of breathing, facial esthetics, and overall satisfaction was one (10%), two (20%), and four (40%), respectively; in the with-deficiency group, it was four (20%) for all.

The median VAS scores for satisfaction for both groups are shown in **Table 5**. The without-deficiency group reported the highest level of satisfaction with breathing, followed in descending order by facial esthetics and overall satisfaction, while the with-deficiency group reported the highest level of satisfaction with facial esthetics and overall satisfaction, followed by satisfaction with breathing. On comparison of the median VAS satisfaction scores between the two groups, the degree of satisfaction with breathing ($P = 0.713$), satisfaction with facial esthetics ($P = 0.983$), and overall satisfaction ($P = 0.681$) did not differ significantly.

DISCUSSION

This study compared the treatment efficacy and changes in facial esthetics after MMA between OSA patients with and without maxillomandibular deficiency. The main findings were as follows: (1) MMA surgery was equally effective in improving respiratory parameters for patients with and without such deficiency; (2) the changes in soft tissue profile measurements following MMA did not differ significantly between the two groups; and (3) the two groups had similar levels of satisfaction with postoperative breathing and facial esthetics, and overall satisfaction with treatment.

The finding that the effect of MMA on respiratory parameters did not differ significantly between patients with and without deficiency is in line with a previous study by Ronchi et al.[17], even though the two studies used different definitions of maxillomandibular deficiency. Ronchi et al. concluded that the improvements in AHI and Epworth Sleepiness Scale (ESS) after MMA were comparable in the OSA patients with and without skeletal anomalies[17]. The present study also found that patient perception of breathing after MMA was mainly positive and similar in both groups, which further supports MMA as an effective treatment option for patients with OSA, even in those without a skeletal deficiency. MMA surgery is generally thought to enlarge the airway space and stiffen the pharyngeal soft tissues by expanding the facial skeletal framework, thereby preventing airway collapse during sleep[24]. The present study found that after MMA, the increase in PAS was comparable in patients with and without deficiency, which may partially explain the equal efficacy in the two groups. Additionally, it was found that neither baseline AHI nor baseline PAS differed between patients with and without deficiency. This may support the notion that the choice of MMA as the primary treatment for OSA

should depend mainly on the disease severity and restriction of PAS rather than on the dentofacial skeletal characteristics[17].

It is interesting to note that although a surgical success rate of 57.1% and 67.5% was observed in the without-deficiency group and with-deficiency group, respectively, the surgical cure rate was only 14.3% for the without-deficiency group and 27.5% for the with-deficiency group. This difference between the surgical success and cure rates has also been observed in other studies on MMA[7, 25]. For the patients whose OSA is improved but not cured after MMA, the authors suggest a collaboration between the surgeon and a sleep specialist to find the potential causes of the residual sleep apnea, and to evaluate the necessity for adjunctive therapy based on the severity of the residual OSA, patient symptoms, and patient preferences.

The patients treated earlier in the study period had a two-dimensionally planned operation, using a standard surgical protocol with the goal of 8-10 mm advancement; those treated later in the study period had a three-dimensionally planned operation in which the degree of advancement was personalized according to multiple patient-related factors, such as the severity of the OSA, skeletal pattern, and facial characteristics. It was anticipated that the degree of MMA advancement would be greater in patients with deficiency than in those without deficiency, however there was no significant difference between the two groups in the degree of advancement of A-point and B-point. This was because approximately 70% of the study population were treated with a standard surgical protocol. To further optimize the OSA treatment with MMA, future research should compare the surgical outcomes between the standard and personalized planned MMA.

According to the literature, the facial soft tissue should be evaluated 6 months after orthognathic surgery, in order to allow it to heal nearly completely[26]. In this study, the facial profile was assessed at least 6 months after surgery (mean 12.8 months); the role of residual oedema in the observed soft tissue changes is thus likely to be negligible. After MMA, the protrusion of the upper lip, lower lip, and chin relative to TVL increased significantly, accompanied by a decrease in nasal prominence, nasolabial angle, and facial convexity. These findings are consistent with those of previous studies[27, 28]. A finding of interest is that when examining the lip position to E-line[29], the protrusion of the upper lip and lower lip increased significantly after MMA, but the increase was less than the increase relative to

TVL. This is because the increased prominence of the chin can balance the lip protrusion relative to the E-line[30]. According to Ricketts' analysis, the upper lip and lower lip in patients of White European descent should be estimated 4 mm and 2 mm behind the E-line respectively[29], with variations among different ethnicities. For both groups, the median of the postoperative UL–E-line (without-deficiency group −3.8 mm; with-deficiency group −3.0 mm) and postoperative LL–E-line (without-deficiency group −1.7 mm; with-deficiency group −2.0 mm) were similar to the norms reported by Ricketts. However, due to the unknown ethnicities of the present study population, this conclusion should be considered with care. Taken together, the findings suggest that although MMA can significantly alter the soft tissue facial profile, the balance between the nose, lips, and chin is acceptable for patients with and without deficiency.

Another point to be noted is that no significant difference was found between patients with and without deficiency with regard to the changes in facial profile measurements. Conley and Boyd[27] evaluated the facial soft tissue changes following MMA for the treatment of OSA, and concluded that the changes in soft tissue corresponded to nearly 90% of the underlying skeletal movements for most anatomical sites of the upper lip, lower lip, and chin. In the present study, the magnitude of the skeletal advancement did not differ significantly between the two groups. It is therefore not surprising that the corresponding changes in facial profile were comparable in the two groups.

Interestingly, despite the significant differences observed between the two groups in postoperative facial profile measurements, there was no significant difference between the two groups in perception of facial esthetics. This suggests that these objective soft tissue measurements may not play an important role in patient satisfaction with facial esthetics. This is further supported by the results of the post-hoc Spearman correlation analysis on the correlation between the facial esthetics satisfaction score on the one hand and soft tissue changes and post-surgical soft tissue variables on the other hand, in which only the change in LL–E-line was negatively associated with the degree of satisfaction with facial esthetics ($r = -0.542$, $P = 0.002$). Thus, it can be advocated that the position of the lower lip in relation to the E-line should be integrated into the MMA surgery plan for OSA treatment. It is important to note that most people do not look at themselves in profile but rather look straight in a mirror, and while there are some soft tissue changes that can be observed by a discerning eye from frontal

view, they are far less obvious than profile changes. Another point to be noted is that the patients might have imposed their own cultural bias during the subjective evaluation[31]. Additionally, it is likely that OSA patients, especially those without a baseline maxillomandibular deficiency, accept their alteration in facial esthetics due to the improvement in OSA, as the main motivation for MMA in these patients is treatment of the OSA. Nevertheless, no significant correlation was found between the facial esthetics satisfaction score and the improvement in AHI in this study population.

The study results should be interpreted with caution due to certain limitations. Firstly, as with any retrospective analysis, a weakness of the study was the inability to control the data. There is also a potential concern for selection bias, as only 60% of the total MMA cohort were enrolled in this study. However, no significant differences in baseline characteristics (age, sex distribution, BMI, neck circumference, and baseline AHI) were observed between the patients who were included in the study and those who were not. Furthermore, half of the study population did not respond to the questionnaire, which might have caused a non-response bias[32]. In addition, the incorporation of genioplasty or genioglossus advancement as an additional procedure in MMA should be considered as a confounding factor. Nevertheless, given that the additional procedure was only performed in six patients, it might not have played a leading role in the results observed. Counterclockwise rotation involved in MMA may also have an impact on respiratory function and facial esthetics. However, since counterclockwise rotation was not a main focus of interest in this study and was performed equally in both groups (47.6% vs 52.5%, $P = 0.717$), it was decided not to take it into consideration in the analyses. Lastly, the study cohort comprised predominantly middle-aged and elderly male patients with a relatively high BMI (overweight) and of unknown ethnicity. This limits the generalizability of the findings. Larger, prospective multicentre studies are needed to further confirm the current findings. Additionally, a validated questionnaire would be preferable for the subjective assessments in future research.

Within the limitations of this study, it is concluded that there is no significant difference in the effects of MMA on respiratory function and facial esthetics between OSA patients with and without maxillomandibular deficiency. This supports the view that MMA can also be considered as an appropriate treatment for OSA patients without maxillomandibular deficiency.

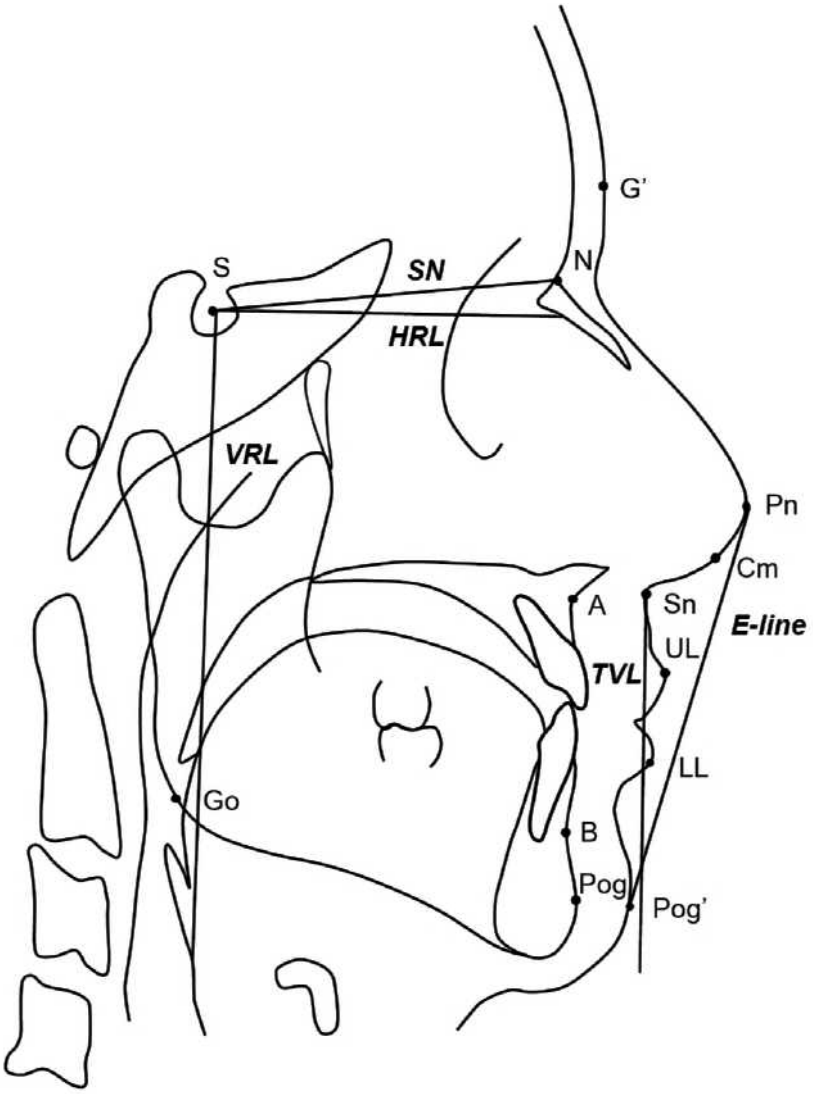

Figure 1. Cephalometric landmarks and reference lines. Landmarks: S, sella; N, nasion; A, A-point; B, B-point; Go, gonion; Pog, pogonion; G', soft tissue glabella; Pn, pronasale; Cm, columella; Sn, subnasale; UL, upper lip; LL, lower lip; Pog', soft tissue pogonion. Reference lines: SN, a plane running through S and N; HRL, horizontal reference line, a line through S at 7° from SN; VRL, vertical reference line, a perpendicular line dropping from HRL and passing through S; TVL, true vertical line, a line perpendicular to HRL and passing through Sn; E-line, a line running through Pn and Pog'.

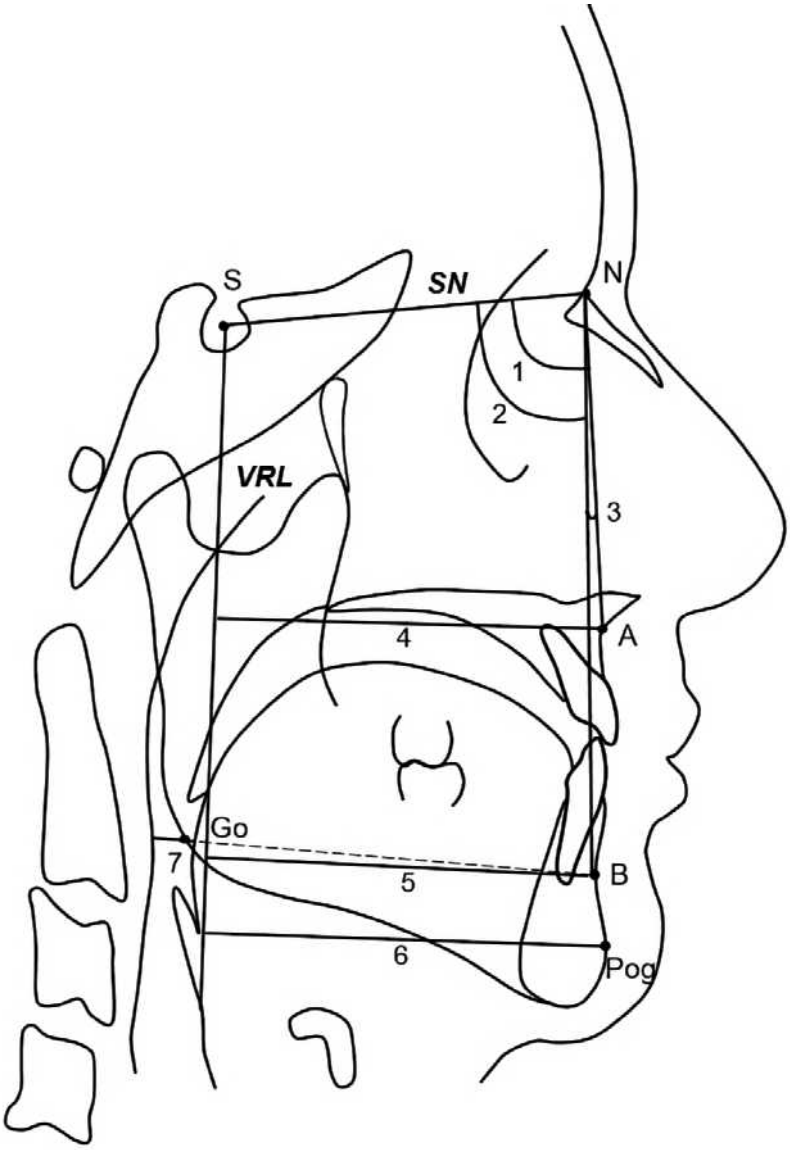

Figure 2. Hard tissue and upper airway cephalometric measurements. 1, S–N–A-point angle (SNA); 2, S–N–B-point angle (SNB); 3, A-point–N–B-point angle (ANB); 4, distance from A-point to VRL (A–VRL); 5, distance from B-point to VRL (B–VRL); 6, distance from Pog to VRL (Pog–VRL); 7, posterior airway space, width of the airway along Go–B-point line (PAS).

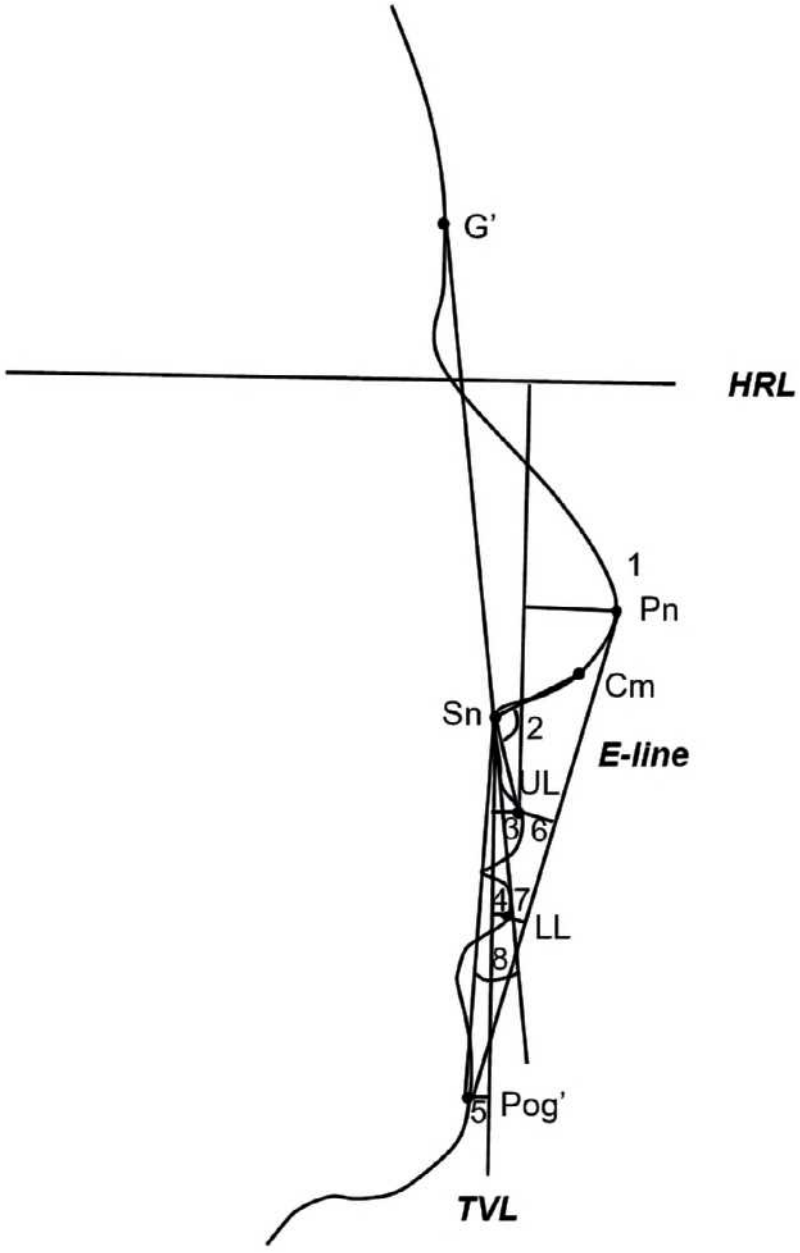

Figure 3. Soft tissue cephalometric measurements. 1, nasal prominence, distance from Pn to a line perpendicular to HRL and passing through UL; 2, nasolabial angle, Cm–Sn–UL angle; 3, distance from UL to TVL (UL–TVL); 4, distance from LL to TVL (LL–TVL); 5, distance from Pog' to TVL (Pog'–TVL); 6, distance from UL to E-line (UL–*E*-line); 7, distance from LL to E-line (LL–E-line); 8, facial convexity, G'–Sn–Pog' angle.

Table 1. Baseline characteristics in without deficiency group and with deficiency group

	Without deficiency (n = 21)	With deficiency (n = 40)	*P*-value[a]
Demographic variables			
Male:female	19:2	29:11	0.194
Age, years	50.0 (46.0, 57.5)	51.0 (43.3, 59.0)	0.992
BMI, kg/m^2	29.6 (26.7, 31.5)	28.9 (25.9, 31.2)	0.976
Neck circumference, cm	42.0 (39.8, 44.3)	43.0 (29.0, 46.0)	0.546
Polysomnographic variables			
AHI, events/h	41.6 (32.1, 62.6)	52.2 (35.3, 69.6)	0.168
ODI, events/h	44.9 (28.7, 62.1)	51.0 (29.5, 70.0)	0.438
LSAT, %	81.0 (79.0, 86.0)	79.0 (73.0, 84.0)	0.221
Cephalometric variables – upper airway			
PAS, mm	8.5 (6.5, 10.5)	8.7 (6.9, 11.7)	0.690
Cephalometric variables – soft tissue[b]			
Nasolabial prominence, mm	15.8 (13.3, 20.0)	18.3 (14.4, 20.7)	0.065
Nasolabial angle, degree	119.7 (113.2, 125.2)	121.0 (113.8, 129.1)	0.347
UL–TVL, mm	1.2 (-0.6, 3.4)	-0.1 (-2.4, 2.1)	**0.017**
LL–TVL, mm	0.2 (-2.0, 1.2)	-4.4 (-7.0, -2.6)	**<0.001**
Pog'–TVL, mm	-5.1 (-8.0, 0.2)	-13.5 (-18.1, -9.6)	**<0.001**
UL–E-line, mm	-6.0 (-9.8, -3.1)	-4.0 (-6.7, -1.4)	0.132
LL–E-line, mm	-4.3 (-6.9, -2.7)	-2.6 (-7.1, -0.6)	0.397
Facial convexity, degree	7.1 (3.2, 12.3)	13.4 (5.8, 18.8)	**0.011**

AHI, apnea hypopnea index; BMI, body mass index; LL–E-line, distance of lower lip to E-line; LL–TVL, distance of lower lip to true vertical line; LSAT, lowest oxygen desaturation; ODI, oxygen desaturation index; PAS, posterior airway space; Pog'–TVL, distance of soft tissue pogonion to true vertical line; UL–E-line, distance of upper lip to E-line; UL–TVL, distance of upper lip to true vertical line.

Data presented as median (interquartile range).

[a] *P*-value for the comparison of the without-deficiency and with-deficiency groups; $P<0.05$ was considered statistically significant.

[b] For UL–TVL, LL–TVL, Pog'–TVL, UL–E-line, and LL–E-line, a positive value is for a position in front of the TVL or E-line, and a negative value is for a posterior position.

Table 2. Surgical characteristics and airway space in without deficiency group and with deficiency group

	Without deficiency (n = 21)	**With deficiency (n = 40)**	***P*-value[a]**
Adv. A, mm	5.9 (4.8, 9.2)	7.7 (5.9, 9.1)	0.536
Adv. B, mm	7.9 (6.4, 10.6)	9.9 (7.7, 13.4)	0.064
Adv. Pog, mm	9.0 (4.8, 11.4)	10.4 (8.3, 13.1)	0.046
Counterclockwise rotation, n (%)	10 (47.6)	21 (52.5)	0.717
Genioglossus advancement, n (%)	0 (0)	1 (2.5)	1.000
Genioplasty, n (%)	1 (4.8)	4 (10)	0.828
T0 PAS, mm	8.5 (6.5, 10.5)	8.7 (6.9, 11.7)	0.690
T1 PAS, mm	14.2 (12.2, 16.0)	13.3 (10.8, 17.0)	0.643
ΔPAS, mm	6.2 (2.3, 8.0)	4.6 (3.3, 5.7)	0.264

Adv. A, advancement degree of A-point; Adv. B, advancement degree of B-point; Adv. Pog, advancement degree of pogonion; PAS, posterior airway space; T0, preoperative; T1, postoperative; Δ, postoperative and preoperative change.

Cephalometric data presented as median (interquartile range), additional surgical techniques presented as number with percentage.

[a] P-value for the comparison of the without-deficiency and with-deficiency groups; $P < 0.05$ was considered statistically significant.

Table 3. Preoperative and postoperative polysomnographic values in without deficiency group and with deficiency group

	Without deficiency (n = 21)				With deficiency (n = 40)				Without deficiency vs With deficiency	
	Preoperative (T0)	Postoperative (T1)	*P*-value T0 vs T1	Δ	Preoperative (T0)	Postoperative (T1)	*P*-value T0 vs T1	Δ	*P*-value[a]	*P*-value[b]
AHI, events/h	41.6 (32.1, 62.6)	11.1 (6.2, 27.1)	**<0.001**	-28.0 (-44.4, -10.8)	52.2 (35.3, 69.6)	10.3 (4.9, 21.9)	**<0.001**	-34.1 (-52.9, -21.8)	0.094	0.490
ODI, events/h	44.9 (28.7, 62.1)	19.1 (9.9, 28.1)	**0.005**	-27.0 (-34.4, -5.8)	51.0 (29.5, 70.0)	20.0 (7.7, 33.3)	**<0.001**	-26.0 (-46.6, -12.3)	0.284	0.851
LSAT, %	81.0 (79.0, 86.0)	86.0 (84.8, 89.0)	**<0.001**	5.0 (2.5, 9.0)	79.0 (73.0, 84.0)	87.0 (81.3, 89.0)	**<0.001**	6.0 (2.0, 9.0)	0.612	0.876

AHI, apnea hypopnea index; LSAT, lowest oxygen desaturation; ODI, oxygen desaturation index; Δ, postoperative and preoperative change.
Data presented as median (interquartile range).
[a] *P*-value for the comparison of the preoperative to postoperative change (Δ) between the without-deficiency and with-deficiency groups.
[b] *P*-value for the comparison of the postoperative values between the without-deficiency and with-deficiency groups. For all tests, $P < 0.05$ was considered statistically significant.

Table 4. Preoperative and postoperative soft tissue measurements in without deficiency group and with deficiency group

	Without deficiency (n = 21)				With deficiency (n = 40)				Without deficiency vs With deficiency	
	Preoperative (T0)	Postoperative (T1)	*p*-value T0 vs T1	Δ	Preoperative (T0)	Postoperative (T1)	*P*-value T0 vs T1	Δ	*P*-value[a]	*P*-value[b]
Nasolabial prominence, mm	15.8 (13.3, 20.0)	11.0 (7.0, 15.5)	**<0.001**	-4.6 (-6.7, -3.7)	18.3 (14.4, 20.7)	13.5 (9.3, 16.1)	**<0.001**	-5.1 (-6.6, -3.9)	0.649	0.167
Nasolabial angle, degree	119.7 (113.2, 125.2)	111.9 (108.4, 118.5)	**0.005**	-5.0 (-9.8, 0.3)	121.0 (113.8, 129.1)	115.3 (109.9, 125.6)	**<0.001**	-6.4 (-10.8, 0.2)	0.909	0.200
UL–TVLc, mm	1.2 (-0.6, 3.4)	5.2 (3.4, 7.1)	**<0.001**	2.8 (2.2, 5.8)	-0.1 (-2.4, 2.1)	2.4 (0.6, 5.1)	**<0.001**	3.1 (1.9, 4.3)	0.195	**0.002**
LL–TVLc, mm	0.2 (-2.0, 1.2)	4.5 (3.1, 7.8)	**<0.001**	4.0 (2.5, 7.0)	-4.4 (-7.0, -2.6)	0.5 (-3.0, 2.3)	**<0.001**	4.3 (2.5, 7.1)	0.738	**<0.001**
Pog'–TVLc, mm	-5.1 (-8.0, 0.2)	1.6 (-3.5, 4.5)	**<0.001**	5.8 (0.8, 8.2)	-13.5 (-18.1, -9.6)	-6.4 (-11.4, -4.2)	**<0.001**	6.8 (3.2, 9.6)	0.148	**<0.001**
UL–E-linec, mm	-6.0 (-9.8, -3.1)	-3.8 (-6.8, -1.2)	**0.003**	2.6 (-0.6, 3.8)	-4.0 (-6.7, -1.4)	-3.0 (-5.3, -5.1)	**0.046**	0.8 (-0.9, 2.5)	0.173	0.456
LL–E-linec, mm	-4.3 (-6.9, -2.7)	-1.7 (-4.8, 1.2)	**0.001**	2.4 (-0.1, 4.1)	-2.6 (-7.1, -0.6)	-2.0 (-3.7, 1.5)	**0.002**	1.1 (-0.4, 3.2)	0.403	0.735
Facial convexity, degree	7.1 (3.2, 12.3)	4.0 (1.0, 9.7)	**0.070**	-2.2 (-5.5, 2.8)	13.4 (5.8, 18.8)	11.1 (4.6, 14.3)	**<0.001**	-2.7 (-6.8, -0.3)	0.502	**0.012**

LL–E-line, distance of lower lip to E-line; LL–TVL, distance of lower lip to true vertical line; Pog'–TVL, distance of soft tissue pogonion to true vertical line; UL–E-line, distance of upper lip to E-line; UL–TVL, distance of upper lip to true vertical line; Δ, postoperative and preoperative change.
Data presented as median (interquartile range).
[a] *P*-value for the comparison of the preoperative to postoperative change (Δ) between the without-deficiency and with-deficiency groups.
[b] *P*-value for the comparison of the postoperative values between the without-deficiency and with-deficiency groups. For all tests, $P < 0.05$ was considered statistically significant.
[c] For UL–TVL, LL–TVL, Pog'–TVL, UL–E-line, and LL–E-line, a positive value is for a position in front of the TVL or E-line, and a negative value is for a posterior position.

Table 5. Patients' satisfaction in without deficiency group and with deficiency group

	Without deficiency (n = 10)	**With deficiency (n = 20)**	***P*-value[a]**
Breathing	7.0 (2.8, 9.0)	6.5 (5.0, 8.0)	0.713
Facial esthetics	6.5 (4.8, 9.0)	7.0 (5.0, 8.0)	0.983
Overall satisfaction	6.0 (1.8, 8.3)	7.0 (3.0, 8.8)	0.681

Data presented as median (interquartile range).
[a] *P*-value for the comparison of the without-deficiency and with-deficiency groups; $P<0.05$ was considered statistically significant.

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CHAPTER 3

Maxillomandibular advancement for obstructive sleep apnea: A retrospective prognostic factor study for surgical response

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ABSTRACT

Objective: To identify potential predictors of surgical response to maxillomandibular advancement (MMA) in patients with obstructive sleep apnea (OSA) from the most common clinically available data (patient-related, polysomnographic, cephalometric, and surgical variables).

Methods: This was a retrospective study comprising of consecutive patients who underwent MMA for moderate to severe OSA. Relevant clinical, polysomnographic, cephalometric, and surgical variables were collected as independent variables (predictors). The association of the independent variables with a favorable surgical response to MMA was assessed in univariate and multivariate analyses.

Results: One hundred patients were included (82% male; mean age of 50.5 years; mean apnea hypopnea index [AHI] of 53.1 events/h). The rate of favorable surgical response was 67.0%. Based on multivariate analysis, patients with cardiovascular disease (CVD) had 0.140 times lower odds to favorably respond to MMA (OR:0.140 [0.038, 0.513], $P = 0.003$). For each 1-unit increase in central apnea index (CAI) and superior posterior airway space (SPAS), there were 0.828 and 0.724 times lower odds to favorably respond to MMA (OR: 0.828 [0.687, 0.997], $P = 0.047$; and 0.724 [0.576, 0.910], $P = 0.006$), respectively.

Conclusion: Within the limitations of this study, it is suggested that the surgical outcome of MMA may be less favorable when OSA patients have certain phenotypic characteristics: the presence of CVD, higher CAI, and larger SPAS. If confirmed in future studies, these variables may guide patient selection for MMA.

Keywords: Obstructive sleep apnea; Maxillomandibular advancement; Surgical response; Predictor

INTRODUCTION

Maxillomandibular advancement (MMA) is a skeletal surgery for treatment of obstructive sleep apnea (OSA), which enlarges the upper airway space and reduces the upper airway collapsibility by displacing the maxilla and mandible anteriorly[1, 2]. Despite the fact that MMA has been demonstrated to be a highly effective therapy for moderate to severe OSA, with a surgical success rate of approximately 85%[3, 4], there are still patients who do not respond as favorably as others to MMA. In order to improve preoperative counselling of patients regarding the chance of surgical response, and also to avoid ineffective therapy and unnecessary burden on nonresponders to MMA, it is essential and clinically meaningful to identify the potential responders and nonresponders to MMA prior to the surgery.

Some factors have been reported to correlate with increased surgical response to MMA, mainly in terms of patient-related characteristics, polysomnographic variables, and surgical characteristics. For example, a meta-analysis suggested that younger age, lower baseline weight, lower baseline apnea hypopnea index [AHI], and greater degree of maxillary advancement were associated with increased surgical response[4]. In addition, a few studies also identified radiographic or drug-induced sleep endoscopy (DISE) predictors of surgical response to MMA[5-7], such as cephalometric minimum retrolingual space[6] and complete anteroposterior epiglottic collapse during DISE[7]. However, the evidence on predictors of MMA surgical outcome is still incomplete. Consequently, the clinicians' ability to predict MMA outcome and pre-select suitable candidates for MMA is still limited and mainly based on the clinician's expertise.

For patients undergoing MMA for OSA, a preoperative assessment in daily clinical practice mainly involves medical and sleep history, physical and radiographic examination, a polysomnography (PSG), and sometimes a DISE. Therefore, the aim of this study was to identify the potential predictors of surgical response to MMA in OSA patients, from the most common clinically available data (patient-related, polysomnographic, cephalometric, and surgical variables).

METHODS

Patient selection

This study recruited consecutive patients who underwent MMA for OSA at the Department of Oral and Maxillofacial Surgery, Amsterdam UMC (location AMC), from September 2011 to July 2021. The further inclusion criteria were the following: (1) age 18 years or older; (2) presence of moderate to severe OSA diagnosed by an overnight PSG; (3) continuous positive airway pressure (CPAP) failure, intolerance, or refusal; and (4) patients with a follow-up PSG recording at least three months after MMA. The exclusion criteria were as follows: (1) patients who declined their data to be used for research purposes; (2) previous history of a LeFort I osteotomy and/or a bilateral sagittal split osteotomy (BSSO); and (3) craniofacial and/or syndromic patients.

Variables

All data were retrospectively collected from patients' electronic files. Recorded baseline characteristics included patient-related variables, respiratory variables as measured by PSG, and cephalometric variables. Postoperative PSG variables and cephalometric measurements were also recorded. The surgical characteristics were determined by preoperative and postoperative cephalograms. The potential predictors of MMA surgical response included the recorded baseline characteristics and surgical characteristics.

Patient-related variables

The collected patient-related variables included age, gender, body mass index (BMI), preoperative physical status represented by the ASA (American Society of Anesthesiology) classification system score[8], specific comorbidities (i.e., hypertension, cardiovascular diseases [CVD][9], diabetes mellitus, and chronic obstructive pulmonary disease), previous history of upper airway surgery for OSA, and the number of lost teeth. The tooth loss was categorized as the following: 0-4 lost teeth, 5-8 lost teeth, 9-31 lost teeth, and 32 lost teeth, i.e., being edentulous[10].

Polysomnography

An overnight PSG was performed preoperatively and at least 3 months postoperatively. All respiratory events were scored according to the American Academy of Sleep Medicine (AASM) criteria[11]. The collected baseline PSG variables included AHI, central apnea index (CAI), mixed apnea index (MAI), positional OSA

or non-positional OSA (positional OSA was defined as an AHI at least twice as high in supine position as in non-supine position[12]), 3% oxygen desaturation index (3% ODI), and lowest oxygen saturation (LSAT).

Postoperative AHI, 3% ODI, and LSAT were collected to assess the surgical outcome. According to Sher's criteria, surgical response was defined as "at least 50% AHI reduction following MMA and a postoperative AHI < 20 events/h"[13].

Cephalometry

All patients underwent a standardized lateral cephalogram preoperatively and at least one week postoperatively. All radiographs were taken with the subjects in natural head position with centric occlusion and lips at rest. Cephalometric analysis was performed by one observer using Viewbox software (Viewbox 4, dHAL Software, Kifissia, Greece). Twenty-two cephalometric variables for skeletal and soft tissue, including the cranial base, face height, maxilla and mandible, soft palate, tongue, hyoid, and upper airway, were measured (**Table 1;** Supplementary **Fig. S1** and **Fig. S2**).

To quantify the reliability of the measurements, the same observer repeated the tracings in 20 randomly selected radiographs one month later.

Maxillomandibular advancement

The MMA procedures were completed by two dedicated OSA surgeons and consisted of a LeFort I osteotomy of the maxilla and a BSSO of the mandible. The maxillomandibular complex was advanced and counterclockwise rotation was performed for selected cases. The surgical variables used in this study included degrees of A-point, B-point and pogonion (Pog) advancement, and presence or absence of anticlockwise rotation. The degrees of A-point, B-point, and Pog advancement were determined by comparing preoperative and postoperative distance between A-point to the true vertical plane (TVP), B-point to TVP, and Pog to TVP, respectively. After MMA, cases with a mandibular plane angle change of ≤ -2 degrees were classified as counterclockwise rotation cases[14].

Statistical analysis

All collected data were analyzed with SPSS (IBM SPSS Statistical version 26, IBM Corp., Armonk, NY, USA). Normality was tested using the Shapiro-Wilk test. Continuous variables were reported as mean and standard deviation when normally distributed

or as median and interquartile range when not normally distributed. Categorical variables were reported as frequency and percentage. To compare the preoperative and postoperative continuous variables, the paired-samples t-test or Wilcoxon signed-rank test was applied in cases of normally or non-normally distributed data, respectively. To compare the continuous variables between responders and nonresponders, the independent-samples t-test or Mann-Whitney U test was used in cases of normally or non-normally distributed data, respectively. Chi-square test was used to compare the categorical variables between responders and nonresponders. The intra-observer reliability of the cephalometric measurements was evaluated using intraclass correlation coefficient (ICC).

Logistic regression was used to identify the variable(s) that was (were) predictive of a favorable response to MMA. First, univariate logistic regression analyses were used to assess the association between each independent variable (predictor) and the surgical response, separately. Multivariate logistic regression with backward selection ($P < 0.05$ for removal) was then used to identify the variables that were independently associated with the surgical response. The independent variables included in the multivariate model were those with a *P*-value of < 0.10 in univariate logistic regression. For variables including age, gender, BMI, baseline AHI, and degrees of maxillary and mandibular advancement, they were forced into the multivariate model regardless of their *P*-values in univariate logistic regression because of their potential importance for MMA surgical outcome[4]. Collinearity diagnostics test was performed using the variance inflation factors (VIF) cutoff value of 5; a variable(s) with VIF greater than 5 was excluded from the multivariate model. Complete case analysis was used to handle the missing values for logistic analysis. A *P*-value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 111 patients underwent MMA for obstructive sleep apnea (OSA). Of these, 100 patients (82% male) were included in this study. The reasons for exclusion from the study were as follows: no follow-up PSG available (n = 4), rejected their data to be used for research (n = 3), mild OSA (n = 3), and craniofacial and/or syndromic patient

(n = 1). Participants were middle aged (50.5 ± 9.9 years) and overweight (BMI = 29.8 ± 4.2 kg/m^2), with a mean baseline AHI of 53.1 ± 21.2 events/h.

Surgical outcome

The mean degrees of A-point, B-point, and Pog advancement were 7.2 ± 2.3 mm, 9.8 ± 4.2 mm, and 9.8 ± 5.1 mm, respectively. The postoperative PSGs were performed 4.0 (3.0-6.0) months after MMA. At the time of postoperative PSG, the mean BMI of the patients was 29.1 ± 4.5 kg/m^2. The major outcomes of the MMA surgery in the total population are shown in **Table 2**. The median AHI was significantly reduced from 51.7 (36.8-68.5) events/h to 12.9 (5.9-23.1) events/h ($P < 0.001$). A favorable surgical response was achieved in 67 of 100 patients (67%), and 19 patients (19%) had an AHI of < 5 events/h postoperatively. The preoperative and postoperative PSG values and upper airway measurements in responders and nonresponders are presented in Supplementary **Table S1**.

Baseline and surgical characteristics and surgical response

Compared to responders, the occurrences of hypertension and CVD were significantly higher in nonresponders ($P = 0.003$ and 0.001, respectively). Preoperative CAI was significantly higher in nonresponders ($P = 0.011$) (**Table 3**). ICC of the cephalometric analysis ranged from 0.859-0.998, which indicated an excellent intra-observer reliability[15]. Of the cephalometric variables, nonresponders had a significantly larger superior posterior airway space (SPAS; $P = 0.002$) than responders (**Table 4**). There were no significant differences between responders and nonresponders in the other baseline characteristics. In terms of surgical characteristics, no significant difference was found between responders and nonresponders (**Table 4**).

Prediction of surgical response

The univariate analyses revealed six independent variables with a *P*-value < 0.1 (Supplementary **Table S2**). After collinearity diagnostics test, all the six variables were included in the multivariate model, including age, hypertension, CVD, CAI, ANB, and SPAS (**Table 5**).

After adjusting for the covariables (gender, BMI, AHI, and degrees of maxillary and mandibular advancement), the multivariate model revealed that the independent factors associated with surgical response were CVD, CAI, and SPAS. Patients with the presence of CVD had 0.140 times lower odds to respond favorably to MMA (OR: 0.140

[0.038, 0.513]; *P* = 0.003) compared with those without. For each 1-unit increase in CAI, there was 0.828 times lower odds to respond favorably to MMA (OR: 0.828 [0.687, 0.997]; *P* = 0.047). For each 1-unit increase in SPAS, there was 0.724 times lower odds to respond favorably to MMA (OR: 0.724 [0.576, 0.910]; *P* = 0.006).

DISCUSSION

The present study aimed to investigate if the most common clinically available data, i.e., patient-related, polysomnographic, cephalometric, and surgical variables, have predictive value on MMA surgical outcome. Our main finding was that among baseline and surgical characteristics, cardiovascular disease (CVD), central apnea index (CAI), and superior posterior airway space (SPAS) were the independent predictors of response to MMA: the presence of CVD is indicative of non-response, and CAI and SPAS are inversely related to a favorable response.

Notably, in the present study, the overall success rate of MMA – 67.0% – was lower than that reported in previous studies[3], which ranged from 70 to 100%. One probable reason for this difference in the success rate between the present study and previous studies is that patients recruited in our institute for MMA have been refractory to multiple therapies (e.g., CPAP, mandibular advancement device, upper airway surgery), or were considered poor candidates for upper airway surgery for various reasons (e.g., central and mixed apneas > 25% of the total AHI[16], multilevel complete collapse during DISE[17]). Thus, for some of our patients, there could be a complex interplay between anatomical and non-anatomical traits in OSA pathogenesis, which might have led to the relatively low success rate in our study. In addition, although baseline DISE was not performed in all the patients, over half of the study population (65/100) received DISE, 52 of whom presented with epiglottic collapse. A recent study from Kastoer et al. suggested that MMA surgery may not be an effective therapy for epiglottic collapse[18].

Prior work has suggested that OSA is associated with CVD[19, 20]. In a recent study consisting of 1717 patients with moderate to severe OSA, the prevalence of CVD was 52%[20]. In the present study, CVD also affects 35% of our study population (26 patients with coronary heart disease, six patients with cerebrovascular disease, and three patients with both coronary heart disease and cerebrovascular disease; seven

of these patients had heart failure), which further supports the notion that CVD is highly prevalent in patients with OSA. Notably, our study is the first to show that the presence of CVD in OSA patients is independently associated with non-response to MMA. We inferred that OSA with coexisting CVD may represent a subtype involving a complex interaction between anatomical and non-anatomical causes of OSA that cannot be fully resolved by MMA. Currently, only very limited evidence can partially support our inference. It has been suggested that chronic hypoxemia and/or high left atrial pressure in heart failure could yield an elevated loop gain via increases in chemosensitivity[21]. Additionally, the increased fluid retention and nocturnal rostral fluid shift in heart failure could narrow the upper airway and increase the extraluminal tissue pressure[22]. In this study population, however, the post-hoc chi-square test showed that there is no significant difference in the percentage of heart failure between responders and nonresponders (6.0% (4/67) vs 9.1% (3/33), $P = 0.874$). Further work should be performed to investigate the underlying pathophysiological mechanism of OSA with coexisting CVD for personalized treatment. Additionally, it is important to take into account the duration of CVD for its severity and to use such severity as an element for subgrouping in order to investigate the contribution of CVD to the surgical outcome of MMA. However, among the 35 patients with CVD, the duration of CVD is only available in 7 patients (10.1 ± 3.9 years, range 6-16 years), which prevents us from further analysis of those patients. Future investigations are necessary to confirm our finding and to explore the association between duration of CVD and MMA surgical response.

In clinical practice, it is not uncommon that individuals with OSA exhibit some proportion of central and/or mixed events, leading to a dilemma in the selection of the most appropriate OSA treatment. Our study demonstrated that a higher preoperative CAI was independently associated with non-response to MMA. This finding is supported by a previous study by Makovey et al.[5], which found that the mean pre-MMA CAI in their failure group was significantly higher than that in their success group (5.7 events/h vs 0.6 events/h; $P = 0.005$). The heterogeneity of pure OSA (i.e., 100% of apneas are obstructive) and predominant OSA (i.e., coexisting obstructive and central apneas, and 50% < obstructive apneas < 100%) has been investigated previously[23]. It was suggested that the pure OSA patient group and predominant OSA patient group have equally elevated upper airway collapsibility (i.e., critical closing pressure [Pcrit]); however, the predominant OSA patients differed from the pure OSA patients in showing less breathing control stability[23]. The finding

that OSA patients with relatively higher baseline CAI are less likely respond favorably to MMA also indicates that in these patients breathing control instability may play a significant role in the development of obstructive events. Recently some studies have suggested that breathing control instability (high loop gain) promotes treatment failure on oral appliance or upper airway stimulation for patients with OSA[24-26]. Future research is required to determine whether treatment for central respiratory instability in predominant OSA patients may help relieve the obstructive events.

So far, little evidence is available on the predictive value of cephalometric variables in terms of surgical response to MMA in OSA patients. In this study, we have included parameters of craniofacial and upper airway morphology such as maxillary and mandibular position, face height, soft palate, and tongue, which have not been assessed together in previous studies on surgical response to MMA. This patient cohort presented only one cephalometric variable that is independently related to MMA surgical response, i.e., SPAS. We found that larger SPAS was independently associated with non-response to MMA. This finding is in line with that in a study by Teitelbaum et al.[6]. Their study showed that the minimal SPAS in their MMA success group was significantly narrower than that in their MMA failure group (4.6 ± 1.3 mm vs 7.2 ± 1.7mm, $P = 0.009$). There are several possible explanations for our finding. First and foremost, in this study cephalograms were taken with the patients awake in upright position. Most of skeletal cephalometric parameters such as cranial base and mandibular length could completely reflected the condition during sleep as they are stable and independent of posture and sleep state, whereas the skeletal parameters that could be affected by mandibular movement (e.g., SNB, ANB) and soft tissue parameters (e.g., soft palate, pharyngeal space) might not. As a consequence, the value of SPAS, as well as some other cephalometric measures, in predicting surgical response to MMA might have been over- or underestimated. Secondly, it has been suggested that airway shape may be a predisposing factor for the development of OSA; patients with OSA are likely to have an elliptical airway with the long axis oriented anteroposteriorly (A-P), and this A-P orientation may adversely affect the airway muscle function which results in airway collapse during sleep[27]. We hypothesize that the OSA patients with larger SPAS are more likely to present with A-P airway orientation. Several previous studies have shown that after MMA there were significant increases in both lateral and A-P airway diameters, and the ratio of A-P and lateral airway dimension tended to be higher[28, 29]. This indicates that MMA surgery may actually exacerbate the A-P airway orientation in some patients,

leading to a less beneficial surgical outcome. Of note, MMA can not only alter the upper airway morphology, but also increase the pharyngeal wall tension[30]. The latter element, i.e., pharyngeal wall tension, was not evaluated and therefore not weighed in this study. Lastly, for OSA patients with a larger pharyngeal airway space, there is a higher possibility that non-anatomical contributors play a more prominent role in the pathogenesis of OSA, which may not be treated with MMA. The predictive value of SPAS for MMA surgical outcome needs further investigation. Furthermore, the predictive value of 3D upper airway parameters (e.g., volume, cross-sectional area) should be also explored.

It is interesting to note that several other predictors recognized previously were found not to be predictive of surgical response in our study, mainly including lower baseline AHI, lower baseline BMI, and larger degree of maxillary advancement[4]. Currently, there is still a question as whether these factors could predict MMA surgical response. In a study from Goodday et al.[31], the efficacy of MMA was evaluated in 13 OSA patients with an AHI higher than 100 events/h, and a favorable surgical response was achieved in 10 of those patients. The authors concluded that MMA was highly effective for patients with extremely severe OSA. Of note, although AHI is currently the most widely used measure of OSA severity, there is a growing recognition in its limitation to predict clinical consequences of OSA and response to OSA treatment[32]. Recently some other alternative measures of OSA severity have been proposed, such as apnea-hypopnea event duration[33] and hypoxic burden[34]. However, our study did not analyze such PSG parameters because these relatively novel measures were not available in the PSG reports of our patients. Future research should explore the value of these alternative measures in predicting response to MMA. Besides, due to the fact that in the study by Goodday et al.[31], eight of nine patients with available BMI values were obese (BMI range 31.2-61.3 kg/m^2) before surgery, and all but one remained obese (BMI range 29-53.9 kg/m^2) after surgery, they assumed that BMI did not appear to influence changes in AHI. With regard to the maxillary advancement, multiple studies have found no correlation between degree of maxillary advancement and a reduction in AHI[35, 36]. Increased airway volume following MMA has been considered to be necessary for improving OSA[28, 37], while Chang et al. reported that there was a plateau effect for the airway volume increase as a result of maxillary advancement[38]. In addition to the potential predictors mentioned above, some other factors of interest to clinicians were also investigated in terms of predicting MMA outcome. For example, tooth loss may be an independent risk factor for OSA[10], but

few evidence is available on the association between the number of lost teeth and treatment outcome for OSA[39]. This study is the first to suggest that MMA outcome is not significantly related to number of lost teeth. Taken together, more research is required to recognize which parameters can reliably predict the surgical response, and thus should be included in the patient selection procedure of MMA for OSA.

The study results should be interpreted with caution due to certain limitations. First, it was a retrospective study, whereas a prospective study would be preferred allowing for better control of the data. Second, our cohort consisted predominantly of middle-aged, overweight males with severe OSA, thus the results may be limited to this patient profile. Furthermore, as we have stated before, given those relatively novel PSG measures of OSA severity (e.g., hypoxic burden) were absent in PSG reports of our patients, such parameters were not included in the analysis. This may also limit the generalizability of our findings. Lastly, the cephalograms were obtained with the patient awake in a standard upright position. Some measurement results, especially the soft tissue measurements, may thus not represent the condition during sleep. This may explain why most of the measurements of upper airway structures cannot be implicated in the surgical outcome. However, from the aspects of cost and/or convenience, an upright cephalogram remains an important imaging technique to evaluate the craniofacial and upper airway anatomy.

CONCLUSION

Within the limitations of the study, it is suggested that the presence of cardiovascular disease, higher central apnea index, and larger superior posterior airway space are independently associated with non-response to MMA for OSA. Our results may further support the concept that OSA is a heterogeneous disorder with multifactorial pathophysiological causes, which highlights the importance of evolving different OSA phenotypes and thereby developing personalized treatment.

Table 1. Overview of cephalometric variables and definitions

	Variable	Definition
Cranial base	S-N	Distance between S and N
	N-S-Ba	Angle from N to S to Ba
Face height	ATFH	Distance between N and Me
	ALFH	Distance between ANS and Me
	PTFH	Distance between S and Go
	MP-SN	Inclination of the mandibular plane in relation to the SN plane
Maxilla and mandible	SNA	Angle from S to N to A
	SNB	Angle from S to N to B
	ANB	Angle from A to N to B
	Maxillary length	Distance between ANS and PNS
	Mandibular corpus length	Distance between Go and Me
Soft palate	SPL	Distance between PNS and UT
	SPT	Maximal diameter of soft palate perpendicular to PNS-UT line
Tongue	TGL	Tongue length as the distance between TT and Eb
	TGH	Maximum tongue height perpendicular to TT-Eb line
Hyoid bone	H-S	Distance between H and S
	H-MP	Distance between H and MP
	H-C3	Distance between H and C3
Upper airway	UAL	Upper airway length as distance between PNS to Eb
	SPAS	Width of airway along parallel line to Go-B line at the level of the midpoint of UT and PNS
	MAS	Width of airway along parallel line to Go-B line through UT
	IAS	Width of airway along Go-B line
Surgical movement	A-TVP	Distance between A to TVP
	B-TVP	Distance between B to TVP
	Pog-TVP	Distance between Pog to TVP

A, A-point (subspinale); ALFH, anterior lower face height; ANS, anterior nasal spine; ATFH, anterior total face height; B, B-point (supramentale); Ba, basion; C3, the most anterior-inferior point of the third cervical vertebra; Eb, epiglottis base; Go, gonion; H, hyoid point; IAS, inferior airway space; MAS, middle airway space; Me, menton; MP, mandibular plane; N, nasion; PNS, posterior nasal spine; Pog, pogonion; PTFH, posterior total face height; S, sella; SN, sella-nasion line; SPAS, superior posterior airway space; SPL, soft palate length; SPT, soft palate thickness; TGH, tongue height; TGL, tongue length; UAL, upper airway length; UT, uvula tip; THP, true horizontal plane; TT, tongue tip; TVP, true vertical plane.

Table 2. Treatment outcome of maxillomandibular advancement in the total population

Variable	Preoperative (n = 100)	Postoperative (n = 100)	*P*-value
AHI, events/h	51.7 (36.8-68.5)	12.9 (5.9-23.1)	**<0.001**
ODI 3%, events/h	51.0 (34.3-66.6)	21.2 (10.5-30.2)	**<0.001**
LSAT, %	79.5 (73.0-84.0)	86.0 (82.0-89.0)	**<0.001**

AHI, apnea hypopnea index; LSAT, lowest oxygen saturation; n, number of patients; ODI 3%, 3% oxygen desaturation index.
Data presented as median (interquartile range).
P-value for the comparison of the preoperative versus postoperative values; $P < 0.05$ was considered statistically significant.

Table 3. Patient-related variables and polysomnographic variables in responders and nonresponders

Variable	Responder (n = 67)	Nonresponder (n = 33)	*P*-value
Patient-related variables			
Age, years	49.0 (41.0-59.0)	54.0 (45.5-58.0)	0.162
Male, n (%)	54 (80.6)	28 (84.8)	0.603
BMI, kg/m^2	29.7 (27.4-32.4)	29.8 (28.2-32.0)	0.652
ASA-score, n (%)			
I	17 (25.4%)	6 (18.2%)	0.487
II	38 (56.7%)	18 (54.5%)	
III	12 (17.9%)	9 (27.3%)	
Hypertension, n (%)			
Absence	49 (73.1)	14 (42.4)	**0.003**
Presence	18 (26.9)	19 (57.6)	
CVD, n (%)			
Absence	51 (76.1)	14 (42.4)	**0.001**
Presence	16 (23.9)	19 (57.6)	
DM, n (%)			
Absence	58 (86.6)	29 (87.9)	1.000
Presence	9 (13.4)	4 (12.1)	
COPD, n (%)			
Absence	64 (95.5)	31 (94.0)	1.000
Presence	3 (4.5)	2 (6.0)	
Previous upper airway surgery, n (%)			
Absence	40 (59.7)	20 (60.6)	0.931
Presence	27 (40.3)	13 (39.4)	
Lost teeth, n (%)			
0-4 lost teeth	15 (22.4)	4 (12.1)	0.527
5-8 lost teeth	28 (41.8)	13 (39.4)	
9-31 lost teeth	16 (23.9)	10 (30.3)	
32 lost teeth	8 (11.9)	6 (18.2)	

Table 3. continued

Variable	Responder (n = 67)	Nonresponder (n = 33)	*P*-value
Polysomnographic variables			
AHI, events/h	54.2 ± 20.9	50.9 ± 21.9	0.474
CAI, events/h	0.4 (0.2-1.4)[a]	1.5 (0.4-6.3)[b]	**0.011**
MAI, events/h	1.9 (0.2-9.1)[a]	5.6 (0.8-14.6)[b]	0.129
Positional/non-positional OSA, n (%)			
Positional OSA	22 (43.1)	11 (37.9)	0.649
Non-positional OSA	29 (56.9)	18 (62.1)	
ODI 3%, events/h	52.4 ± 22.3	51.5 ± 21.0	0.866
LSAT, %	79 (71.0-84.0)	80 (76.0-85.0)	0.236

AHI, apnea hypopnea index; ASA, American Society of Anesthesiology; BMI, body mass index; CAI, central apnea index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; LSAT, lowest oxygen saturation; MAI, mixed apnea index; n, number of patients; ODI 3%, 3% oxygen desaturation index; OSA, obstructive sleep apnea.
Continuous data presented as mean ± standard deviation or median (interquartile range), categorical data presented as number with percentage.
P-value for the comparison of the responders versus nonresponders; $P<0.05$ was considered statistically significant.
[a] Number of patients = 55; [b] Number of patients = 29.

Table 4. Cephalometric variables and surgical variables in responders and nonresponders

Variable	Responder	Nonresponder	*P*-value
Cephalometric variables (responder: n = 64; nonresponder: n = 31)			
Cranial base			
S-N, mm	70.0 ± 3.6	70.6 ± 4.0	0.408
N-S-Ba, degree	130.0 (126.5-132.2)	131.2 (128.2-134.5)	0.076
Face height			
ATFH, mm	122.0 ± 7.9	124.5 ± 9.7	0.197
ALFH, mm	71.6 ± 7.0	73.7 ± 8.3	0.213
PTFH, mm	80.0 ± 7.9	82.2 ± 8.1	0.222
MP-SN, degree	36.7 ± 8.4	36.7 ± 10.9	0.979
Maxilla and mandible			
SNA, degree	80.3 ± 3.6	80.0 ± 4.0	0.760
SNB, degree	75.1 ± 4.1	76.5 ± 4.7	0.149
ANB, degree	5.2 ± 2.6	3.7 ± 4.2	0.093
ANS-PNS, mm	53.0 ± 3.4	52.8 ± 4.2	0.745
Go-Me, mm	65.0 ± 6.4	66.7 ± 5.9	0.226
Soft palate			
SPL, mm	39.6 ± 7.0	40.4 ± 5.9	0.561
SPT, mm	9.9 (8.6-11.4)	11.0 (9.4-11.9)	0.096
Tongue			

Table 4. continued

Variable	Responder	Nonresponder	*P*-value
TGL, mm	84.0 (79.8-87.3)	83.7 (79.7-88.1)	0.795
TGH, mm	36.5 ± 3.9	35.2 ± 4.6	0.156
Pharyngeal dimensions and hyoid bone position			
UAL, mm	76.8 ± 6.4	78.8 ± 7.7	0.249
SPAS, mm	7.3 (5.5-9.2)	8.8 (7.6-11.0)	**0.002**
MAS, mm	9.9 ± 2.6	10.8 ± 3.4	0.172
IAS, mm	8.9 ± 3.1	9.2 ± 3.0	0.625
H-S, mm	118.0 ± 9.5	120.7 ± 9.6	0.197
MP-H, mm	25.4 ± 5.5	25.9 ± 5.9	0.682
H-C3, mm	39.4 ± 4.8	41.4 ± 6.7	0.105
Surgical variables (responder: n = 63; nonresponder: n = 29)			
Advancement degree of A-point, mm	7.0 ± 2.5	7.4 ± 1.9	0.485
Advancement degree of B-point, mm	10.0 ± 4.3	9.6 ± 4.0	0.678
Advancement degree of Pog, mm	9.8 ± 5.2	9.9 ± 5.2	0.909
Counterclockwise rotation, n (%)			
Absence	29 (46.0)	10 (34.5)	0.298
Presence	34 (54.0)	19 (65.6)	

A, A-point; ALFH, anterior lower face height; ANS, anterior nasal spine; ATFH, anterior total face height; B, B-point; Ba, basion; C3, the most anterior-inferior point of the third cervical vertebra; Go, gonion; H, hyoid bone; IAS, inferior airway space; MAS, middle airway space; Me, menton; mm, millimeter; MP, mandibular plane; N, nasion; n, number of patients; PNS, posterior nasal spine; PTFH, posterior total face height; S, sella; SPL, soft palate length; SPAS, superior posterior airway space; SPT, soft palate thickness; TGL, tongue length; TGH, tongue height; UAL, upper airway length.

Continuous data presented as mean ± standard deviation or median (interquartile range), categorical data presented as number with percentage.

P-value for the comparison of the responders versus nonresponders; $P<0.05$ was considered statistically significant.

Table 5. Logistic regression model for predicting surgical response to maxillomandibular advancement

Independent variable	Univariate analysis				Multivariate analysis (adjusted for the covariables: gender, BMI, AHI, advancement of A-point, and advancement of B-point)			
	Coefficient B	SE	OR (95%CI)	*P*-value	Coefficient B	SE	OR (95%CI)	*P*-value
Age	-0.041	0.023	0.959 (0.917-1.003)	0.070				
Hypertension								
Absence	Ref.							
Presence	-1.307	0.447	0.271 (0.113-0.650)	0.003				
CVD								
Absence	Ref.				Ref.			**0.003**
Presence	-1.465	0.454	0.231 (0.095-0.563)	0.001	-1.964	0.662	0.140 (0.038-0.513)	
CAI	-0.191	0.080	0.826 (0.707-0.966)	0.017	-0.189	0.095	0.828 (0.687-0.997)	**0.047**
ANB	0.144	0.074	1.155 (1.000-1.334)	0.051				
SPAS	-0.242	0.083	0.785 (0.666-0.924)	0.004	-0.323	0.117	0.724 (0.576-0.910)	**0.006**

ANB, angle from A-point to nasion to B-point; CAI, central apnea index; CI, confidence interval; CVD, cardiovascular disease; OR, odds ratio; Ref., reference category; SE, standard error; SPAS, superior posterior airway space.

SUPPLEMENTARY MATERIAL

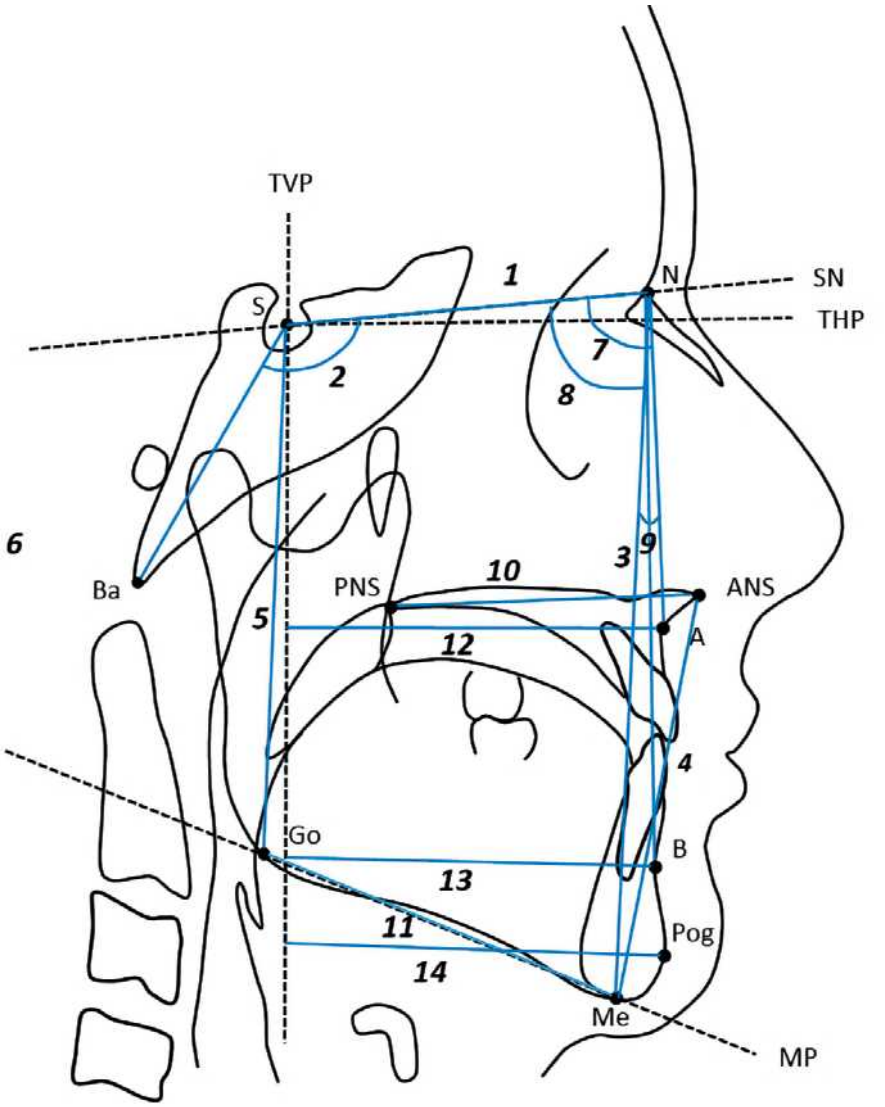

Fig. S1. Landmarks, reference lines, and the corresponding hard tissue variables used in the study. Landmarks: A, A-point (subspinale); ANS, anterior nasal spine; B, B-point (supramentale); Ba, basion; Go, gonion; Me, menton; N, nasion; PNS, posterior nasal spine; Pog, pogonion; S, sella. Reference lines: MP, mandibular plane; SN, sella-nasion line; THP, true horizontal plane, plane through point S at 7° clockwise from SN plane; TVP, true vertical plane, plane through point S perpendicular to THP. Hard tissue variables: 1, S-N; 2, N-S-Ba; 3, ATFH (anterior total face height, N-Me); 4, ALFH (anterior lower face height, ANS-Me); 5, PTFH (posterior total face height, S-Go); 6, MP-SN; 7, SNA; 8, SNB; 9, ANB; 10, maxillary length (ANS-PNS); 11, mandibular corpus length (Go-Me); 12, A-TVP; 13, B-TVP; 14, Pog-TVP.

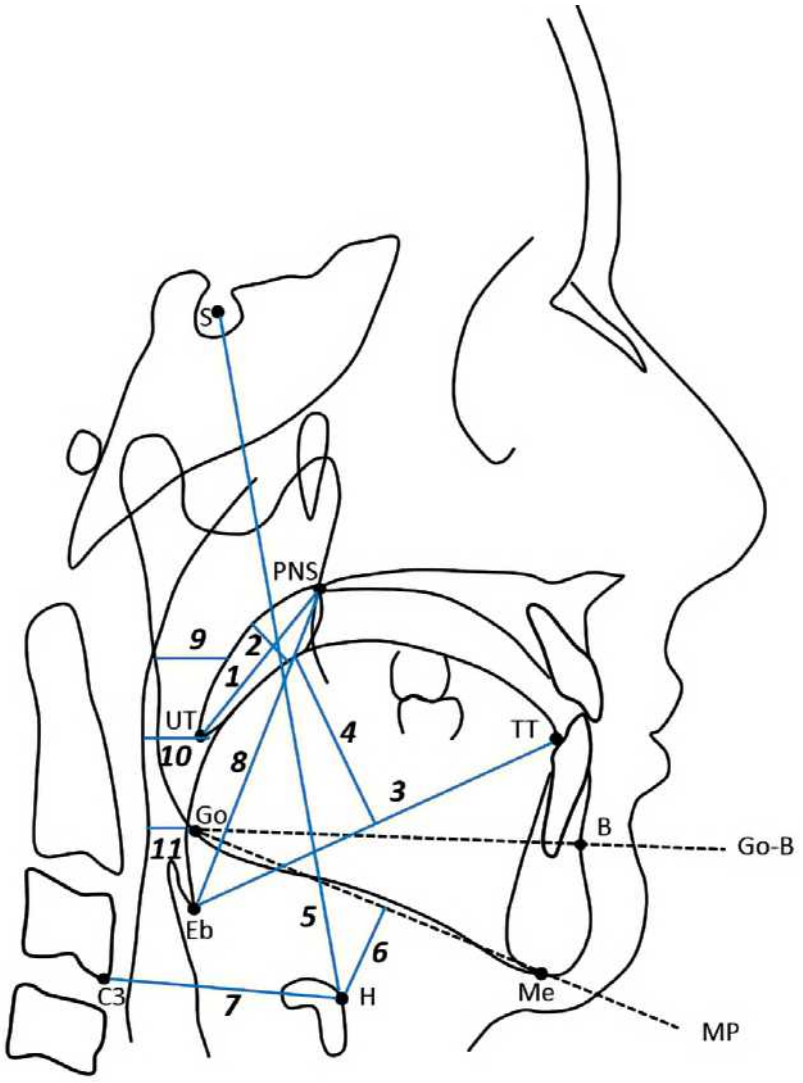

Fig. S2. Landmarks, reference lines, and the corresponding soft tissue variables used in the study. Landmarks: B, B-point (supramentale); C3, the most anterior-inferior point of the third cervical vertebra; Eb, epiglottis base; Go, gonion; H, hyoid point; Me, menton; UT, uvula tip; PNS, posterior nasal spine; TT, tongue tip. Reference lines: Go-B, plane between Go and B; MP, mandibular plane. Soft tissue variables: 1, SPL (soft palate length); 2, SPT (soft palate thickness); 3, TGL (tongue length); 4, TGH (tongue height); 5, H-S; 6, H-MP; 7, H-C3; 8, UAL (upper airway length); 9, SPAS (superior posterior airway space); 10, MAS (middle airway space); 11, IAS (inferior airway space).

Table S1. Preoperative and postoperative polysomnographic values and upper airway measurements in responders and nonresponders

Variables	Responder (n = 67)	Nonresponder (n = 33)	*P*-value
Polysomnographic variables			
Preop AHI, events/h	51.8 (37.1-68.6)	51.6 (35.2-69.3)	0.474
Postop AHI, events/h	8.3 (4.5-13.0)	33.0 (23.0-42.9)	**<0.001**
Preop ODI 3%, events/h	48.7 (35.3-68.9)	57.0 (29.5-66.0)	0.866
Postop ODI 3%, events/h	11.2 (9.2-20.7)	33.6 (25.8-50.3)	**<0.001**
Preop LSAT, %	79 (71.0-84.0)	80 (76.0-85.0)	0.236
Postop LSAT, %	87.5 (82.0-89.3)	85.0 (82.0-87.0)	**0.019**
Upper airway measurements			
Preop UAL, mm	76.8 ± 6.4	78.8 ± 7.7	0.249
Postop UAL, mm	75.1 ± 7.5	77.5 ± 9.5	0.189
Preop SPAS, mm	7.3 (5.5-9.2)	8.8 (7.6-11.0)	**0.002**
Postop SPAS, mm	12.5 (10.4-15.3)	14.0 (11.7-16.1)	0.143
Preop MAS, mm	10.0 (7.9-12.0)	10.8 (8.0-13.5)	0.172
Postop MAS, mm	14.9 (12.8-18.4)	17.4 (12.8-20.0)	0.202
Preop IAS, mm	8.4 (6.7-11.5)	8.9 (6.5-11.3)	0.625
Postop IAS, mm	13.6 (10.9-16.0)	15.3 (11.5-17.5)	0.266

AHI, apnea hypopnea index; IAS, inferior airway space; LSAT, lowest oxygen saturation; MAS, middle airway space; n, number of patients; ODI 3%, 3% oxygen desaturation index; Postop, postoperative; Preop, preoperative; SPAS, superior posterior airway space; UAL, upper airway length.
Data presented as mean ± standard deviation or median (interquartile range).
P-value for the comparison of the responders versus nonresponders; $P<0.05$ was considered statistically significant.

Table S2. Univariate analysis of patient-related, polysomnographic, cephalometric, and surgical variables for predicting surgical response to maxillomandibular advancement

Variable	Coefficient B	SE	OR (95%CI)	*P*-value
Patient-related variables				
Age, years	-0.041	0.023	0.959 (0.917-1.003)	**0.070**
Gender				
Female	Ref.			
Male	-0.299	0.575	0.742 (0.240-2.291)	0.604
BMI, kg/m^2	-0.005	0.051	0.996 (0.901-1.100)	0.930
ASA-score				
I	Ref.			
II	-0.294	0.554	0.745 (0.251-2.209)	0.596
III	-0.754	0.648	0.471 (0.132-1.676)	0.245
Hypertension				
Absence	Ref.			
Presence	-1.307	0.447	0.271 (0.113-0.650)	**0.003**
CVD				
Absence	Ref.			
Presence	-1.465	0.454	0.231 (0.095-0.563)	**0.001**

Table S2. continued

Variable	Coefficient B	SE	OR (95%CI)	*P*-value
DM				
Absence	Ref.			
Presence	0.118	0.643	1.125 (0.319-3.963)	0.855
COPD				
Absence	Ref.			
Presence	-0.319	0.939	0.727 (0.115-4.574)	0.734
Previous upper airway surgery				
Absence	Ref.			
Presence	0.038	0.435	1.038 (0.443-2.434)	0.931
Lost teeth				
0-4 lost teeth	Ref.			
5-8 lost teeth	-0.555	0.655	0.574 (0.159-2.074)	0.397
9-31 lost teeth	-0.852	0.692	0.427 (0.110-1.657)	0.219
32 lost teeth	-1.034	0.780	0.356 (0.077-1.640)	0.185
Polysomnographic variables				
AHI, events/h	0.007	0.010	1.007 (0.987-1.028)	0.470
CAI, events/h	-0.191	0.080	0.826 (0.707-0.966)	**0.017**
MAI, events/h	-0.013	0.016	0.987 (0.957-1.018)	0.408
Positional/non-positional OSA				
Non-positional OSA	Ref.			
Positional OSA	0.216	0.476	1.241 (0.489-3.154)	0.650
ODI 3%, events/h	0.002	0.011	1.002 (0.980-1.025)	0.864
LSAT, %	-0.033	0.026	0.967 (0.919-1.018)	0.967
Cephalometric variables				
Cranial base				
S-N, mm	-0.049	0.059	0.952 (0.848-1.069)	0.404
N-S-Ba, degree	0.002	0.005	1.002 (0.993-1.012)	0.627
Face height				
ATFH, mm	-0.035	0.027	0.966 (0.917-1.018)	0.197
ALFH, mm	-0.038	0.030	0.963 (0.907-1.022)	0.212
PTFH, mm	-0.036	0.030	0.964 (0.910-1.022)	0.221
MP-SN, degree	0.001	0.025	1.001 (0.954-1.050)	0.979
Maxilla and mandible				
SNA, degree	0.018	0.060	1.019 (0.906-1.145)	0.757
SNB, degree	-0.076	0.053	0.927 (0.836-1.028)	0.150
ANB, degree	0.144	0.074	1.155 (1.000-1.334)	**0.051**
ANS-PNS, mm	0.020	0.060	1.020 (0.907-1.147)	0.742
Go-Me, mm	-0.044	0.036	0.957 (0.892-1.027)	0.225
Soft palate				
SPL, mm	-0.020	0.033	0.981 (0.919-1.047)	0.557
SPT, mm	-0.086	0.086	0.918 (0.775-1.086)	0.318

Table S2. continued

Variable	Coefficient B	SE	OR (95%CI)	*P*-value
Tongue				
TGL, mm	-0.029	0.033	0.971 (0.911-1.035)	0.371
TGH, mm	0.076	0.054	1.079 (0.971-1.199)	0.158
Pharyngeal dimensions and hyoid bone position				
UAL, mm	-0.038	0.033	0.963 (0.903-1.027)	0.248
SPAS, mm	-0.242	0.083	0.785 (0.666-0.924)	**0.004**
MAS, mm	-0.105	0.077	0.900 (0.773-1.047)	0.173
IAS, mm	-0.036	0.072	0.965 (0.837-1.112)	0.621
H-S, mm	-0.031	0.024	0.969 (0.924-1.016)	0.196
MP-H, mm	-0.016	0.040	0.984 (0.910-1.063)	0.678
H-C3, mm	-0.066	0.042	0.936 (0.863-1.015)	0.110
Surgical variables				
Advancement degree of A-point, mm	-0.068	0.097	0.934 (0.772-1.130)	0.481
Advancement degree of B-point, mm	0.024	0.057	1.024 (0.916-1.146)	0.675
Advancement degree of Pog, mm	-0.005	0.046	0.995 (0.910-1.088)	0.908
Counterclockwise rotation				
Absence	Ref.			
Presence	-0.311	0.476	0.733 (0.288-1.862)	0.513

A, A-point; AHI, apnea hypopnea index; ALFH, anterior lower face height; ANS, anterior nasal spine; ASA, American Society of Anesthesiology; ATFH, anterior total face height; B, B-point; Ba, basion; BMI, body mass index; C3, the most anterior-inferior point of the third cervical vertebra; CAI, central apnea index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; Go, gonion; H, hyoid bone; IAS, inferior airway space; LSAT, lowest oxygen saturation; MAI, mixed apnea index; MAS, middle airway space; Me, menton; mm, millimeter; MP, mandibular plane; N, nasion; ODI 3%, 3% oxygen desaturation index; OR, odds ratio; OSA, obstructive sleep apnea; PNS, posterior nasal spine; PTFH, posterior total face height; Ref., reference category; S, sella; SE, standard error; SPAS, superior posterior airway space;SPL, soft palate length; SPT, soft palate thickness; TGL, tongue length; TGH, tongue height; UAL, upper airway length.

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CHAPTER 4

Evaluation of drug-induced sleep endoscopy as a tool for selecting patients with obstructive sleep apnea for maxillomandibular advancement

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ABSTRACT

Objectives: (1) To investigate if drug-induced sleep endoscopy (DISE) findings are predictive of surgical response for patients undergoing maxillomandibular advancement (MMA) for obstructive sleep apnea (OSA) and (2) to investigate the predictive value of the jaw thrust maneuver during DISE in terms of surgical response to MMA.

Methods: A retrospective cohort study was conducted in patients with OSA who underwent a baseline polysomnography (PSG) and DISE followed by MMA and a 3- to 6-month follow-up PSG between September 1, 2011, and September 30, 2020.

Results: Sixty-four patients with OSA (50 males [78.1%]; mean ± SD age = 51.7 ± 9.5 years; mean ± SD apnea-hypopnea index = 49.0 ± 20.8 events/h) were included. Thirty-nine patients were responders, and 25 were nonresponders. Adjusting for baseline characteristics and surgical characteristics (e.g., age, baseline apnea-hypopnea index, degree of maxillary advancement), patients with complete anteroposterior epiglottic collapse had 0.239 times lower odds for response to MMA (95% confidence interval, 0.059-0.979; $P = 0.047$). No significant relationship was found between complete concentric velum collapse and MMA response. There was no statistically significant association between effect of jaw thrust maneuver during DISE on upper airway patency and treatment outcome of MMA.

Conclusions: This study indicates that DISE is a promising tool to identify patients who will or will not respond to MMA for treating OSA. Patients with complete anteroposterior epiglottic collapse may be less suitable candidates for MMA.

Keywords: Maxillomandibular advancement; Drug-induced sleep endoscopy; Obstructive sleep apnea; Surgical response

INTRODUCTION

Of the surgical options available to patients with obstructive sleep apnea (OSA), maxillomandibular advancement (MMA), a combination of a LeFort I osteotomy with a bilateral sagittal split osteotomy (BSSO), has been shown to be the most effective surgical option for OSA, with the exception of tracheostomy[1]. The reported surgical success rate for MMA is 85.0%[2]. Previous studies have recognized some patient characteristics as predictors of surgical response to MMA – mainly age, weight, and baseline AHI[3, 4] – but there is room for improvement.

Drug-induced sleep endoscopy (DISE), proposed by Croft and Pringle[5] in 1991, is an endoscopic examination performed during pharmacologically induced sleep in order to determine the exact site(s) of upper airway collapse. DISE is a unique and dynamic method for upper airway evaluation in patients with OSA, which can facilitate the treatment decision-making process for OSA. Since DISE plays a substantial role in otolaryngologic upper airway surgery and upper airway stimulation for OSA[6-8], it is therefore of interest to explore its role in identifying suitable candidates for MMA.

Only a few studies have evaluated upper airway collapse patterns using DISE before and after MMA[9, 10]. Of interest, it is suggested that MMA may not be effective in correcting the collapse at the level of epiglottis[10]. All in all, the association between baseline DISE findings and surgical outcome of MMA remains debatable.

Therefore, the aim of this study was to investigate if the sites, patterns, and degrees of upper airway collapse during DISE, along with the individual characteristics, results of other diagnostic modalities, and surgical characteristics, were predictive of surgical response for patients undergoing MMA for treating OSA. We hypothesized that DISE findings could predict the surgical outcome of MMA in OSA patients, and that the presence of epiglottic collapse and complete concentric collapse at the level of the palate (CCCp) may be associated with surgical failure of MMA. In addition, the predictive value of jaw thrust during DISE was also investigated in terms of surgical outcome of MMA.

METHODS

Study participants

This retrospective clinical trial was approved by the Medical Ethical Committee of the Amsterdam University Medical Centers (Amsterdam UMC) (location Academic Medical Center [AMC]) (reference number W19_171 #19.210). All patients were given the option to decline the use of their data in this study.

Consecutive patients with OSA were enrolled in the study if they underwent DISE at the Department of Otolaryngology of OLVG in Amsterdam prior to MMA at the Department of Oral and Maxillofacial Surgery of Amsterdam UMC (location AMC), between September 1, 2011 and September 30, 2020. The further inclusion criteria were as follows: (1) age 18 years or older, (2) presence of OSA (AHI ≥ 5 events/h) diagnosed by polysomnography (PSG) preoperatively, (3) continuous positive airway pressure therapy failure or intolerance, (4) patients who underwent baseline DISE, and (5) patients with follow-up PSG at least 3 months after MMA. The exclusion criteria were (1) patients who declined the use of their data for this study and (2) patients with incomplete data.

Variables

All data were retrospectively collected and recorded in the patients' electronic file. Recorded baseline characteristics were age, sex, body mass index, neck circumference, previous OSA upper airway surgery, respiratory variables as measured by PSG, DISE findings, and cephalometric measurements. Postoperative respiratory variables determined using PSG and postoperative cephalometric measurements were recorded. Degrees of maxillary and mandibular advancement were obtained by preoperative and postoperative cephalometric analysis. Primary outcomes were DISE findings (independent variables) and surgical response (dependent variables). Secondary outcomes of interest were the other baseline characteristics, postoperative PSG variables, and postoperative cephalometric measurements. We adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for reporting in observational studies[11].

Polysomnography

All patients underwent a full-night PSG preoperatively and at least 3 months postoperatively to assess the surgical outcome. The PSG method has been described

in a previous study[12]. All respiratory events were recorded according to the American Academy of Sleep Medicine 2007 criteria[13]. Collected PSG data consisted of AHI, oxygen desaturation index (ODI), and lowest oxygen saturation (LSAT). Surgical response was defined as a postoperative AHI < 20 events/h with > 50% reduction of AHI based on Sher's criteria[14].

Drug-induced sleep endoscopy

A standard DISE procedure was performed by a specific physician experienced in DISE with a trained nurse anesthetist, in a semi-dark and silent outpatient endoscopy room with standard anesthetic equipment[15]. Sedation was induced by intravenous administration of propofol using a target-controlled infusion pump. Proper sedation level was achieved when the patient showed hyporesponsiveness to verbal and tactile stimuli or when the patient began to snore. A fiberoptic laryngoscope was used to visualize the patients' upper airway. The upper airway was assessed starting in a supine position without jaw thrust and subsequently with manually performed jaw thrust. During the jaw thrust, the trained nurse anesthetist gently advanced the patient's mandible. The advancement was estimated to be 5 mm.

The Velum Oropharynx Tongue base Epiglottis (VOTE) system was used to document the DISE findings. Patterns of collapse (anteroposterior, lateral, and concentric) and degrees of collapse (0: no obstruction; 1: partial obstruction; and 2: complete obstruction) were recorded at the most common levels of upper airway obstruction (velum, oropharynx, base of tongue, and epiglottis)[16]. The total VOTE score was calculated as the sum of the collapse degree at each site of obstruction for a maximum score of 8.

During the jaw thrust maneuver, patients were categorized as "total resolution" when upper airway collapse was completely resolved (i.e., total VOTE score was reduced to zero), and as "partial resolution" when collapse was partially resolved (i.e., VOTE score was reduced but larger than zero).

Collected DISE data included levels, patterns and degrees of upper airway collapse in supine position and its corresponding total VOTE score, and categorization of patients during the jaw thrust maneuver.

Maxillomandibular advancement surgery

All patients underwent a standardized MMA procedure by 2 dedicated OSA surgeons, consisting of a LeFort I osteotomy and a BSSO with rigid internal fixation[4]. Additional procedures included genioplasty in five cases and genioglossal advancement in 1 case.

Cephalometric measurements

Preoperative and postoperative cephalometric measurements were performed using the following skeletal landmarks: sella (S), nasion (N), A-point (A) and B-point (B). A true horizontal plane (HP) (plane through point S at 7° clockwise from the SN plane) and vertical plane (plane through point S perpendicular to the HP) were constructed. The measured parameters included SNA, SNB, ANB, advancement degree of the maxilla (i.e., advancement degree of A-point), and advancement degree of the mandible (i.e., advancement degree of B-point) (**Figure 1**)[4].

Data collection and statistical analysis

Statistical analysis was performed using SPSS version 26 (IBM Corp, Armonk, NY, USA). Descriptive statistical analysis was performed for all demographic and outcome variables and reported as mean and standard deviation (SD) for continuous variables and frequency and percentage for categorical variables. Normality was tested using the Shapiro-Wilk test. To compare quantitative variables between responders and nonresponders to MMA, the independent-samples t-test or Mann-Whitney U test was used in cases of normally or nonnormally distributed data, respectively. To compare the preoperative and postoperative values, the paired-samples t-test or Wilcoxon signed-rank test was applied in cases of normally or nonnormally distributed data, respectively. Collapse patterns in DISE findings were compared between responders and nonresponders with the chi-square test or Fisher's exact test.

The association between collapse patterns and surgical response was investigated using logistic regression. In cases of insufficient numbers of events in certain collapse patterns, the DISE findings regarding degree of collapse were recategorized (i.e., "no collapse" vs "collapse"; and "non-complete collapse" vs "complete collapse") to ensure the power of the logistic regression analysis and accuracy of the regression coefficients. When the numbers of events were still small after recategorization, the specific collapse patterns were not included as independent variables. Univariate logistic regression analyses were used to assess the association between each independent

variable and the response to MMA separately. Multivariate logistic regression was used to identify the variables that were independently associated with the response to MMA. The independent variables included in the model were those with *P*-value of < 0.10 in univariate logistic regression. Additionally, the potential confounders consisting of age, gender, BMI, baseline AHI, degree of maxillary advancement, and degree of mandibular advancement were also included in the models[3]. A forward stepwise procedure was used to select the best logistic regression model, and the goodness-of-fit of the model was assessed using the Hosmer-Lemeshow test. A *P*-value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

In total, 101 patients underwent MMA for OSA. Thirty-seven patients who did not undergo baseline DISE were excluded, among whom 2 patients had no postoperative PSG data. Therefore, 64 patients were included. There was no significant difference in baseline characteristics and surgical outcome between patients with and without baseline DISE (see **Table S1** in the supplemental material).

Among the included 64 patients, sixty-two patients (96.9%) had CPAP failure or intolerance, two patients (3.1%) refused to try CPAP, and 29 patients (45.3%) underwent other upper airway surgeries (e.g., uvulopalatopharyngoplasty) prior to MMA. A detailed overview of baseline characteristics is summarized in **Table 1**.

Surgical outcome

After MMA, the mean degree of advancement was 7.1 ± 2.4 mm in maxilla and 9.3 ± 4.3 mm in mandible (**Table 1**). **Table 2** shows the preoperative and postoperative anteroposterior skeletal pattern based on SNA, SNB, and ANB, and PSG variables. Postoperatively, the total mean AHI was significantly decreased from 49.0 ± 20.8 events/h to 16.4 ± 13.3 events/h ($P < 0.001$). In total, 39 patients (60.9%) were responders, and 25 patients (39.1%) were nonresponders.

The baseline characteristics and surgical characteristics in responders and nonresponders are summarized in **Table 1**. No statistically significant difference in any parameter was found between the 2 groups.

Upper airway collapse pattern

An overview of the distribution of levels of upper airway collapse in the present cohort is shown in a Venn diagram (**Figure 2**). As shown, velum collapse was the most commonly present (98.4%), followed by base of tongue (90.6%), epiglottis (84.4%), and oropharynx collapse (51.6%). All patients had multilevel collapse of the upper airway, predominantly a combination of velum, base of tongue, and epiglottic collapse (43.8%), and a combination of velum, oropharyngeal, base of tongue, and epiglottic collapse (35.9%). Fifty-four (84.4%) patients had a complete collapse at multiple levels in the upper airway.

In 64 patients, velum collapse was present either as anteroposterior collapse (n = 42/64; 65.6%) or concentric collapse (n = 21/64; 32.8%). Oropharynx collapse only occurred in lateral configuration, and base of tongue collapse only occurred in anteroposterior pattern. Epiglottis collapse was present either as anteroposterior collapse (n = 53/64; 82.8%) or lateral collapse (n = 1/64; 1.6%).

The mean total degree of obstruction – based on total VOTE score – was 5.8 ± 1.5 in the total population. No significant difference was found between responders and nonresponders in the mean total VOTE score (5.6 ± 1.4 vs 6.2 ± 1.5; $P = 0.079$).

Table 3 presents the upper airway collapse patterns in responders and nonresponders. As shown, responders had a significantly higher occurrence of anteroposterior velum collapse. In contrast, nonresponders had a significantly higher occurrence of concentric velum collapse and complete anteroposterior epiglottic collapse.

Prediction of surgical outcome

In the first model ("no collapse" vs "collapse"), univariate logistic regression showed a significant relationship between response to MMA and anteroposterior velum collapse (odds ratio [OR], 3.611; 95% confidence interval [CI], 1.224-10.654; $P = 0.020$), indicating that patients with the presence of anteroposterior velum collapse had 3.611 times higher odds to respond to MMA; and a significant relationship between nonresponse to MMA and concentric velum collapse (OR, 0.325; 95%CI, 0.110-0.959; $P = 0.042$), indicating that patients with the presence of concentric velum collapse had 0.325 times lower odds to respond to MMA (**Table 4**). No predictor of surgical response was found in multivariate logistic regression when controlling for the confounders.

In the second model ("non-complete collapse" vs "complete collapse"), univariate analysis revealed a significant relationship between MMA response and complete anteroposterior epiglottic collapse (OR, 0.246; 95%CI, 0.027-0.854; *P* = 0.027), indicating that patients with the presence of complete anteroposterior epiglottic collapse had 0.246 times lower odds to respond to MMA (**Table 4**). The association remained significant in multivariate logistic regression (OR, 0.239; 95% CI, 0.059-0.979; *P* = 0.047) when controlling for the confounders, indicating that patients with the presence of complete anteroposterior epiglottic collapse had 0.239 times lower odds to respond to MMA. No other predictor regarding collapse patterns, baseline characteristics, and surgical characteristics was found. The Hosmer-Lemeshow test indicated that the fit of the model was good (*P* > 0.999).

In this study population, patients were categorized as "total resolution" (n = 16) and as "partial resolution" (n = 48) with jaw thrust. The rates of surgical response in "total resolution" group and "partial resolution" group were 75% and 56.3% respectively, while logistic analysis revealed that there was no significant association between change of upper airway collapse with jaw thrust and response to MMA (*P* = 0.190).

Treatment outcome in patients with and without complete anteroposterior epiglottic collapse

In patients with complete anteroposterior epiglottic collapse (n = 43), the mean AHI decreased from 47.1 ± 20.8 events/h to 19.2 ± 14.7 events/h compared with 52.9 ± 20.7 events/h to 10.6 ± 6.8 events/h in patients without complete anteroposterior epiglottic collapse (n = 21). The mean reduction in AHI following MMA in patients with complete anteroposterior epiglottic collapse was 27.9 ± 20.9 events/h vs 42.3 ± 23.1 events/h in patients without complete anteroposterior epiglottic collapse (*P* = 0.015). The response rates were 51.1% and 81.0% in patients with and without complete anteroposterior epiglottic collapse, respectively.

DISCUSSION

This study is the first to determine whether patients' response to MMA in OSA treatment is predicted by the levels, patterns, and degrees of upper airway collapse identified during DISE along with baseline characteristics and surgical characteristics. In addition, we assessed the value of the jaw thrust maneuver during DISE in the

prediction of the surgical outcome of MMA. Our key findings were as follows: 1) among baseline characteristics, surgical characteristics, and DISE findings, only the presence of complete anteroposterior epiglottic collapse was independently associated with failure of MMA in treating OSA, and 2) while the surgical response rate in patients without upper airway obstruction during jaw thrust tends to be higher than that in those with upper airway obstruction during jaw thrust, no significant association was found between jaw thrust maneuver and response to MMA.

In this study, epiglottic collapse was observed in 84.4% of the OSA patients, which was higher than the 9.7-73.5% previously described[17, 18]. First, this may be due to the fact that our patients presented with more severe OSA than the patients recruited in other studies[18-20]. Second, secondary epiglottic collapse caused by tongue compression was not separated from primary epiglottic collapse. To date, knowledge about treatment for epiglottic collapse is still limited. The available evidence shows that continuous positive airway pressure[21] and mandibular advancement device[22] may be ineffective for dealing with epiglottic collapse, while positional therapy has been proven to provide favorable results for these patients due to the association between epiglottic collapse and positional OSA[23, 24]. In addition, epiglottic surgery has been suggested to be a good option for correcting epiglottic collapse[25]. There is currently lack of evidence on the effectiveness of MMA in addressing epiglottic collapse. Our study demonstrated that the presence of complete epiglottic collapse on preoperative DISE was independently associated with surgical failure. This finding is supported by a prospective study by Kastoer et al.[10], who used DISE to assess upper airway collapse pattern in 14 OSA patients before and after MMA, and found that six of eight patients (75%) who had preoperative epiglottic collapse exhibited residual collapse postoperatively[10]. They assumed that MMA seemed to be ineffective in treating epiglottic collapse. It should be noted that epiglottic collapse can be classified as primary or secondary collapse, these two types of collapse may have different predictive value of surgical outcome of MMA. However, our study did not distinguish them because this information was absent in some DISE reports based on VOTE score. Furthermore, in the present study, only a few patients presented with no collapse or partial collapse of the tongue base. For this reason, a subgroup analysis of the patients with complete anteroposterior epiglottic collapse based on degrees of the tongue base collapse was difficult to conduct. Due to the limited availability of data, future investigations aimed at this specific DISE finding (i.e., complete anteroposterior epiglottic collapse [primary or secondary collapse]) is necessary. If

our finding is confirmed in future research, this DISE phenotype could be a useful tool for patient selection for MMA surgery.

Another specific DISE phenotype, CCCp, has been defined as an absolute contraindication to upper airway stimulation[8]. CCCp was also found to be a negative predictor for a mandibular advancement device[26]. In the past few years, evidence has been accumulating that MMA is a solution for OSA patients presenting with CCCp. In 2 published studies by Liu et al.[9] and Kastoer et al.[10], it was demonstrated that all CCCp observed during baseline DISE was eliminated after MMA. Kastoer et al.[10] also concluded that the reduction in AHI after MMA was equal in patients with and without CCCp. In this study, no relationship was found between CCCp and MMA response in multivariate logistic regression. Hence, our study suggests that CCCp may not be an adverse DISE finding toward MMA response. In other words, patients with CCCp, who are denied upper airway surgery, upper airway stimulation, or mandibular advancement device therapy for OSA might still be candidates for MMA.

Different passive maneuvers can be performed during DISE with the aim of predicting the response to some specific treatment modalities. Jaw thrust is often used to predict the effect of MAD on OSA because of the same mechanism, i.e., mandibular protrusion[27]. Although jaw thrust can stimulate only mandibular advancement, one would intuitively think that, if the obstruction disappears after jaw thrust, the patient would respond favorably to MMA surgery. However, this has not yet been confirmed by scientific evidence. The present study indicates that there is no significant correlation between this maneuver and response to MMA. This is probably due to the fact that the degrees of mandibular advancement are inconsistent between jaw thrust and MMA surgery. More importantly, the effect on upper airway patency of maxillary advancement cannot be mimicked during DISE. Nevertheless, it is interesting to note that the surgical response rate in patients whose upper airway collapse is totally resolved by jaw thrust tends to be higher than that in other patients undergoing MMA. The predictive value of jaw thrust during DISE for MMA surgical response needs further investigation.

In our study population, the surgical success rate of MMA was 60.9%, which was lower than that in published studies[2, 3, 28, 29]. This may be explained by differences in patient populations between our institute and other centers. First, multiple complete obstructions were observed in the majority of our patients during DISE, and the mean

total VOTE score in our study population was higher than in some other studies[30-32], which may hint at the treatment complexity for these patients[12]. Moreover, 43 of the 64 patients had complete anteroposterior epiglottic collapse, which may be a negative DISE finding for MMA. Second, half of the patients had failure of single-level or multilevel surgery prior to MMA. In some of these nonresponders to upper airway surgery, nonanatomical traits may play a prominent role in the etiology of OSA[33], making them poorer candidates for MMA. Hence, further improving patient selection for MMA therapy – with the use of screening and diagnostic tools – is crucial in increasing its efficacy and cost-effectiveness, and in reducing patient morbidity.

Unlike clinical routine applications for OSA patients before MMA (e.g., PSG, lateral cephalogram, cone beam computed tomography), the indication for DISE has not been fully settled. It was suggested that DISE might be indicated either before any type of surgery, or after surgical correction of volume abnormalities observed on clinical examination, or after failure of primary surgery[7]. Among the routine diagnostic modalities prior to MMA, only PSG has been widely proven to play a role in patient selection for MMA, for which a lower AHI is predictive of increased surgical success[3, 34]. Our study suggests that patients with complete anteroposterior epiglottic collapse observed during DISE may be at increased risk of surgical failure. Therefore, if the predictive value of DISE for MMA response is confirmed in future research, DISE may be considered as the standard application before MMA surgery.

The authors are aware of the limitations of this study. First, DISE was not performed preoperatively in one-third of patients undergoing MMA for OSA in our institution; however, the baseline characteristics and surgical outcome were comparable between the patients with and without baseline DISE. Second, the interrater and intrarater reliability of DISE cannot be judged and/or enhanced due to the nature of a retrospective study. Third, the VOTE classification is simplistic and may overlook interaction between the upper airway structure[35]. Furthermore, as stated before, our study did not distinguish primary and secondary epiglottic collapse because this information was absent in some DISE reports based on VOTE classification. Additionally, the numbers of events for some specific DISE variables were limited in our study population and 2 DISE phenotypes (lateral velum collapse and lateral epiglottic collapse) were therefore not included as independent factors in logistic analysis. However, given the relative low incidence of these 2 patterns of obstruction in patients with OSA[36], the generalizability of our findings may not be diminished.

Last, in addition to having a small sample size, it is important to note that the study was limited by the study population being predominantly males of relatively low BMI and unknown race/ethnicity. Thus, the results may be limited to this patient profile.

Future prospective studies with larger population are certainly needed to confirm our findings and to further explore the value of DISE in predicting surgical response to MMA for OSA. In this way, primary and secondary epiglottic collapse will be differentiated and numbers of each DISE phenotype will be sufficient to perform the statistical analysis. Additionally, multilevel obstruction is prevalent in patients with moderate to severe OSA[37]. It may be the case that certain combinations of collapse levels are associated with the surgical outcome of MMA for OSA. Future research in this field is also necessary to answer this question.

CONCLUSION

This study suggests that DISE can be a promising tool in order to identify less suitable candidates for MMA in OSA treatment. The presence of complete anteroposterior epiglottic collapse is associated with a higher possibility of MMA treatment failure. Prospective, larger-scale studies are required to further evaluate the use of DISE in predicting response to MMA.

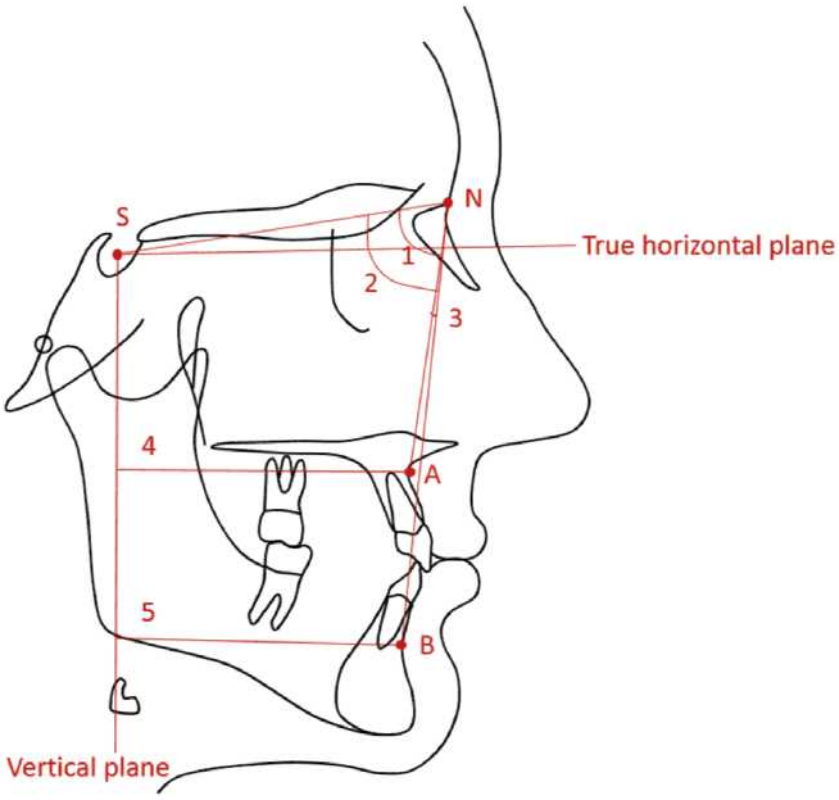

Figure 1. Cephalometric measurements. 1, SNA (degree); 2, SNB (degree); 3, ANB (degree); 4, A-point to vertical plane (mm); 5, B-point to vertical plane (mm).

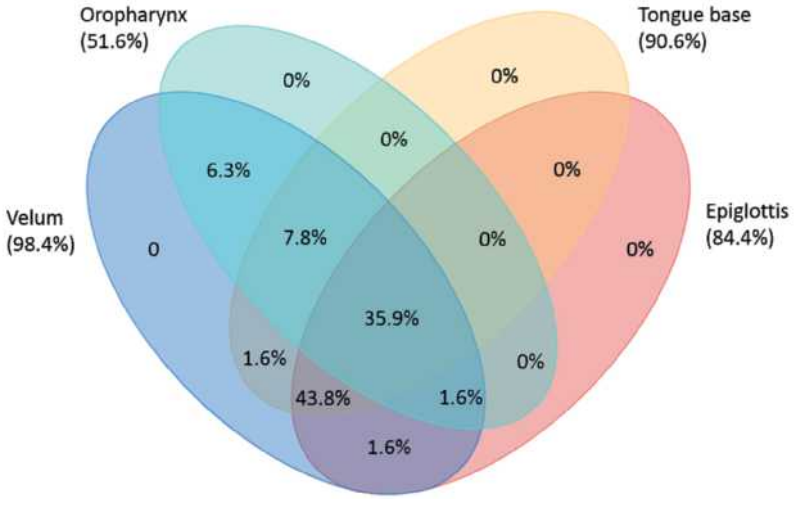

Figure 2. A Venn diagram showing the percentages of collapse in each single level and multi levels

Table 1. Baseline characteristics and surgical characteristics of the total population, responders and nonresponders

Variable	Total (n = 64)	Responders (n = 39)	Nonresponders (n = 25)	*P*-value
Age, years	51.7 ± 9.5	51.1 ± 9.6	52.7 ± 9.3	0.506
Male:female	50:14	28:11	22:3	0.126
BMI, kg/m^2	28.7 ± 4.0	28.4 ± 3.6	29.2 ± 4.5	0.413
Neck circumference, cm	41.7 ± 3.8	41.1 ± 3.2	42.6 ± 4.4	0.140
Previous OSA upper airway surgery, n (%)	29 (45.3)	16 (41.0)	13 (52.0)	0.390
AHI, events/h	49.0 ± 20.8	52.3 ± 18.4	43.7 ± 23.5	0.107
ODI, events/h	46.4 ± 21.2	48.0 ± 19.6	44.0 ± 23.8	0.501
LSAT, %	77.8 ± 10.5	76.0 ± 12.5	80.6 ± 5.3	0.395
SNA, degree	80.1 ± 3.5	79.9 ± 3.1	80.5 ± 4.2	0.536
SNB, degree	75.8 ± 4.1	75.4 ± 4.0	76.6 ± 4.1	0.292
ANB, degree	4.4 ± 3.1	4.7 ± 2.5	3.9 ± 3.8	0.416
Adv A, mm	7.1 ± 2.4	7.9 ± 2.5	6.7 ± 2.3	0.275
Adv B, mm	9.3 ± 4.3	9.9 ± 4.9	7.8 ± 3.1	0.067

Adv A, advancement degree of A-point; Adv B, advancement of degree of B-point; AHI, apnea-hypopnea index; ANB, A-point–Nasion–B-point angle; BMI, body mass index; LSAT, lowest oxygen saturation; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; SNA, sella–nasion–A-point angle; SNB, sella–nasion–B-point angle.

Continuous data presented as mean ± standard deviation, categorical data presented as number with percentage.

P-value for the comparison of the responders and nonresponders; $P < 0.05$ was considered statistically significant.

Table 2. Cephalometric analysis and polysomnographic variables before and after maxillomandibular advancement in total population, responders and nonresponders

Variable	Total population (n = 64)	Responders (n = 39)	Nonresponders (n = 25)
Cephalometric variables			
Pre-op SNA, degree	80.1 ± 3.5	79.9 ± 3.1	80.5 ± 4.2
Post-op SNA, degree	87.0 ± 5.1	87.1 ± 4.4	87.0 ± 6.2
Pre-op SNB, degree	75.8 ± 4.1	75.4 ± 4.0	76.6 ± 4.1
Post-op SNB, degree	81.6 ± 4.8	81.5 ± 4.3	81.7 ± 5.6
Pre-op ANB, degree	4.4 ± 3.1	4.7 ± 2.5	3.9 ± 3.8
Post-op ANB, degree	5.7 ± 3.1	6.0 ± 2.1	5.3 ± 4.1
Polysomnographic variables			
Pre-op AHI, events/h	49.0 ± 20.8	52.3 ± 18.4	43.7 ± 23.5
Post-op AHI, events/h	16.4 ± 13.3	8.8 ± 5.1	28.2 ± 13.5
Pre-op ODI, events/h	46.4 ± 21.2	48.0 ± 19.6	44.0 ± 23.8
Post-op ODI, events/h	22.0 ± 14.6	14.1 ± 7.8	33.0 ± 14.9
Pre-op LSAT, %	77.8 ± 10.5	76.0 ± 12.5	80.6 ± 5.3
Post-op LSAT, %	85.6 ± 4.6	86.4 ± 5.4	84.6 ± 2.9

AHI, apnea-hypopnea index; ANB, A-point–Nasion–B-point angle; LSAT, lowest oxygen saturation; ODI, oxygen desaturation index; SNA, sella–nasion–A-point angle; SNB, sella–nasion–B-point angle.

Data presented as mean ± standard deviation.

Table 3. Drug-induced sleep endoscopy findings in responders and nonresponders

Level: pattern of collapse	Responders (n = 39)			Nonresponders (n = 25)		
	No collapse (%)	Partial collapse (%)	Complete collapse (%)	No collapse (%)	Partial collapse (%)	Complete collapse (%)
Velum						
Anteroposterior	**9 (23.1)** *	4 (10.3)	26 (66.7)	**13 (52.0)** *	1 (4.0)	11 (44.0)
Lateral	39 (100.0)	0 (0)	0 (0)	25 (100.0)	0 (0)	0 (0)
Concentric	**30 (76.9)** *	0 (0)	9 (23.1)	**13 (52.0)** *	1 (4.0)	11 (44.0)
Oropharynx: lateral	18 (46.2)	9 (23.1)	12 (30.8)	13 (52.0)	3 (12.0)	9 (36.0)
Base of tongue: anteroposterior	5 (12.8)	10 (25.6)	24 (61.5)	1 (4.0)	5 (20.0)	19 (76.0)
Epiglottis						
Anteroposterior	10 (25.6)	7 (17.9)	**22 (56.4)** †	1 (4.0)	3 (12.0)	**21 (84.0)** †
Lateral	38 (97.4)	0 (0)	1 (2.6)	25 (100.0)	0 (0.0)	0 (0.0)

Data presented as number of patients with percentage.
* Significance accepted at *P*-value < 0.05 for no collapse: responders vs nonresponders.
† Significance accepted at *P*-value < 0.05 for complete collapse: responders vs nonresponders.

Table 4. Univariate logistic regression for DISE variables

Collapse site and pattern	OR [95% CI]	*P*-value
Collapse degree: no collapse vs collapse		
Velum anteroposterior		
No collapse	Ref.	Ref.
Collapse	3.611 [1.224-10.654]	**0.020**
Velum lateral	NA	NA
Velum concentric		
No collapse	Ref.	Ref.
Collapse	0.325 [0.110-0.959]	**0.042**
Oropharynx lateral		
No collapse	Ref.	Ref.
Collapse	1.264 [0.462-3.456]	0.648
Base of tongue anteroposterior		
No collapse	Ref.	Ref.
Collapse	0.283 [0.031-2.582]	0.263
Epiglottis anteroposterior		
No collapse	Ref.	Ref.
Collapse	0.106 [0.014-1.012]	**0.051**
Epiglottis lateral	NA	NA
Total VOTE score	0.740 [0.514-1.067]	0.107
Jaw thrust maneuver effect		
Partial resolution	Ref.	Ref.
Total resolution	2.333 [0.657-8.285]	0.190
Collapse degree: non-complete collapse vs complete collapse		
Velum anteroposterior		
Non-complete collapse	Ref.	Ref.
Complete collapse	2.545 [0.906-7.151]	**0.076**
Velum lateral	NA	NA
Velum concentric		
Non-complete collapse	Ref.	Ref.
Complete collapse	0.382 [0.129-1.131]	**0.082**
Oropharynx lateral		
Non-complete collapse	Ref.	Ref.
Complete collapse	0.790 [0.273-2.287]	0.664
Base of tongue anteroposterior		
Non-complete collapse	ref.	ref.
Complete collapse	0.505 [0.165-1.551]	0.233
Epiglottis anteroposterior		
Non-complete collapse	Ref.	Ref.
Complete collapse	0.246 [0.027-0.854]	**0.027**
Epiglottis lateral	NA	NA
Total VOTE score	0.740 [0.514-1.067]	0.107
Jaw thrust maneuver effect		
Partial resolution	Ref.	Ref.
Total resolution	2.333 [0.657-8.285]	0.190

CI, confidence interval; DISE, drug-induced sleep endoscopy; NA, not applicable; OR, odds ratio; Ref, reference category; VOTE, Velum Oropharynx Tongue base Epiglottis.

SUPPLEMENTARY MATERIAL

Table S1. Baseline characteristics of patients with and without baseline drug-induced sleep endoscopy

Variable	Patients with baseline DISE (n = 64)	Patients without baseline DISE (n = 37)	*P*-value
Age, years	51.7 ± 9.5	49.2 ± 9.5	0.200
Male:female	50:14	31:6	0.492
BMI, kg/m²	28.7 ± 4.0	30.4 ± 5.3	0.075
Neck circumference, cm	41.7 ± 3.8	43.4 ± 4.4	0.141
Previous OSA upper airway surgery, n (%)	29 (45.3)	13 (35.1)	0.317
AHI, events/h	49.0 ± 20.8	50.6 ± 26.1	0.738
ODI, events/h	46.4 ± 21.2	53.1 ± 29.3	0.303
LSAT, %	77.8 ± 10.5	76.3 ± 10.8	0.552
SNA, degree	80.1 ± 3.5	80.5 ± 5.4	0.700
SNB, degree	75.8 ± 4.1	74.8 ± 6.7	0.392
ANB, degree	4.4 ± 3.1	6.0 ± 3.2	0.089
Responder:nonresponder	39:25	23:14	0.639

AHI, apnea-hypopnea index; ANB, A-point–Nasion–B-point angle; BMI, body mass index; DISE, drug-induced sleep endoscopy; LSAT, lowest oxygen saturation; ODI, oxygen desaturation index; SNA, sella–nasion–A-point angle; SNB, sella–nasion–B-point angle.

Continuous data presented as mean ± standard deviation, categorical data presented as number with percentage.

P-value for the comparison of the patients with baseline DISE and patients without baseline DISE.

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CHAPTER

Maxillomandibular advancement versus multilevel surgery for treatment of obstructive sleep apnea: A systematic review and meta-analysis

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ABSTRACT

Multilevel surgery (MLS) and maxillomandibular advancement surgery (MMA) are two established options in surgical management of obstructive sleep apnea (OSA), which target different levels of airway obstruction. The objective of this review was to comparatively evaluate the clinical efficacy and safety of MMA and MLS in the treatment of OSA. MEDLINE and Embase databases were searched for studies on MMA and/or MLS in OSA patients. Twenty MMA studies and 39 MLS studies were identified. OSA patients who underwent MMA showed significant improvements in apnea-hypopnea index (AHI), lowest oxygen saturation (LSAT), oxygen desaturation index (ODI), and Epworth sleepiness scale (ESS) by -46.2 events/h, 13.5%, -30.3 events/h, and -8.5, respectively. The pooled rates of surgical success and cure for MMA were 85.0% and 46.3%, respectively. Patients who underwent MLS showed significant improvements in AHI, LSAT, ODI, and ESS by -24.7 events/h, 8.7%, -19.1 events/h, and -5.8, respectively. The pooled surgical success and cure rates for MLS were 65.1% and 28.1%, respectively. The rates of major complication of MMA and MLS were 3.2% and 1.1%, respectively, and the rate of minor complication of MMA was higher than that of MLS. We conclude that both MMA and MLS are effective treatment options for OSA. Compared to MLS, MMA may be more effective in improving OSA. However, the complication rate of MMA is higher.

Keywords: Obstructive sleep apnea; Maxillomandibular advancement; Multilevel surgery; Surgery; Systematic review; Meta-analysis

INTRODUCTION

Obstructive sleep apnea (OSA), a potentially life-threatening sleep-related breathing disorder, is characterized by repetitive partial or complete obstruction of the upper airway during sleep, causing hypoxemia and sleep fragmentation[1]. A recent systematic review reported that the overall prevalence of OSA ranges from 9% to 38% in the general adult population[2].

Continuous positive airway pressure (CPAP) is generally accepted as a first-line therapy for patients with moderate to severe OSA[3]. However, the clinical efficacy of CPAP can be hampered by its often low compliance rate, prompting a substantial proportion of OSA patients to seek therapeutic alternatives, such as a mandibular advancement device (MAD) and surgical treatment[4]. Surgical treatment is a viable alternative for patients who have specific surgically correctable anatomical abnormalities, which play an important role in upper airway obstruction[5].

Moderate to severe OSA is usually characterized by multilevel obstructions[6], hence the surgical interventions aimed to correct only one region cannot eliminate all obstructions in the upper airway. In 1986, Riley et al.[7] have first proposed multilevel surgery (MLS) for OSA patients with multiple obstructions. Today, MLS for OSA is widely accepted as treatment modality in case of multilevel obstruction.

MLS however, is not suitable for all OSA patients. Another commonly employed surgical procedure that targets multiple levels is maxillomandibular advancement (MMA), which has been demonstrated to be the most effective surgical option for OSA[8]. The reported surgical success rate for MMA is 86.0%[9].

Currently, there is still no universally accepted guideline of surgical procedures for OSA given the variations in anatomy, disease severity, patient comorbidities, and patient preference. For OSA cases with diffusely complex or multiple sites of obstruction, the indications and staged protocols of surgical treatment remain unclear. When there is no generally accepted indicative results of clinical, laboratory, or endoscopic examination in patients with moderate to severe OSA (e.g., significant skeletal-dental deformity, complete concentric collapse at velum observed with drug-induced sleep endoscopy [DISE]), some surgeons are inclined to start with MLS and keep MMA as a reserve therapeutic option in case of surgical failure, while others

prefer to start with MMA as the primary treatment option. Thus, further definition of the role of MMA and MLS in the treatment protocol for OSA is called for, which is vital for both patients and physicians in final decision-making regarding the choice of surgery type. To our knowledge, only one systematic review[10] published in 2010 has compared MMA and MLS for OSA treatment, but only regarding the aspect of clinical efficacy, which places emphasis on the need for an updated and thorough assessment and comparison of the two types of surgical interventions. Thus, the aim of this systematic review was to comprehensively evaluate and compare the treatment outcome of MMA and MLS for OSA treatment, through the assessment of apnea-hypopnea index (AHI) and Epworth sleepiness scale (ESS) as primary outcomes. The secondary objective was to investigate the differences in complication rates for both treatment options.

METHODS

In accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement, the protocol for the systematic review was registered (PROSPERO ID: CRD42020152077;https://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42020152077).

Selection criteria

The inclusion criteria were as follows: (1) adult patients (> 18 years old) with OSA diagnosed by means of polysomnography (PSG; AHI ≥ 5 events/h); (2) patients that underwent MMA or one-phase MLS (at least one velopharyngeal and one hypopharyngeal surgery in single stage); (3) studies that reported pre- and postoperative PSG data; (4) studies with a follow-up ≥ 6 months; (5) studies with the following designs: randomized controlled trials (RCTs), quasi-experimental studies, and cohort studies; and (6) English language.

Studies were excluded from the review if: (1) sample size < 10 patients; (2) studies with patients who underwent other adjunctive procedures at the time of MMA (e.g., tonsillectomy, uvulopalatopharyngoplasty, partial glossectomy); and (3) preliminary studies in which the findings had been nested in other studies with larger sample size and/or longer follow-up.

Literature Search

With the assistance of an information specialist, a literature search was performed using the MEDLINE and Embase database on May 6, 2020. Search terms and full search strategies used for each database utilized are available as supplementary information (Supplementary **Table S1a** and **S1b**).

Study selection

Two reviewers (NZ and ZH) independently selected studies for further assessment by title and abstract review. All potentially eligible studies were retrieved in full texts for further evaluation. In case of disagreement, a third reviewer (JH) was consulted. The reference lists of the retrieved papers were manually checked by NZ and ZH.

Data extraction

A specially designed data-extraction form was used to extract data from the included studies. Extracted information included:

- General information: article title, year of publication, and first author.
- Study characteristics: study design and length of follow-up.
- Participant characteristics: sample size, age, gender, and body mass index (BMI) (kg/m^2).
- Intervention and setting: specific surgical technique.
- Outcome data: results of pre- and postoperative PSG, including apnea-hypopnea index (AHI), respiratory disturbance index (RDI), lowest saturation of oxygen (LSAT), and oxygen desaturation index (ODI); pre- and postoperative Epworth sleepiness scale (ESS) score; surgical success rate and cure rate; postoperative complications; and duration of hospital stay.

Data were extracted by NZ and ZH independently. Discrepancies were resolved through discussion with JH. If RDI was reported in a study, it would be extracted as AHI, since these two respiratory parameters have been consolidated based on the 2013 American Academy of Sleep Medicine's manual for the scoring of sleep and associated events[11]. We defined "surgical success" as "at least 50% reduction in AHI following surgery accompanied by a postoperative AHI of < 20 events/h"[12], and "surgical cure" as "a postoperative AHI < 5 events/h"[13]. If there were multiple follow-up data in the results, the data with the longest follow-up time were selected.

Quality assessment

Methodologic quality assessment of each study was performed by NZ and ZH independently, and any discrepancies were resolved through discussion with JH.

The risk of bias of included RCTs were assessed using the Cochrane Collaboration "Risk of bias" tool[14]. Six domains of bias, including selection, attribution, detection, performance, reporting, and other bias, were classified as "low risk", "high risk" or "unclear risk". The total quality of each study was considered as good (low risk of bias for at least 3 items), fair (low risk of bias for 2 items), or low (low risk for no items or 1 item)[15].

The quality assessment of non-randomized studies was based on the Methodological Index for Non-Randomized Studies (MINORS), which is a validated tool for the methodological assessment of non-randomized surgical studies[16]. The MINORS tool includes 12 items for comparative studies, the first eight being specifically for non-comparative studies. Each item was scored as 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate). The global ideal score was 24 for comparative studies and 16 for non-comparative studies. The categorization of comparative studies was as follows: 0-6 "very low quality", 7-10 "low quality", 11-15 "fair quality", and ≥ 16 "high quality". For non-comparative studies, the total score of 0-4 indicates very low quality, 5-7 indicates low quality, 8-12 indicates fair quality, and ≥13 indicates high quality[17].

The studies categorized as "high risk of bias" or "low/very low quality" were excluded from the meta-analysis.

Statistical analysis

The weighted mean () and weighted standard deviation () of parameters (age, BMI, AHI, LSAT, and ESS) were calculated using the following equations, respectively[18]:

$$\overline{x}^{*} = \frac{\sum_{i=1}^{N} w_i x_i}{\sum_{i=1}^{N} w_i}$$

$$\overline{SD}^{*} = \sqrt{\frac{\sum_{i=1}^{N} w_i \left(x_i - \overline{x}^{*}\right)^2}{\frac{(M-1)}{M} \sum_{i=1}^{N} w_i}}$$

N is the number of observations; M is the number of nonzero weights; W_i are the weights; and x_i are the observations.

The inverse variance methods for meta-analysis was conducted to pool the results of AHI, LSAT, and ESS, respectively, and rendered a weighted mean difference (WMD) and its associated 95% confidence interval (CI). The magnitude of the effect was interpreted through the value of standardized mean difference (SMD); small = 0.2, medium = 0.5 and large = 0.8[19]. The random effects model and fixed effects model were used depending on the presence of heterogeneity. Heterogeneity between studies was evaluated by Cochran *Q* statistic, with a statistical heterogeneity cutoff of $P < 0.10$[20], as well as I^2 statistic with cutoff of 25% (low), 50% (moderate), and 75% (high)[21]. Pooled surgical success and cure rates were generated in the meta-analysis by using the DerSimonian-Laird random effects pooling method.

Given the inconsistency of surgical interventions utilized in MLS, the subgroup analysis was done for the subsets of study groups according to the combination of different target levels of surgery (surgery addressing obstruction at the levels of soft palate and tongue base – subgroup 1; soft palate and hyoid – subgroup 2; and soft palate, tongue base, and hyoid – subgroup 3). Based on current literature, it is suggested that increasing preoperative severity of OSA is likely an important predictor of treatment failure[9, 22], combined with the heterogeneity of patients' baseline AHI in the analyzed studies. Therefore, we calculated separate pooled estimates for studies with different range of mean baseline AHI (AHI < 40 events/h; 40 events/h ≤ AHI ≤ 70 events/h; AHI > 70 events/h). These cut-off values were determined based on the range of average baseline AHI of all included studies. A subgroup analysis was also conducted in the studies with long follow-up periods (≥ 2 years). The comparison of the estimates for each outcome between MMA and MLS was performed by using Z test, as proposed by Altman and Bland[23].

Risk of publication bias across studies was assessed by Begg's test and Egger's test, with *P*-value of <0.05 suggesting the presence of bias. Sensitivity analyses were conducted to assess the stability of the results. Statistical analyses were conducted using Review Manager version 5.3 (Cochrane Centre, Copenhagen, Denmark) and Stata version 16.0 (StataCorp LLC, College Station, USA).

RESULTS

The PRISMA flow diagram of study selection progress is described in Supplementary **Fig. S1**. The search in the electronic database resulted in 3051 publications after deduplication, from which 172 full articles were retrieved for further full-text evaluation.

MMA group Twenty studies were identified[24-43]. One of these was an RCT, one was a retrospective quasi-experimental study, nine were prospective cohort studies, and nine were retrospective cohort studies. Their characteristics are shown in **Table 1**. The mean follow-up period from surgery to postoperative PSG was 25.4 months (range, 6.0 months-12.5 years).

MLS group Thirty-nine articles fulfilled the inclusion criteria, including one article added from hand searching of included articles' reference lists[22, 44-81]. One was a randomized controlled trial, five were prospective quasi-experimental studies, six were retrospective quasi-experimental studies, eleven were prospective cohort studies, and 17 were retrospective cohort studies. Their characteristics are shown in **Table 2**. The mean follow-up period from surgery to postoperative PSG was 9.9 months (range, 6.0 months-3.3 years).

Quality assessment of individual studies

MMA group The only RCT[41] was considered of good quality (Supplementary **Fig. S2**). Of the non-randomized studies, two studies were classified as "high quality", and the other 17 studies as "fair quality" (Supplementary **Table S2a**).

MLS group The only RCT[53] was considered of fair quality (Supplementary **Fig. S2**). Of the non-randomized studies, seven studies were classified as "high quality", twenty-nine studies as "fair quality", and two studies as "low quality" (Supplementary **Table S2b**).

Demographic data

MMA group Twenty studies on MMA were reviewed. Excluding duplication of data yielded a total of 528 distinct patients, most of whom were overweight (weighted BMI: 28.6 ± 6.6 kg/m^2) males (78.9%) with a weighed mean age of 42.9 years (**Table 3**).

MLS group As shown in **Table 3**, the identified studies produced a pooled data set of 1712 OSA patients who underwent MLS. The majority of the patients were obese (weighted BMI: 29.1 ± 4.2 kg/m^2) males (85.0%) with a weighted mean age of 45.5 years.

Respiratory parameters

MMA group One study[35] was excluded from the meta-analysis, because the data of a small subset of the patients with longer follow-up time were reported in another study[34]. As shown in **Table 3**, nineteen studies, describing 393 patients with weighted preoperative AHI of 57.3 ± 26.6 events/h, reported a statistically significant improvement in AHI of -46.2 events/h (95%CI, -52.4 to -39.9, $P < 0.001$), LSAT of 13.5% (95%CI, 10.5 to 16.5, $P < 0.001$), and ODI of -30.3 events/h (95%CI, -46.3 to -14.2, $P < 0.001$) (Supplementary **Fig. S3**). The SMDs of AHI, LSAT, and ODI were -2.90 (95%CI, -3.40 to -2.40) (large effect), 1.49 (95% CI, 1.21 to 1.76) (large effect), and -2.61 (95%CI, -4.23 to -1.00) (large effect), respectively.

MLS group Two studies[44, 62] were excluded from the meta-analysis because of the low methodological quality. As shown in **Table 3**, thirty-seven studies, totaling 1639 patients with weighted preoperative AHI of 42.2 ± 21.0 events/h, reported a statistically significant improvement in AHI of -24.7 events/h (95%CI, -28.1 to -21.4, $P < 0.001$), LSAT of 8.7% (95%CI, 6.2 to 11.1, $P < 0.001$), and ODI of -19.1 events/h (95%CI, -34.2 to -4.0, $P = 0.010$) (Supplementary **Fig. S4**). The SMDs of AHI, LSAT, and ODI were -1.79 (95%CI, -2.06 to -1.52) (large effect), 1.06 (95%CI, 0.79 to 1.34) (large effect), and -1.18 (95%CI, -1.74 to -0.62) (large effect), respectively. The results of weighted data for three subgroups according to the different target levels of obstructive sites addressed by surgery were summarized in **Table 4** (Supplementary **Fig. S5**).

The improvements of AHI and LSAT after MMA were significantly higher than after MLS, with *P*-value of <0.001 and 0.014, respectively. No significant difference in the improvement of ODI between MMA and MLS was found.

Subjective outcomes

MMA group Seven studies, totaling 164 patients with weighted preoperative ESS of 14.1 ± 5.4, reported a significant decrease of 8.5 (95%CI, -12.2 to -4.9, $P < 0.001$) (**Table 3**; Supplementary **Fig. S3**). The ESS SMD was -2.15 (95%CI, -3.06 to -1.24) (large effect).

MLS group Twenty-nine studies, totaling 1309 patients with weighted preoperative ESS of 12.6 ± 4.4, reported a significant reduction of -5.8 (95%CI, -6.6 to -5.0, $P < 0.001$) (**Table 3**; Supplementary **Fig. S4**). The ESS SMD was -1.51 (95%CI, -1.78 to -1.25) (large effect). The results of subgroup analysis based on surgical technique were shown in **Table 4** (Supplementary **Fig. S5**)

No significant difference in the improvement of ESS between MMA and MLS was found.

Surgical success and cure

MMA group The pooled rate of surgical success reported in 15 studies (n = 340) was 85.0% (95%CI, 76.4% to 91.9%), and the pooled rate of surgical cure reported in five studies (n = 130) was 46.3% (95%CI, 38.0% to 54.7%).

MLS group The overall pooled rate of surgical success reported in 31 studies (35 MLS groups, n = 1339) was 65.1% (95%CI, 60.6% to 69.5%), and the overall pooled rate of surgical cure was 28.1% (95%CI, 13.2% to 46.1%) in five studies (5 MLS groups, n = 221). The pooled surgical success and cure rates for each subgroup with regard to surgical technique were listed in **Table 4.**

The overall pooled surgical success rate of MMA was significantly higher than that of MLS ($P < 0.001$), and no significant difference was found in the pooled surgical cure rate between these two therapies.

Severity of OSA: impact on results

All MMA study groups were divided into the following three cohorts with respect to the mean baseline AHI: less than 40 events/h, from 40 events/h to 70 events/h, and greater than 70 events/h. For MLS groups, they were only divided into two cohorts according to the mean baseline AHI, due to the absence of included MLS studies with mean baseline AHI > 70 events/h.

Baseline AHI less than 40 events/h

MMA group In **Table 5**, three studies, totaling 60 patients with weighted preoperative AHI of 35.7 ± 13.7 events/h, reported a significant improvement in AHI of -27.1 events/h ($P < 0.001$), and ESS of -12.7 ($P = 0.002$) (Supplementary **Fig. S3**). No study described LSAT. Only one study with 34 patients reported data concerning the preoperative and postoperative ODI (34.7 ± 12.5 events/h and 5.4 ± 4.1 events/h ($P < 0.001$), respectively). The pooled rates of success and cure were 94.0% (95%CI, 74.3% to 99.9%) and 50.0% (95%CI, 35.7% to 64.2%), respectively.

MLS group In **Table 5**, fifteen studies, comprising 706 patients with weighted preoperative AHI of 30.7 ± 15.6 events/h, showed a significant improvement in AHI of -16.7 events/h ($P < 0.001$), LAST of 4.4% ($P = 0.001$), and ESS of -5.4 ($P < 0.001$) (Supplementary **Fig. S4**). No significant improvement of ODI was found. The pooled

rates of success and cure were 57.1% (95%CI, 51.7% to 62.5%) and 44.7% (95%CI, 33.2% to 56.4%), respectively.

Compared to the MLS, the AHI reductions after MMA was significantly higher, with *P*-values of 0.030. The pooled surgical success rate of MMA was significantly higher than MLS ($P < 0.001$), while there is no difference in the surgical cure rates between these two types of therapies.

Baseline AHI from 40 events/h to 70 events/h

MMA group In **Table 5**, twelve studies, comprising 257 patients with weighted preoperative AHI of 55.7 ± 23.0 events/h, reported a significant improvement in AHI of -44.1 events/h ($P < 0.001$), LSAT of 11.6% ($P < 0.001$), ODI of -30.4 events/h ($P = 0.030$), and ESS of -7.0 ($P < 0.001$) (Supplementary **Fig. S3**). The pooled rates of success and cure were 82.3% (95%CI, 69.1% to 92.5%) and 44.0% (95%CI, 33.1% to 55.3%), respectively.

MLS group In **Table 5**, twenty-two studies, comprising 933 patients with weighted preoperative AHI of 51.0 ± 20.3 events/h, showed a significant improvement in AHI of -30.7 events/h ($P < 0.001$), LAST of 9.9% ($P < 0.001$), ODI of -28.6 events/h ($P < 0.001$), and ESS of -6.1 ($P < 0.001$) (Supplementary **Fig. S4**). The pooled rates of success and cure were 70.5% (95%CI, 65.4% to 75.3%) and 17.4% (95%CI, 7.1% to 31.0%), respectively.

The reduction in AHI after MMA was significantly higher than that after MLS ($P < 0.001$), and no difference was found in the improvement of LSAT, ODI, and ESS postoperatively between these two therapies. The pooled surgical cure rate of MMA was significantly higher than that of MLS ($P = 0.020$), while there was no difference in the surgical success rates between these two therapies.

Baseline AHI greater than 70 events/h

MMA group As shown in **Table 5**, four studies, totaling 76 patients with weighted preoperative AHI of 79.8 ± 28.9 events/h, reported a significant improvement in AHI of -71.8 events/h ($P < 0.001$), LSAT of 18.7% ($P < 0.001$), and ESS of -7.9 ($P < 0.001$) (Supplementary **Fig. S3**). No study described ODI. The pooled rate of success was 84.2% (95%CI, 75.5% to 91.3%). One study reported a surgical cure rate of 46.2%.

Long-term follow-up outcomes

MMA group Four studies[26, 27, 34, 42] reported long-term follow-up (≥ 2 years) in 98 OSA patients treated by MMA. At a mean follow-up of 8.9 years, a reduction of AHI was shown from 60.8 ± 25.2 to 13.1 ± 15.1 events/h. The meta-analysis showed a statistically significant improvement of -45.2 events/h (95%CI, -59.6 to -30.9, $P < 0.001$). Only one study with 40 patients presented long-term follow-up LSAT, reporting preoperative LSAT of 67.5 ± 14.8% and postoperative LSAT of 86.3 ± 3.9%. Surgical success rates were available for only two studies (90% and 41.4 %, respectively).

MLS group Three studies[67, 77, 81] with 114 patients presented long-term follow-up (≥ 2 years) data. In two of these studies, totaling 68 patients who had undergone uvulopalatopharyngoplasty (UPPP) and tongue base suspension with a mean follow-up of 2.8 years, AHI and ESS score decreased from 48.8 ± 17.8 events/h to 14.9 ± 21.5 events/h, 12.1 ± 4.3 to 7.5 ± 5.9, respectively. The WMD between pre- and post-surgery were -27.4 events/h (95%CI, -50.4 to -4.4, $P = 0.020$) and -4.5 (95%CI, -6.2 to -2.8, $P < 0.001$), respectively. One of the two studies with 54 patients presented long-term follow-up LSAT increasing from 76.2 ± 12.4% preoperatively to 82.2 ± 11.2% postoperatively ($P = 0.009$). Another study with 14 patients reported long-term follow-up ODI from 30.3 ± 16.9 events/h preoperatively to 15.5 ± 13.2 events/h postoperatively ($P < 0.001$). Surgical success rates were 78% and 57.1%, respectively. In the third study consisting of 46 patients who had undergone uvulopalatal flap, genioglossus advancement, and hyoid suspension with a mean follow-up of 3.3 years, AHI and ESS score decreased from 47.9 ± 8.4 events/h to 18.6 ± 4.1 events/h, 15.9 ± 2.7 to 7.3 ± 2.7, respectively; the LAST increased from 81.2 ± 2.9% to 87.2 ± 3.1%. The surgical success rate was 65.2%.

Surgical morbidity and mortality

MMA group The average length of hospitalization for OSA patients who underwent MMA was 3.5 days (range 2.3 days to 8 days). Among studies reporting participants' complications (n = 346)[24, 26, 29, 35, 39-43], no death was encountered. The rate of major complication was 3.2%, including ten re-operations for removal of osteosynthesis screws and plates (n = 8)[26, 29, 42] and maxillary non-union (n = 2)[24, 42], and one sudden dyspnea[41].The most frequent minor complication was facial paresthesia caused by the impairment of inferior alveolar nerve and/or maxillary nerve. In total, 76.9% of patients (n = 266) had transient facial paresthesia in mandibular and/or infraorbital areas, and 18.5% of patients (n = 64) reported persistent symptoms (mean follow-up of 6.0 years).

Excluding facial paresthesia, the rate of other minor complications was 10.1%, consisting of developed malocclusion (n = 13), temporomandibular disorders (n = 11), local infection (n = 5), minor postoperative wound pain (n = 2), unfavorable split (n = 1), loss of an interdental gingiva(n = 1), a perforation of the palate (n = 1), and transient unilateral angulus oris deviation (n = 1). Besides, only 9 of 206 patients perceived worsening of their facial appearance after MMA[24, 26, 28, 37, 39-43].

MLS group After surgery, patients required 4.1 days (range 1.25 ± 0.44 days to 16 ± 2 days) of hospitalization. No death was reported in 1386 patients[22, 44-46, 48-51, 53, 56-60, 62, 63, 65-71, 73-75, 77-81]. The rate of major complications was 1.1%, including nine postoperative bleedings necessitating surgical exploration or surgical treatment[51, 53, 64, 74], five pillar extrusion requiring removal and replacement[60], and one pneumonia[78].

The minor complications included postoperative pain (n = 160), tongue discomfort (n = 74), velopharyngeal insufficiency (n = 70), dysphagia (n = 65), dysarthria (n = 25), odynophagia (n = 22), ulceration (n = 21), taste change (n = 14), and others (n = 112), which yield the minor complication rate of 40.6%. The majority of these complications were self-limited or could be cured by conservative treatment, with the exception of nine persistent complications: taste disturbance (n = 1)[64], dysphonia and dysphagia (n = 1)[53], oropharyngeal globus sensation (n = 2)[48], and dysphagia (n = 5)[51].

Publication bias and sensitivity analysis

Both Begg's test and Egger's test suggested no significant publication bias for the included MMA and MLS studies (Supplementary **Fig. S6** and **S7**). The sensitivity analysis indicating high stability and robustness of the results (Supplementary **Fig. S8** and **S9**).

DISCUSSION

Respiratory parameters, and surgical success and cure

Although there are no comparative trials between MMA and MLS, greater improvement of OSA was found in MMA studies by pooling results from both surgical options, in terms of surgical success rate and improvement in the respiratory parameters. The observed superiority of MMA over MLS in treating OSA is explained by enlargement of the entire retropalatal and retrolingual airway by expanding the skeletal framework, while MLS cannot. Currently, there are a few studies[25, 31, 40] reporting the significant

increases in pharyngeal airway volume (PAV) in OSA patients treated with MMA, by 60.5%, 35.7% and 35.4%, respectively. However, to our knowledge, only Chiffer et al.[54] quantitatively measured the volumetric changes in upper airway before and after MLS for treating OSA. They found a significant increase in PAV by 19.4%. Therefore, we inferred that the extent of the enlargement of the pharyngeal space could be associated with the therapeutic efficacy of upper airway surgery. Further investigation is essential to fully understand the treatment mechanisms of MMA and MLS, which may partly clarify the reason of differences in surgical outcome between them.

The discrepancy of surgical results between MMA and MLS varies with the different preoperative OSA severity. For example, there are benefits of MMA over MLS for the success rate in patients with baseline AHI < 40 events/h, and for the cure rate in patients with baseline AHI from 40 events/h to 70 events/h. The current evidence suggests that the pathophysiological causes of OSA are multifactorial and likely varies considerably between individuals, which puts an emphasis on personalized management for OSA based on its underlying causes[5]. Given the variable efficacy of these two types of surgeries, especially of MLS, careful selection of patients is needed. Therefore, one important objective in future research should be the identification of the factors that determine the success or failure in OSA patients treated by MMA or MLS. For the nonresponders to upper airway surgery, non-anatomical traits may play a prominent role as well in the etiology of OSA.

In MLS, precise identification of sites of airway collapse is imperative for favorable surgical outcome[82, 83], rather than only the severity of OSA. Among all the identified MLS studies, nasopharyngoscopy with Muller maneuver or DISE were performed preoperatively, except in four studies[55, 59, 60, 78]. The significant improvement in OSA was noted in the three MLS subgroups with regard to surgical technique and the largest improvement in AHI was seen in subgroup 3 . In one study[53], it was also demonstrated that compared with combined UPPP and tongue base radiofrequency ablation, combined hyoid suspension, UPPP, and tongue base radiofrequency ablation obtained better treatment outcome. However, due to the limited studies on subgroups 2 and 3, it is not possible to match each subgroup for baseline characteristics, which lead to the difficultly in comparing the clinical outcome between them in our study. Of interest is that in OSA surgery, palatal resection techniques such as UPPP are presently regarded as obsolete and are being replaced by modern reconstructive techniques, such as expansion sphincter pharyngoplasty,

because of better clinical outcome and less side effects[84]. These better results are reported in both single level surgery and MLS[49, 78]. In addition, upper airway stimulation[85], an emerging treatment option for moderate to severe OSA, has been found to be an effective therapy able to achieve success rate of 75% in patients with OSA[86]. Interest in this emerging treatment modality has been increasing during the past decade. In the premise of precisely identifying anatomical abnormalities of the upper airway, the development of surgical techniques may further optimize the surgical outcome for well-selected patients with OSA. The comparison of clinical efficacy and safety between contemporary approaches and older ones for OSA is called for in future studies.

Subjective outcomes

Of note, not only the improvement in AHI but also the patients' subjective feeling should be taken into consideration when evaluating the efficacy of surgical interventions for OSA. Regrettably, ESS score was the only overlapping subjective index which was frequently reported in both MMA and MLS studies, leading to the impossibility of comprehensive comparison of other subjective outcomes (e.g., quality of life outcomes). There are studies that have assessed the improvement brought by MMA and MLS in patient's subjective feelings, such as snoring[40, 58, 59, 87], and bodily pain[87, 88]. Both surgery modalities can significantly improve patient's subjective feeling. However, the comparison of improvement in quality of life between them should be addressed in future studies.

Long-term follow-up outcomes

The follow-up period of the included MMA studies ranges from 6 months to 12.5 years, and that of the included MLS studies ranges from 6 months to 3.3 years. Most of the retrieved studies reported short-term surgical outcomes at 6 months after surgery. In our study, a significant decrease in AHI of 45.23 events/h was shown, at a mean follow-up of 8.9 years after MMA. In a meta-analysis by Camacho et al.[89], it was demonstrated that OSA patients who were treated with MMA maintained improvements in AHI, sleepiness, and LSAT in the long term (4 years to < 8 years). However, the mean AHI increased to moderate OSA (mean AHI = 23.1 events/h) in the very long term (≥ 8 years). The longest follow-up result in MMA was reported by Pottel et al.[87], the long-term (range 14-20 years) success rate of nine patients performed MMA was 44.44%, and the short-term (within 2 years) success rate was 66.67%. Vigneron et al.[42] reported that the long-term (mean 12.5 years) success rate of MMA was 100% in young patients (age < 45) with BMI < 25kg/m^2, AHI < 45 events/h, SNB < 75°, narrow retrolingual space

(< 8 mm), and preoperative orthodontics. Marked weight gain and significant skeletal relapse can counterbalance the positive effect of MMA in the long-term, while there is no consensus on the effect of aging in long-term outcome of MMA[34, 87]. Compared with the studies on MMA, currently, there are less studies on MLS evaluating the long-term surgical outcome. Hou et al.[90] performed combined midline glossectomy and UPPP in 34 patients and reported short-term (6 months) and long-term (5 years) outcome. At 6 months, the surgical success and cure rate were 79.41% and 17.65%, respectively; at 5 years, the surgical success and cure rate were 20.59% and 50%, respectively. The longest follow-up result of MLS was reported by Andsberg et al.[91]. In this study, 16 patients had undergone UPPP combined with midline glossectomy and followed up 1 year and 8.4 years after surgery. The success rates were 59% and 56%, respectively; and the cure rates were 32% and 25%, respectively. The weight of these patients did not change during the follow-up period, which may explain the long-term stable outcome. Neruntarat et al.[67] also found that patients with significant weight gain were at risk of recurrence of OSA. Based on the current literature, we concluded that the benefits of MMA and MLS persist for most patients with moderate-to-severe OSA over a long-term follow-up time. Marked weight gain after surgery and significant skeletal relapse after MMA may negatively influence the stability of clinical outcome. Thus, a recommendation regarding weight control and regular follow-up postoperatively are crucial for OSA patients. Moreover, due to the limited availability of data, the long-term outcome and the factors related to relapse require further investigation.

Surgical morbidity and mortality

Despite the apparent benefits, concerns about the safety and complications of surgical therapy for OSA still exist. In our study, both MMA and MLS were noted to be generally safe surgical therapies for OSA. Riley et al.[92] concluded that OSA patients with apnea index higher than 70 events/h and LSAT less than 80% were at high risk of postoperative complication. Sensory disturbance in the territory of the inferior alveolar nerve was the most common complication of MMA, and the main predisposing factors were the degree of mandibular advancement, the patient's advanced age, and addition of a genioplasty[93]. One study[24] demonstrated that the complication rate of MMA increased with increasing age, in particular after 45 years old. In a study of 487 consecutive OSA patients treated by MLS, Pang et al.[94] concluded that the overall complication rate was 7.1%, which is lower than our result. Besides, they pointed out that patients with severe OSA (AHI > 60 events/h and

LSAT < 80%) might be at high risk of postoperative oxygen desaturation. Although the major postoperative complication rate was low, patients who underwent MMA or MLS for treating OSA were recommended to be closely monitored after surgery[95, 96]. According to the available evidence, generally, more attention should be paid to the patients with highly severe OSA, who could be vulnerable to the postoperative complication, no matter after MMA or MLS.

Limitations

The results presented here should be considered in the context of several limitations. Firstly, the majority of the included studies are non-randomized studies, thus the level of evidence is limited inherently by the study design. Moreover, the overall quality of evidence was fair, with moderate risk of bias in the majority of studies included in the analysis, as evidenced by the Cochrane Collaboration "Risk of bias" tool and MINORS tool. However, unlike other medical areas, the randomized evaluations of surgical interventions are difficult to conduct. Secondly, there was high heterogeneity in most of the parameters pooled by meta-analysis, which may be attributed to a variety of potential confounding factors, i.e., patient characteristics, surgical techniques, follow-up time, and techniques of PSG scoring. Thirdly, only articles in English were included in our study, which may result in the language bias[20]. Fourthly, since the comparison between MMA and MLS was clarified by separately pooling results from studies on these two types of surgery, it was not possible to quantify the differences in surgical outcomes between MMA and MLS for treatment of OSA. By the means of quasi-experimental studies or comparative cohort studies, the lack of comparative studies between MMA and MLS for treating OSA should be addressed in the future.

CONCLUSION

This systematic review and meta-analysis demonstrate that both MMA and MLS are effective treatment options for OSA with an acceptable rate of morbidity. However, regardless of disease severity, MMA may offer greater improvements in AHI compared to MLS, although this conclusion is based on separate analysis of MMA and MLS studies. The rates of major complication and minor complication of MMA are both higher than those of MLS.

Table 1. Characteristics of studies on maxillomandibular advancement surgery

Study	Design	N	Age (years) (mean± SD)	% Male	Degree of advancement (mm) (mean±SD)		Follow-up (mean ±SD)	BMI (mean ±SD)	
					Max	Mand		Pre-op	Post- op
Bettega et al. 2000	Retro	20	44.4± 10.6	90	11.8± 0.5	11.8± 0.5	6m	26.9± 4.3	25.4± 3.3
Bianchi et al. 2014	Retro	10	45±14	100	10	10	6m		
Boyd et al. 2015	Pro	14			7.0± 2.3	9.2± 3.3	6.6±2.8y		
Conradt et al. 1997	Retro	15	44±12	93.3			>2y	28.3± 3.4	
Gerbino et al. 2014	Pro	10	44.9		9.2± 1.2	10.4± 2.2	6m	31.6± 5.5	28± 1.4
Goh et al. 2003	Pro	11	42.8±8.2	100	10	10	7.7m	29.4± 4.6	27.2± 3.3
Goodday et al. 2016	Retro	13	37.8±8.6	84.6			9.6m	38.8± 10.9	37.3± 8.0
Hsieh et al. 2014	Pro	16	33±7.9	75			12±8m	22.0± 3.3	
Kastoer et al. 2019	Pro	14	51.1±7.3	57.1			6m	25.7± 3.7	
Li et al. 1999	Retro	175	43.5± 11.5	83			6m		
Li et al. 2000	Retro	40	45.6± 20.7	82.5	10.8± 2.7	10.8± 2.7	4.2±2.7y	31.4± 6.7	32.2± 6.3
Li et al. 2001	Retro	52	46.6±6.7	82.7	10.5± 1.5		6m	32.0± 6.0	
Li et al. 2002	Pro	12	47.3±9.8	75	10.5± 1.2	10.5± 1.2	6m	33.5± 6.2	32.3± 4.1
Liao et al. 2015	Pro	20	33.4±6.5	85			14± 9.3m	22.4± 3.4	
Liu et al. 2016	Retro	20	44±12	85	7±1.4		6m	27±4.6	27.4± 4.6
Rubio-Bueno et al. 2017	Pro	34	40.8± 13.9	41.2	4.9± 3.2	10.4± 3.9	6m	27.6± 4.5	25.5± 4.3
Veys et al. 2017	Pro	10	44.7±9.5	80	4.8± 2.8	8.3± 2.3	6m		
Vicini et al. 2010	RCT	25	49.1±9.1	92		11	13± 2.5m	32.7± 5.8	31.4± 6.5
Vigneron et al. 2017	Retro	29	40.7± 12.6		8.4± 4.1	11.7± 5.1	12.5± 3.5y	24.6±4	
Wu et al. 2019	Retro	28	37.2± 11.8	53.6	2.0± 3.1	8.8± 3.7	>1y	24.2± 5.1	

AHI, apnea-hypopnea index (events/h); BMI, body mass index (kg/m^2); Day, days in hospital; ESS, Epworth sleepiness scale; LSAT, lowest oxygen saturation (%); m, months; Max, maxilla; Mand, mandible; N, number of patients; Post-op, postoperative; Pre-op, preoperative; Pro, prospective; RCT, randomized controlled trial; Retro, retrospective; y, years.

[a] Respiratory disturbance index (RDI) in this study was extracted as AHI.

[b] The number of patients was 9.

[c] This study defined surgical success as an AHI < 15 events/h with ≥ 50% reduction in postoperative AHI.

[d] This study did not define the criteria of surgical success.

[e] This study defined surgical success as a RDI < 15 events/h with ≥ 50% reduction in postoperative RDI.

[f] This study defined surgical success as a postoperative RDI < 20 events/h.

AHI (mean ±SD)		LSAT (mean±SD)		ODI (mean±SD)		ESS (mean±SD)		% Success	% Cure	Day
Pre-op	Post- op	Pre-op	Post- op	Pre-op	Post-op	Pre-op	Post- op			
59.3± 29.0	11.1± 8.9	82±11	90±7					75[c]		7
56.8± 5.2	12.3± 5.5									
50.0± 20.0	8.0± 10.7									2.3
51.4± 16.9	8.5± 9.4									
69.8± 35.2	17.3± 16.7			59.5± 5.3	9.1± 8.0			80[d]		
70.7± 15.9	11.4± 7.4	58.6± 12.3	83.9±8.8					81.8		4.2
117.9± 9.2	16.1± 26.2					12.9± 5.5[b]	5.0± 4.1[b]	76.9	46.2	
35.7±18	4.8± 4.4							100		
40.2± 25.6	9.9± 7.2			13.5± 8.6	4.0± 3.5	13±6	9±7			
72.3± 26.7[a]	7.2± 7.5[a]	63.2± 17.5	86.6±3.4					95[e]		2.4
71.2± 27.0[a]	7.6± 5.1[a]	67.5± 14.8	86.3±3.9					90[e]		2.4
61.6± 23.9[a]	9.2±8[a]	75.9± 10.6	87.5±4.7					90[f]		
75.3± 26.4[a]	10.4± 10.8[a]	74.2±12	86.9±6.7					83.3[f]		
41.6± 19.2	5.3±4	80.2± 9.7	88.9±5			11.9± 7.3	7±3	100[c]		
53.6± 26.6	9.5± 7.4	80.9± 8.9	94.1±3.5	38.7± 30.3	8.1± 9.2	17±4.8	5.7± 2.7	90	50	
38.3± 10.7	6.5± 4.3			34.7± 12.5	5.4± 4.1	17.4± 5.4	0.8± 1.4	100	52.9	<2
26.8± 12.7	12.3± 14.4					14.1± 5.9	5.7± 3.0	70	40	
56.8± 16.5	8.1±7					11.6± 2.8	7.7± 1.3	88	36	<7
56.6±24	25.5± 20.6		83.1±5.8				7.5± 4.7	41.4		5-8
59.3± 14.5	10.9± 3.3	73.4± 10.8	87.9±3.7			12.8± 2.8	6.9± 2.5	85.7	46.4	

Table 2. Characteristics of studies on multilevel surgery

Study	Design	N	Age (years) (mean ± SD)	% Male	Follow-up (mean ± SD)	BMI (mean ±SD)		AHI (mean±SD)	
						Pre-op	Post- op	Pre-op	Post- op
Subgroup 1. Soft palate level & tongue base level									
Aynaci et al. 2018	Retro	20	41.7± 8.4	85	6m			25.1± 6.0	13.40± 3.0
		20	45.0± 7.1	80	6m			36.4± 4.9	10.0± 1.9
Babademez et al. 2010	Retro	16	41.3± 10.5	100	6m	29.6± 2.5	29.5± 2.6	20.1± 10.5	8.9±6.5
Bostanci et al. 2016	Retro	82	50.5± 9.2	92.7	6m	30.6± 3.0		47.3± 18.7	19.9± 17.4
Cambi et al. 2019	Retro	20	55.6± 9.1	85	6m	30.1± 2.3	28.9± 2.4	49.3± 18.5	19.4± 10.1
Cammaroto et al. 2017	Retro	10	58.4± 9.9		≥6m	26.8± 3.7		34.0± 14.0	22.9± 13.3
		10	52.8± 11.4		≥6m	27.0± 2.1		35.6± 13.9	9.6±9.3
		10	48.2± 11.4		≥6m	28.8± 2.6		37.8± 21.6	13.5± 7.8
Ceylan et al. 2009	Pro	26	46.3± 3.9	88.5	1y	28.6± 3.8		29.6± 7.8	16.1± 3.9
Chen et al. 2019	Pro	22	40.5± 6.8	90.9	6m	29.1± 3.5	28.9± 3.6	66.4± 17.0	35.1± 18.5
Chen et al. 2014	Pro	24	42.3± 8.3	100	1y	27.5± 2.7		46.1± 13.3	26.2± 18.9
		26	43±9.4	100	1y	26.6± 2.4		51.8± 14.7	25.2± 7.9
Chen et al. 2018-group 2	RCT	45			6m			49.7± 7.4	27.0± 4.0
Chiffer et al. 2015	Pro	18		83.3	6-24m	34.2± 6.9	32.2± 7.2	53.9± 25.4	19.8± 22.1
Emara et al. 2011	Pro	23			6m	27.5± 1.1		40.7± 17.4	15.4± 10.7
Eun et al. 2008	Pro	66	44.7± 10.6	87.9	6m	27.6± 3.4	27.4± 3.2	22.9± 14.7[a]	13.9± 18.7[a]
Friedman et al. 2003	Retro	143	47.0± 11.7	72.7	≥6m	31.5± 4.8		43.9± 23.7	28.1± 20.6
Friedman et al. 2007	Retro	122	42.2± 11.4	65.6	12.2± 4.2m	28.3± 5.0		23.2± 7.6	14.5± 10.2
Gunbey et al. 2015	Pro	42	47.1± 14.5	69	6m	32.6± 8.4	31.2± 9.1	35.8± 12.1	15.3± 9.8
Hendler et al. 2001	Retro	33	47±10.5	84.8	6m	32.6± 7.0		60.2± 29.9[b]	28.8± 27.4[b]
Li et al. 2016	Retro	30	41.5± 9.4	90	6-8m	26.4± 3.0	25.5± 3.0	48.4± 16.9	16.5± 11.2
Li et al. 2016	Retro	25	42±9	80	6-8m	26.5± 3.0	25.6± 2.9	45.7± 21.7	12.8± 8.2
Li et al. 2013	Retro	45	40.3± 12.8	100	6m	27.7± 3.6	27.4± 3.4	39.4± 17.8	8.9±5.9
Lin et al. 2010	Retro	43	39	95.3	6m	27.9± 3.9	28.0± 3.9	51.5± 25.4	23.4± 24.7
Neruntarat et al. 2009	Pro	72	35.8± 10.9	95.8	14.2± 1.8m	28.8± 2.4	30.9± 2.8	35.6± 9.2	16.8± 3.2
Omur et al. 2005	Retro	22	44.5± 8.0		14.0± 6.7m	30.3± 3.8	29.2± 3.3	47.5± 15.7[b]	17.3± 14.2[b]

LSAT (mean± SD)		ODI (mean±SD)		ESS (mean±SD)		% Success	% Cure	Day (mean±SD)
Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op			
80.3± 6.0	91.9± 1.7			19.8± 2.5	11.1± 1.5			1.3±0.4
78.8± 3.5	96.3± 1.2			20.1± 1.7	6.5±1.3			2.6±0.8
84.6± 3.4	86.6± 2.0					62.5		
75.7± 8.9	82.3± 7.4	44.8± 21.4	17.7± 15.9			74.4		
69.5± 9.9	80.0± 7.4			12.7± 4.3	7.7±4.5	60		5.2±0.9
				12.3± 4.2	8.5±5.4	50		6.7±1.3
				13.0± 4.5	4.9±3.9	90		7.1±1.5
				10.4± 2.5	3.9±3.6	90		7.1±3.2
86.8± 8.9	94.6± 4.9			10.8± 3.2	8.2±2.7	53.8[c]		
61.9± 12.5	67.8± 19.3					63.6[d]		
60.3± 7.3	76.9± 4.0			13.0± 2.6	8.5±2.0	64.4	11.1	
						61		
78.9± 12.6	87.2± 11.1			14.2± 2.3	8.3±3.9	86.9		
79.1± 5.7[a]	79.4± 16.5[a]			11.4± 5.0	7.5±4.5	53.6	50	2
81.4± 10.4	85.9± 9.8			15.2± 3.1	8.3±3.9			
88.9± 4.8	90.4± 4.3			9.7±3.9	6.9±3.3	47.5		
72.4± 15.2	80.4± 12.3							
76.4± 8.5	82.4± 5.4			10.9± 4.7	8.7±3.9	73		
77.1± 10.5	83.3± 5.6			9.6±4.9	7.5±4.3	80		5.6±1.3
66±16	83±5			12.9± 4.9	3.4±2.9	51.1	37.8	7
75.5± 10.4	82.1± 10.9			12.8± 5.1	10.0± 4.3	60.5		
85.6± 3.4	88.2± 2.4			14.2± 3.4	8.2±2.5	55.6		1
				13.9± 2.2	5.4±4.3	81.8[e]		3.8±1.6

Table 2. continued

Study	Design	N	Age (years) (mean ± SD)	% Male	Follow-up (mean ± SD)	BMI (mean ±SD)		AHI (mean±SD)	
						Pre-op	Post- op	Pre-op	Post- op
Plzak et al. 2013	Retro	79	50.5± 9.1	78.5	6m	28.1± 3.1	28.3± 3.5	28.7± 17.1	14.1± 18.2
Sezen et al. 2011	Pro	12	48.3± 8.8	83.3	1y	30.9± 2.8	30.6±2.7	28.8± 10.7	15.3± 11.1
Toh et al., 2014	Retro	20	47.1± 11.4	80	8.2± 3.2m	26.9± 2.9	26.2± 3.0	41.3± 22.1	13.5± 17.1
Tsou et al. 2018	Retro	36	40.2± 9.1	88.9	1y	26.9± 2.9	26.1± 2.9	25.1± 17.5	17.5± 18.9
Turhan et al. 2015	Pro	90	48	91.1	6m	30.7		51.8± 18.8	20.5± 17.7
Vicente et al. 2006	Pro	54	47.3± 4.5	92.6	3y	29.6± 4.8	28.1± 4.8	52.8± 14.9	14.1± 23.5
Vicini et al. 2014	Retro	12	49.6± 11.3	100	≥6m	28.2± 2.7	27.0± 2.1	38.4± 19.7	19.8± 14.1
		12	54.2± 10.8	75	≥6m	27.3± 2.0	26.1± 2.0	38.5± 14.3	9.9±8.6
Wang et al. 2013	Retro	36	44	86.1	1y	29.2± 2.9	28.9± 2.8	59.8± 20.5	23.2± 18.4
Yuksel et al. 2016	Pro	14	41.4± 8.9	92.9	2y	30.8± 3.7		33.2± 18.9	18.0± 11.3
Subgroup 2. Soft palate level & hyoid level									
Benazzo et al. 2008	Retro	109	51.3± 9.4	100	6m	28.2± 3.1	27.7± 2.9	37.0± 19.1	18.7± 16.0
El-Anwar et al. 2018	Pro	20	47.1± 9.2		6-14m	33.4± 2.5		48.8± 31.6	24.5± 10.9
Tantawy et al. 2018	Pro	32	46±4.7	43.8	6-14m	33.4± 2.0		68.4± 25.3	25.6± 9.5
Subgroup 3. Soft palate level & tongue base level & hyoid level									
Chen et al. 2018-group 1	RCT	45			6m			52.3± 6.3	14.9± 2.2
Cillo et al. 2013	Retro	13	43.0± 2.4	100	18± 3.6m			28.3± 13.2	12.1± 8.2
Neruntarat et al. 2003	Retro	46	40.1± 4.2	82.6	3.3± 0.5y	28.9± 2.1	31.1± 2.7	47.9± 8.4[b]	18.6± 4.1[b]
Sorrenti et al. 2006	Retro	10	51.7±7	100	14.6m	31.0± 2.5	28.5± 2.4	54.7± 11.5	9.4±5.4
Sun et al. 2008	Pro	31	41±9.8	100	6m	28.5± 3.2	28.4± 3.6	65.9± 23.8	28.6± 29.1
Yi et al. 2011	Pro	26	47	84.6	6m	29.3	28.0	65.6± 17.6	30.1± 23.1

AHI, apnea-hypopnea index (events/h); BMI, body mass index (kg/m^2); Day, days in hospital; ESS, Epworth sleepiness scale; LSAT, lowest oxygen saturation (%); m, months; N, number of patients; Post-op, postoperative; Pre-op, preoperative; Pro, prospective; RCT, randomized controlled trial; Retro, retrospective; y, years.

[a] The number of patients was 58.

[b] Respiratory disturbance index (RDI) in this study was extracted as AHI.

[c] This study defined surgical success as an AHI < 20 events/h with ≥ 50% reduction in postoperative AHI and a postoperative ESS score < 10.

[d] This study defined surgical success as ≥ 50% reduction in postoperative AHI.

[e] This study defined surgical success as a RDI < 20 events/h with ≥ 50% reduction in postoperative RDI.

[f] This study defined surgical success as an AHI < 15 events/h with ≥ 50% reduction in postoperative AHI.

[g] This study defined surgical success as an AHI < 20 events/h with ≥ 50% reduction in postoperative AHI and a postoperative ESS score < 11.

[h] This study defined surgical success as an AHI < 20 events/h with significant clinical improvement reported by patients.

LSAT (mean± SD)		ODI (mean±SD)		ESS (mean±SD)		% Success	% Cure	Day (mean±SD)
Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op			
		15.1± 8.2	10.3± 7.9	10.6± 3.8	7.3±3.2	51.7		3
				14.8± 2.5	7.6±3.2	50[f]		
72.9± 19.3	84.5± 7.1			13.0± 2.8	5.6±4.4	55	35	4.1±0.7
				11.9± 4.3	10.2± 4.3	66.7		
75.6± 9.3	82.4± 6.6	48.0± 19.5	18.2± 15.5			74.4		
76.2± 12.4	82.2± 11.2			12.2± 3.3	8.2±6.1	78[g]		
				13.75±4	7.6±4.4	33.3		8.3±2.4
				12±4.9	4.4±4.1	83.3		7.3±1.5
70.5± 12.4	85.6± 10.0			12.2± 5.8	5.5±3.6	66.7		
		30.3± 16.9	15.5± 13.2	11.9± 7.0	5.0±4.4	57.1		
				10.5± 3.1	7.2±2.3	61.5		
73.5± 14.8	84±5.3			12.6± 5.6	4.1±2.7			
66.8± 11.3	83.2± 2.9			13.8± 5.4	5.2±1.6			
58.7± 8.3	86.0± 5.4			12.8± 2.2	6.0±1.3	84.4	11.1	
				15.2± 3.0	6.3±3.9			
81.2± 2.9	87.2± 3.1			15.9± 2.7	7.3±2.7	65.2[e]		
77±6.2	90.7±3			14.3	5.3	100		16±2
72.7± 11.9	75.0± 12.5			17.1± 4.1	8.9±4.9	64.5[h]		
74±28	82.8			13.5± 5.9	6.8±5.2	46.2		

Table 3. Summary of weighted data for studies on maxillomandibular advancement surgery and multilevel surgery

Variable		Pre-op		Post-op		Change			P^b
		N	Weighted mean ± SD	N	Weighted mean ± SD	WMD	95% CI	P^a	
Age, years	MMA	504	42.9 ± 11.3						
	MLS	1313	45.5 ± 10.8						
BMI, kg/m²	MMA	359	28.6 ± 6.6	185	29.4 ± 6.2				
	MLS	1420	29.1 ± 4.2	878	28.4 ± 4.1				
AHI, events/h	MMA	393	57.3 ± 26.6	393	10.4 ± 11.2	-46.2	[-52.4, -39.9]	**<0.001**	**<0.001**
	MLS	1639	42.2 ± 21.0	1639	19.0 ± 16.4	-24.7	[-28.1, -21.4]	**<0.001**	
LSAT, %	MMA	203	74.4 ± 12.9	203	88.1 ± 5.5	13.5	[10.5, 16.5]	**<0.001**	**0.014**
	MLS	1164	76.7 ± 12.5	1164	84.2 ± 9.5	8.7	[6.2, 11.1]	**<0.001**	
ODI, events/h	MMA	78	35.1 ± 22.8	78	6.3 ± 6.4	-30.3	[-46.3, -14.2]	**<0.001**	0.322
	MLS	265	36.3 ± 22.5	265	15.5 ± 14.1	-19.1	[-34.2, -4.0]	**0.010**	
ESS	MMA	164	14.1 ± 5.4	164	4.8 ± 4.1	-8.5	[-12.2, -4.9]	**<0.001**	0.143
	MLS	1309	12.6 ± 4.4	1309	7.3 ± 3.9	-5.8	[-6.6, -5.0]	**<0.001**	
Success rate, %	MMA	340				85.0	[76.4, 91.9]	**<0.001**	**<0.001**
	MLS	1339				65.1	[60.6, 69.5]	**<0.001**	
Cure rate, %	MMA	130				46.3	[38.0, 54.7]	**<0.001**	0.135
	MLS	221				28.1	[13.2, 46.1]	**<0.001**	

AHI, apnea-hypopnea index; BMI, body mass index; CI, confidence interval; ESS, Epwoth sleepiness scale; LSAT, lowest oxygen saturation; MLS, multilevel surgery; MMA, maxillomandibular advancement; N, number of patients; Post-op, postoperative; Pre-op, preoperative; SD, standard deviation; WMD, weighted mean difference.

[a] Z-test for overall effect size.

[b] Z-test for comparison the difference between two estimates.

Table 4. Summary of weighed data for studies on multilevel surgery – three subgroups according to the different target levels of obstructive sites addressed by surgery

Variable	Pre-op		Post-op		Change		
	N	Weighted mean ± SD	N	Weighted mean ± SD	WMD	95% CI	*P*[a]
Subgroup 1. Soft palate level & tongue base level							
Age, years	1052	45.2 ± 11.2					
BMI, kg/m²	1172	29.0 ± 4.3	682	28.4 ± 4.4			
AHI, events/h	1307	40.4 ± 20.3	1307	18.7 ± 16.6	-22.7	[-25.7, -19.7]	**<0.001**
LSAT, %	980	77.9 ± 12.1	980	84.2 ± 9.8	7.2	[5.0, 9.3]	**<0.001**
ODI, events/h	265	36.3 ± 22.5	265	15.5 ± 14.1	-19.1	[-34.2, -4.0]	**0.010**
ESS	987	12.4 ± 4.3	987	7.5 ± 4.1	-5.2	[-6.1, -4.4]	**<0.001**
Success rate, %	1072				64.2	[59.3, 68.9]	**<0.001**
Cure rate, %	176				33.0	[16.1, 52.5]	**<0.001**
Subgroup 2. Soft palate level & hyoid level							
Age, years	161	49.7 ± 8.9					
BMI, kg/m²	161	29.9 ± 3.7	109	27.7 ± 2.9			
AHI, events/h	161	44.7 ± 25.4	161	20.8 ± 14.6	-28.4	[-45.2, -11.5]	**0.001**
LSAT, %	52	69.4 ± 13.0	52	83.5 ± 3.9	14.1	[8.5, 19.8]	**<0.001**
ODI, events/h							
ESS	161	11.4 ± 4.2	161	6.4 ± 2.5	-6.7	[-10.8, -2.5]	**0.002**
Success rate, %	109				61.5		
Cure rate, %							
Subgroup 3. Soft palate level & tongue base level & hyoid level							
Age, years	100	41.9 ± 7.3					
BMI, kg/m²	87	29.0 ± 2.7	87	29.8 ± 3.3			
AHI, events/h	171	54.0 ± 17.4	171	20.1 ± 17.0	-33.4	[-39.7, -27.1]	**<0.001**
LSAT, %	132	71.2 ± 12.4	132	84.2 ± 8.8	12.4	[0.6, 24.3]	**0.040**
ODI, events/h							
ESS	161	14.8 ± 3.9	161	7.1 ± 3.7	-7.8	[-8.9, -6.7]	**<0.001**
Success rate, %	158				72.4	[55.3, 86.7]	**<0.001**
Cure rate, %	45				11.1		

AHI, apnea-hypopnea index; BMI, body mass index; CI, confidence interval; ESS, Epworth sleepiness scale; LSAT, lowest oxygen saturation; N, number of patients; Post-op, postoperative; Pre-op, preoperative; SD, standard deviation; WMD, weighted mean difference.

[a] Z-test for overall effect size.

Table 5. Summary of weighted data for studies on maxillomandibular advancement surgery and multilevel surgery in OSA patients with baseline AHI less than 40, from 40 to 70, and greater than 70 events/h

Variable		Pre-op		Post-op		Change			P^b
		N	Weighted mean ± SD	N	Weighted mean ± SD	WMD	95% CI	P^a	
Baseline AHI less than 40 events/h									
Age, years	MMA	60	39.4 ± 12.4						
	MLS	706	45.2 ± 11.7						
BMI, kg/m²	MMA	50	25.8 ± 4.9	34	25.5 ± 4.3				
	MLS	693	28.5 ± 4.2	501	28.4 ± 4.2				
AHI, events/h	MMA	60	35.7 ± 13.7	60	7.0 ± 7.3	-27.1	[-36.0, -18.2]	**<0.001**	**0.030**
	MLS	706	30.7 ± 15.6	706	15.1 ± 13.3	-16.7	[-19.9, -13.4]	**<0.001**	
LSAT, %	MMA								
	MLS	347	83.0 ± 10.5	347	87.0± 9.3	4.4	[1.9, 6.8]	**0.001**	
ODI, events/h	MMA	34	34.7 ± 12.5	34	5.4 ± 4.1	-29.3	[-33.7, -24.9]	**<0.001**	
	MLS	93	17.4 ± 11.3	93	11.1 ± 9.0	-8.2	[-17.6, 1.1]	0.080	
ESS	MMA	44	16.7 ± 5.6	44	1.9 ± 2.8	-12.7	[-20.8, -4.7]	**0.002**	0.076
	MLS	648	11.5 ± 4.7	648	7.1 ± 3.6	-5.4	[-6.6, -4.2]	**<0.001**	
Success rate, %	MMA	60				94.0	[74.3, 99.9]	**<0.001**	**<0.001**
	MLS	651				57.1	[51.7, 62.5]	**<0.001**	
Cure rate, %	MMA	44				50.0	[35.7, 64.2]	**<0.001**	0.579
	MLS	111				44.7	[33.2, 56.4]	**<0.001**	
Baseline AHI from 40 to 70 events/h									
Age, years	MMA	215	44.3 ± 10.6						
	MLS	607	45.8 ± 9.7						
BMI, kg/m²	MMA	233	27.9 ± 6.0	75	28.3 ± 5.3				
	MLS	727	29.7± 4.1	377	28.4 ± 4.1				
AHI, events/h	MMA	257	55.7 ± 23.0	257	11.4 ± 11.4	-44.1	[-47.8, -40.4]	**<0.001**	**<0.001**
	MLS	933	51.0 ± 20.3	933	22.0 ± 17.9	-30.7	[-34.0, -27.5]	**<0.001**	
LSAT, %	MMA	140	77.6 ± 10.7	140	89.1 ± 5.2	11.6	[9.4, 13.8]	**<0.001**	0.387
	MLS	817	74.1 ± 12.3	817	82.9 ± 9.4	9.9	[6.9, 13.0]	**<0.001**	
ODI, events/h	MMA	44	35.4 ± 28.5	44	7.0 ± 7.7	-30.4	[-57.6, -3.1]	**0.030**	0.900
	MLS	172	46.5 ± 20.4	172	18.0 ± 15.6	-28.6	[-32.4, -24.8]	**<0.001**	
ESS	MMA	107	13.2 ± 5.1	107	6.0 ± 4.0	-7.0	[-10.7, -3.4]	**<0.001**	0.633
	MLS	661	13.6 ± 4.2	661	7.5 ± 4.1	-6.1	[-7.1, -5.2]	**<0.001**	
Success rate, %	MMA	204				82.3	[69.1, 92.5]	**<0.001**	0.061
	MLS	688				70.5	[65.4, 75.3]	**<0.001**	
Cure rate, %	MMA	73				44.0	[33.1, 55.3]	**<0.001**	**0.020**
	MLS	110				17.4	[7.1, 31.0]	**<0.001**	

Table 5. continued

Variable		Pre-op		Post-op		Change			P^b
		N	Weighted mean ± SD	N	Weighted mean ± SD	WMD	95% CI	P^a	
Baseline AHI greater than 70 events/h									
Age, years	MMA	76	44.1 ± 16.4						
BMI, kg/m²	MMA	76	32.7 ± 7.7	76	32.4 ± 6.6				
AHI, events/h	MMA	76	79.8 ± 28.9	76	10.0 ± 12.6	-71.8	[-88.4, -55.2]	**<0.001**	
LSAT, %	MMA	63	67.2 ± 14.5	63	86.0 ± 5.6	18.7	[12.7, 24.6]	**<0.001**	
ODI, events/h									
ESS	MMA	13	12.9 ± 5.5	13	5.0 ± 4.1	-7.9	[-11.6, -4.2]	**<0.001**	
Success rate, %	MMA	76				84.2	[75.5, 91.3]	**<0.001**	
Cure rate, %	MMA	13				46.2			

AHI, apnea-hypopnea index; BMI, body mass index; CI, confidence interval; ESS, Epworth sleepiness scale; LSAT, lowest oxygen saturation; MLS, multilevel surgery; MMA, maxillomandibular advancement; N, number of patients; Post-op, postoperative; Pre-op, preoperative; SD, standard deviation; WMD, weighted mean difference.

[a] Z-test for overall effect size.

[b] Z-test for comparison the difference between two estimates.

SUPPLEMENTARY MATERIAL

Table S1a. Search strategy in MEDLINE database

Ovid MEDLINE(R) ALL <1946 to May 6, 2020>		
Step	**Search**	**Result**
1	exp Sleep Apnea Syndromes/ or Snoring/	34066
2	((sleep adj3 (apnea or apnoea or hypopnea or hypopnoea)) or (upper adj airway adj resistance) or (sleep adj disordered adj breathing) or snore or snoring).ti,ab,kf,ot.	39581
3	1 or 2	45774
4	(uvulopalatopharyngoplasty or H-UPPP or HUPPP or UPPP or palatopharyngealplasty or uvulopalatoplasty or uvuloplasty or uvuloflap or uvulopalatal-flap or Z-palatoplasty or palatoplasty or (ablation adj2 palate) or palatal-stiffening or pharyngoplasty or tonsillectomy or ((pillar or palatal) adj implant) or "palatal pillar" or ((uvula or palat* or pharynx or pharyngeal) adj3 (remove or removal or ablation or surgery or surgical or remodel* or resection))).ti,ab,kw.	12813
5	(((midline glossectomy or "genioglossus advancement" or (hypoglossal adj nerve-stimulation) or (transoral adj2 surger*) or (hypogloss* or epiglott* or tongue)) adj5 (surgery or surgical or remove or removal or remodel* or resection or reduction or suspension or coblation or ablation)) or "tongue stabilization" or tonsillectomy or epiglottidectomy or epiglottoplasty or hyoepiglottoplasty).ti,ab,kf.	11418
6	(((hyoid or thyrohyoid) adj (suspension or myotomy or advancement)) or hyoidopexy).ti,ab,kf.	135
7	4 and 5	8555
8	4 and 6	74
9	5 and 6	63
10	7 or 8 or 9	8594
11	(mma or maxillomandibular advancement or bimaxillary surgery or maxillary osteotomy or mandibular advancement or orthognathic surgery).ti,ab,kf.	6451
12	(multilevel or multi-level).ti,ab,kf.	31482
13	10 or 11 or 12	46384
14	3 and 13	2302
15	(case reports or review).pt.	4410761
16	exp animals/ not humans/	4582720
17	15 or 16	8814783
18	14 not 17	1737

Table S1b. Search strategy in EMBASE database

Embase Classic+Embase <1947 to May 6, 2020>		
Step	**Search**	**Result**
1	(uvulopalatopharyngoplasty or H-UPPP or HUPPP or UPPP or palatopharyngealplasty or uvulopalatoplasty or uvuloplasty or uvuloflap or uvulopalatal-flap or Z-palatoplasty or palatoplasty or (ablation adj2 palate) or palatal-stiffening or pharyngoplasty or tonsillectomy or ((pillar or palatal) adj implant) or "palatal pillar" or ((uvula or palat* or pharynx or pharyngeal) adj3 (remove or removal or ablation or surgery or surgical or remodel* or resection))).ti,ab,kw.	17201
2	((((midline glossectomy or "genioglossus advancement" or (hypoglossal adj nerve-stimulation) or (transoral adj2 surger*) or (hypogloss* or epiglott* or tongue)) adj5 (surgery or surgical or remove or removal or remodel* or resection or reduction or suspension or coblation or ablation)) or "tongue stabilization" or tonsillectomy or epiglottidectomy or epiglottoplasty or hyoepiglottoplasty).ti,ab,kw.	15411
3	(((hyoid or thyrohyoid) adj (suspension or myotomy or advancement)) or hyoidopexy).ti,ab,kw.	174
4	1 and 2	11764
5	1 and 3	90
6	2 and 3	79
7	4 or 5 or 6	11815
8	(mma or maxillomandibular advancement or bimaxillary surgery or maxillary osteotomy or mandibular advancement or orthognathic surgery).ti,ab,kw.	8418
9	(multilevel or multi-level).ti,ab,kw.	36392
10	7 or 8 or 9	56398
11	exp 'snoring'/ or exp 'sleep disordered breathing'/ or (sleep adj3 (apnea or apnoea or hypopnea or hypopnoea)).ti,ab. or 'upper airway resistance'.ti,ab. or 'sleep disordered breathing'.ti,ab. or snor*.ti,ab.	78264
12	10 and 11	3391
13	(case report or review).pt.	2490279
14	(exp experimental organism/ or animal tissue/ or animal cell/ or exp animal disease/ or exp carnivore disease/ or exp bird/ or exp experimental animal welfare/ or exp animal husbandry/ or animal behavior/ or exp animal cell culture/ or exp mammalian disease/ or exp mammal/ or exp marine species/ or nonhuman/ or animal.hw.) not human/	7089673
15	13 or 14	9367753
16	12 not 15	2980
17	limit 16 to embase	1713
18	limit 6 to conference abstracts	834
19	17 or 18	2547

Table S2a. Methodological appraisal of the individual studies according to MINORS assessment tool – maxillomandibular advancement surgery

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Total score	Quality
Quasi-experimental study														
Wu et al. 2019	2	2	0	2	1	2	0	0	0	2	0	2	13	Fair
Cohort study														
Bettega et al. 2000	2	2	0	2	1	2	2	0					11	Fair
Bianchi et al. 2014	2	2	0	2	1	2	0	0					9	Fair
Boyd et al. 2015	2	2	2	2	1	2	0	2					13	High
Conradt et al. 1997	2	2	0	2	1	2	2	0					11	Fair
Gerbino et al. 2013	2	2	2	2	1	2	2	0					13	High
Goh et al. 2013	2	2	2	2	0	2	2	0					12	Fair
Goodday et al. 2016	2	2	0	2	0	2	0	0					8	Fair
Hsieh et al. 2014	2	0	2	2	1	2	0	0					9	Fair
Kastoer et al. 2019	2	0	2	2	1	2	2	0					11	Fair
Li et al. 1999	0	2	0	2	0	2	2	0					8	Fair
Li et al. 2000	2	2	0	2	0	2	0	0					8	Fair
Li et al. 2001	2	2	0	2	0	2	0	0					8	Fair
Li et al. 2002	2	1	2	2	0	2	0	0					9	Fair
Liao et al. 2015	2	2	2	2	1	2	0	0					11	Fair
Liu et al. 2015	2	2	0	2	1	2	0	0					9	Fair
Rubio-Bueno et al. 2017	2	2	2	2	1	2	0	0					11	Fair
Veys et al. 2015	2	2	2	2	0	2	0	0					10	Fair
Vigneron et al. 2016	2	2	0	2	1	2	0	0					9	Fair

Q1, a clear study aim; Q2, inclusion of consecutive patients; Q3, prospective collection of data; Q4, endpoint appropriate to the aim of the study; Q5, unbiased assessment of the study; Q6, follow-up period appropriate to the aim of the study endpoint; Q7, loss of follow-up less than 5%; Q8, prospective calculation of the study size; Q9, an adequate control group; Q10, contemporary group; Q11, baseline equivalent of groups; Q12, adequate statistical analysis.

Table S2b. Methodological appraisal of the individual studies according to MINORS assessment tool – multilevel surgery

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Total score	Quality
Quasi-experimental study														
Aynaci et al. 2018	2	0	0	2	0	2	0	0	0	0	0	2	8	Low
Cammaroto et al. 2017	2	0	0	2	1	2	0	0	0	0	2	2	11	Fair
Ceylan et al. 2009	2	2	2	2	0	2	2	0	2	2	2	2	20	High
Chen et al. 2014	2	2	2	2	1	2	0	0	0	2	1	1	15	Fair
El-Anwar et al. 2018	2	2	2	2	0	2	0	0	0	2	0	2	14	Fair
Friedman et al. 2003	2	2	0	2	1	2	0	0	0	0	1	2	12	Fair
Li et al. 2013	2	2	0	2	1	2	0	0	0	2	2	2	15	Fair
Li et al. 2016	2	2	0	2	1	2	0	2	0	2	2	2	17	High
Sezen et al. 2011	2	2	2	2	1	2	0	0	0	2	0	1	13	Fair
Vicini et al. 2014	2	2	0	2	1	2	0	0	0	0	2	2	13	Fair
Yuksel et al. 2016	2	2	2	2	1	2	2	0	0	2	1	2	18	High
Cohort study														
Babademez et al. 2010	2	2	0	2	1	2	2	0					11	Fair
Benazzo et al. 2008	2	2	0	2	1	2	0	0					9	Fair
Bostanci et al. 2016	2	2	0	2	1	2	0	0					9	Fair
Cambi et al. 2019	2	2	0	2	1	2	2	0					11	Fair
Chen et al. 2019	2	2	2	2	1	2	2	0					13	High
Chiffer et al. 2015	2	0	2	2	0	2	2	0					10	Fair
Cillo et al. 2013	2	2	0	2	0	2	0	2					10	Fair
Emara et al. 2011	2	2	2	2	1	2	0	0					11	Fair
Eun et al. 2008	2	0	2	2	1	2	0	0					9	Fair
Friedman et al. 2007	2	2	2*	2	0	2	0	0					10	Fair
Gunbey et al. 2015	2	0	2	2	1	2	0	0					9	Fair
Hendler et al. 2001	2	0	0	2	0	2	0	0					6	Low
Li et al. 2016	2	2	0	2	1	2	0	0					9	Fair
Lin et al. 2010	2	2	2*	2	1	2	0	0					11	Fair
Neruntarat et al. 2003	2	2	0	2	1	2	0	0					9	Fair
Neruntarat et al. 2009	2	2	2	2	1	2	0	0					11	Fair
Omur et al. 2005	2	2	2*	2	1	2	2	0					13	High
Plzak et al. 2013	2	2	0	2	1	2	2	0	0	0	2	2	15	Fair
Sorrenti et al. 2006	2	2	0	2	1	2	2	0					11	Fair
Sun et al. 2008	2	2	0	2	1	2	2	0					11	Fair
Tantawy et al. 2018	2	2	2	2	0	2	0	0					10	Fair
Toh et al. 2014	2	2	2*	2	1	2	0	0					11	Fair
Tsou et al. 2018	2	2	0	2	2	2	0	0					10	Fair
Turhan et al. 2015	2	2	2	2	1	2	2	0					13	High
Vicente et al. 2006	2	2	2	2	0	2	2	0					12	Fair
Wang et al. 2013	2	2	0	2	1	2	2	0					11	Fair
Yi et al. 2011	2	2	2	2	1	2	2	0					13	High

Q1, a clear study aim; Q2, inclusion of consecutive patients; Q3, prospective collection of data; Q4, endpoint appropriate to the aim of the study; Q5, unbiased assessment of the study; Q6, follow-up period appropriate to the aim of the study endpoint; Q7, loss of follow-up less than 5%; Q8, prospective calculation of the study size; Q9, an adequate control group; Q10, contemporary group; Q11, baseline equivalent of groups; Q12, adequate statistical analysis.

* A retrospective study of prospectively collected data.

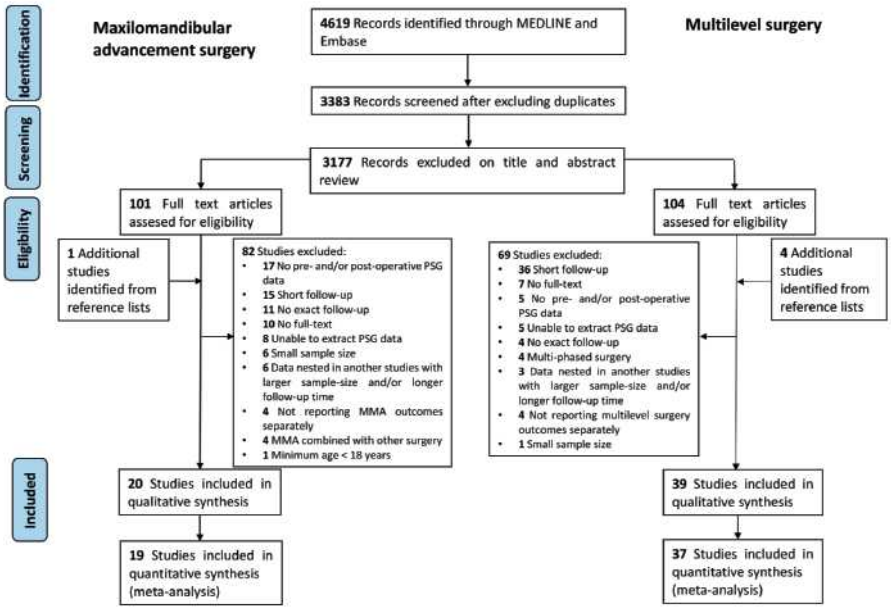


Fig. S1. PRISMA flow diagram of the study selection process

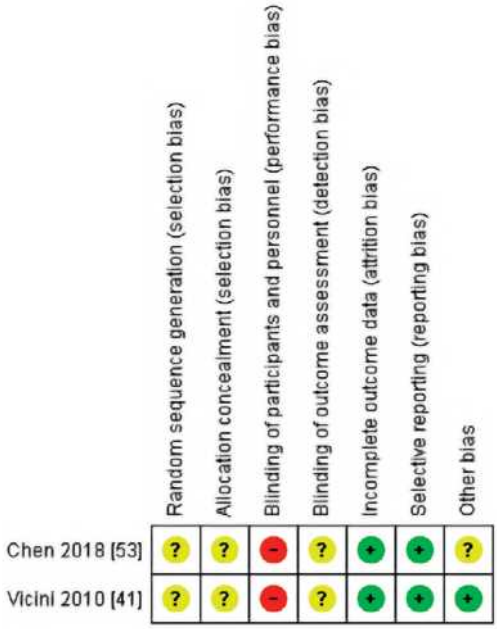
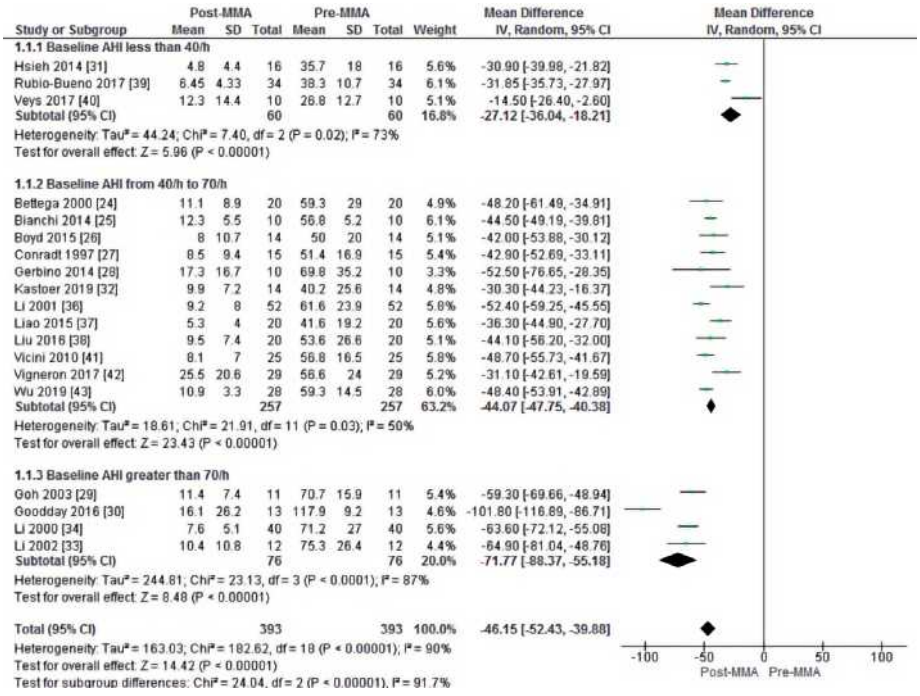
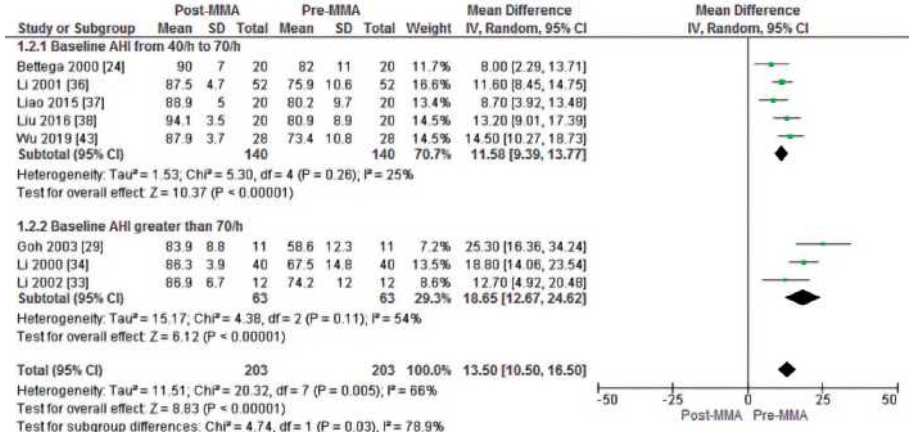


Fig. S2. Risk of bias assessment of randomized controlled trials using the Cochrane Collaboration "Risk of bias" tool

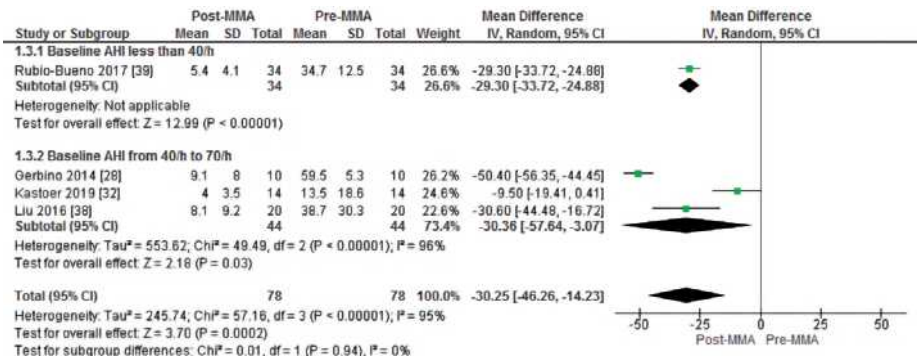
a


Post-MMA
Pre-MMA
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
1.1.1 Baseline AHI less than 40/h
Hsieh 2014 [31] 4.8 4.4 16 35.7 18 16 5.6% -30.90 [-39.98, -21.82]
Rubio-Bueno 2017 [39] 6.45 4.33 34 38.3 10.7 34 6.1% -31.85 [-35.73, -27.97]
Veys 2017 [40] 12.3 14.4 10 26.8 12.7 10 5.1% -14.50 [-26.40, -2.60]
Subtotal (95% CI) 60 60 16.8% -27.12 [-36.04, -18.21]
Heterogeneity: Tau² = 44.24; Chi² = 7.40, df = 2 (P = 0.02); I² = 73%
Test for overall effect: Z = 5.96 (P < 0.00001)
1.1.2 Baseline AHI from 40/h to 70/h
Bettega 2000 [24] 11.1 8.9 20 59.3 29 20 4.9% -48.20 [-61.49, -34.91]
Bianchi 2014 [25] 12.3 5.5 10 56.8 5.2 10 6.1% -44.50 [-49.19, -39.81]
Boyd 2015 [26] 8 10.7 14 50 20 14 5.1% -42.00 [-53.88, -30.12]
Conradt 1997 [27] 8.5 9.4 15 51.4 16.9 15 5.4% -42.90 [-52.69, -33.11]
Gerbino 2014 [28] 17.3 16.7 10 69.8 35.2 10 3.3% -52.50 [-76.65, -28.35]
Kastoer 2019 [32] 9.9 7.2 14 40.2 25.6 14 4.8% -30.30 [-44.23, -16.37]
Li 2001 [36] 9.2 8 52 61.6 23.9 52 5.8% -52.40 [-59.25, -45.55]
Liao 2015 [37] 5.3 4 20 41.6 19.2 20 5.6% -36.30 [-44.90, -27.70]
Liu 2016 [38] 9.5 7.4 20 53.6 26.6 20 5.1% -44.10 [-56.20, -32.00]
Vicini 2010 [41] 8.1 7 25 56.8 16.5 25 5.8% -48.70 [-55.73, -41.67]
Vigneron 2017 [42] 25.5 20.6 29 56.6 24 29 5.2% -31.10 [-42.61, -19.59]
Wu 2019 [43] 10.9 3.3 28 59.3 14.5 28 6.0% -48.40 [-53.91, -42.89]
Subtotal (95% CI) 257 257 63.2% -44.07 [-47.75, -40.38]
Heterogeneity: Tau² = 18.61; Chi² = 21.91, df = 11 (P = 0.03); I² = 50%
Test for overall effect: Z = 23.43 (P < 0.00001)
1.1.3 Baseline AHI greater than 70/h
Goh 2003 [29] 11.4 7.4 11 70.7 15.9 11 5.4% -59.30 [-69.66, -48.94]
Goodday 2016 [30] 16.1 26.2 13 117.9 9.2 13 4.6% -101.80 [-116.89, -86.71]
Li 2000 [34] 7.6 5.1 40 71.2 27 40 5.6% -63.60 [-72.12, -55.08]
Li 2002 [33] 10.4 10.8 12 75.3 26.4 12 4.4% -64.90 [-81.04, -48.76]
Subtotal (95% CI) 76 76 20.0% -71.77 [-88.37, -55.18]
Heterogeneity: Tau² = 244.81; Chi² = 23.13, df = 3 (P < 0.0001); I² = 87%
Test for overall effect: Z = 8.48 (P < 0.00001)
Total (95% CI) 393 393 100.0% -46.15 [-52.43, -39.88]
Heterogeneity: Tau² = 163.03; Chi² = 182.62, df = 18 (P < 0.00001); I² = 90%
Test for overall effect: Z = 14.42 (P < 0.00001)
Test for subgroup differences: Chi² = 24.04, df = 2 (P < 0.00001), I² = 91.7%
-100 -50 0 50 100
Post-MMA Pre-MMA

b


Post-MMA
Pre-MMA
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
1.2.1 Baseline AHI from 40/h to 70/h
Bettega 2000 [24] 90 7 20 82 11 20 11.7% 8.00 [2.29, 13.71]
Li 2001 [36] 87.5 4.7 52 75.9 10.6 52 16.6% 11.60 [8.45, 14.75]
Liao 2015 [37] 88.9 5 20 80.2 9.7 20 13.4% 8.70 [3.92, 13.48]
Liu 2016 [38] 94.1 3.5 20 80.9 8.9 20 14.5% 13.20 [9.01, 17.39]
Wu 2019 [43] 87.9 3.7 28 73.4 10.8 28 14.5% 14.50 [10.27, 18.73]
Subtotal (95% CI) 140 140 70.7% 11.58 [9.39, 13.77]
Heterogeneity: Tau² = 1.53; Chi² = 5.30, df = 4 (P = 0.26); I² = 25%
Test for overall effect: Z = 10.37 (P < 0.00001)
1.2.2 Baseline AHI greater than 70/h
Goh 2003 [29] 83.9 8.8 11 58.6 12.3 11 7.2% 25.30 [16.36, 34.24]
Li 2000 [34] 86.3 3.9 40 67.5 14.8 40 13.5% 18.80 [14.06, 23.54]
Li 2002 [33] 86.9 6.7 12 74.2 12 12 8.6% 12.70 [4.92, 20.48]
Subtotal (95% CI) 63 63 29.3% 18.65 [12.67, 24.62]
Heterogeneity: Tau² = 15.17; Chi² = 4.38, df = 2 (P = 0.11); I² = 54%
Test for overall effect: Z = 6.12 (P < 0.00001)
Total (95% CI) 203 203 100.0% 13.50 [10.50, 16.50]
Heterogeneity: Tau² = 11.51; Chi² = 20.32, df = 7 (P = 0.005); I² = 66%
Test for overall effect: Z = 8.83 (P < 0.00001)
Test for subgroup differences: Chi² = 4.74, df = 1 (P = 0.03), I² = 78.9%
-50 -25 0 25 50
Post-MMA Pre-MMA

c



d

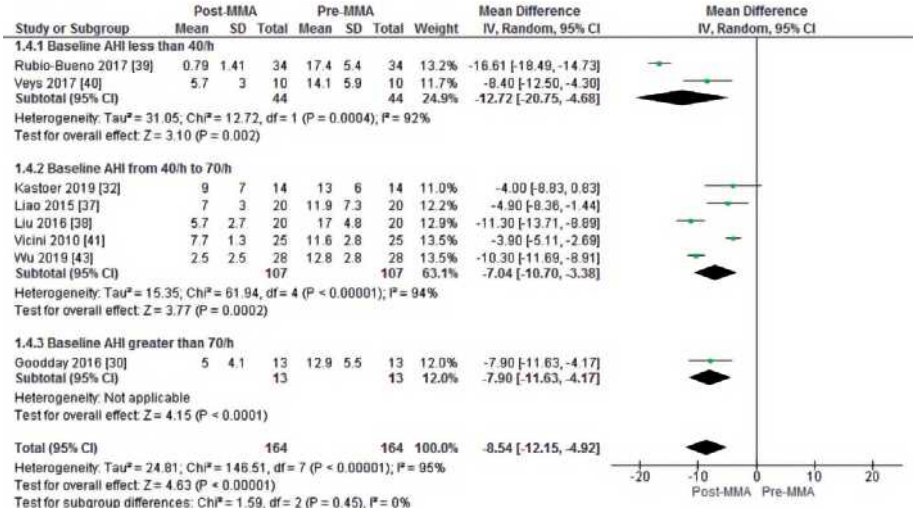
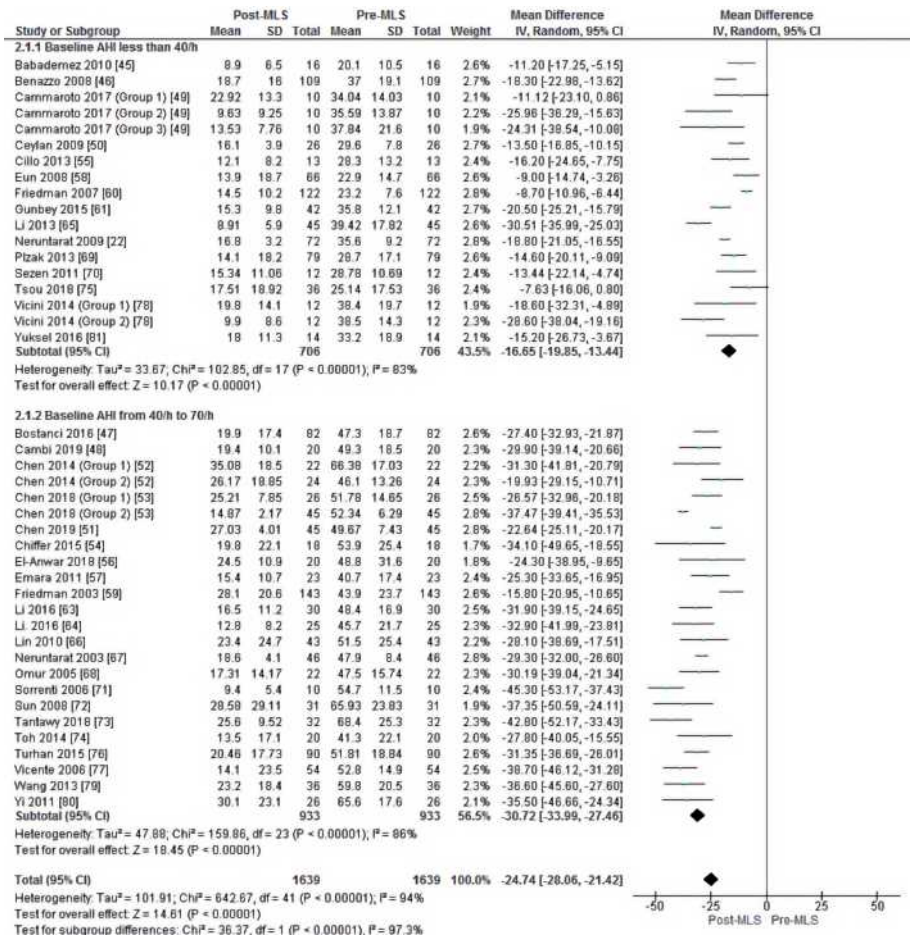
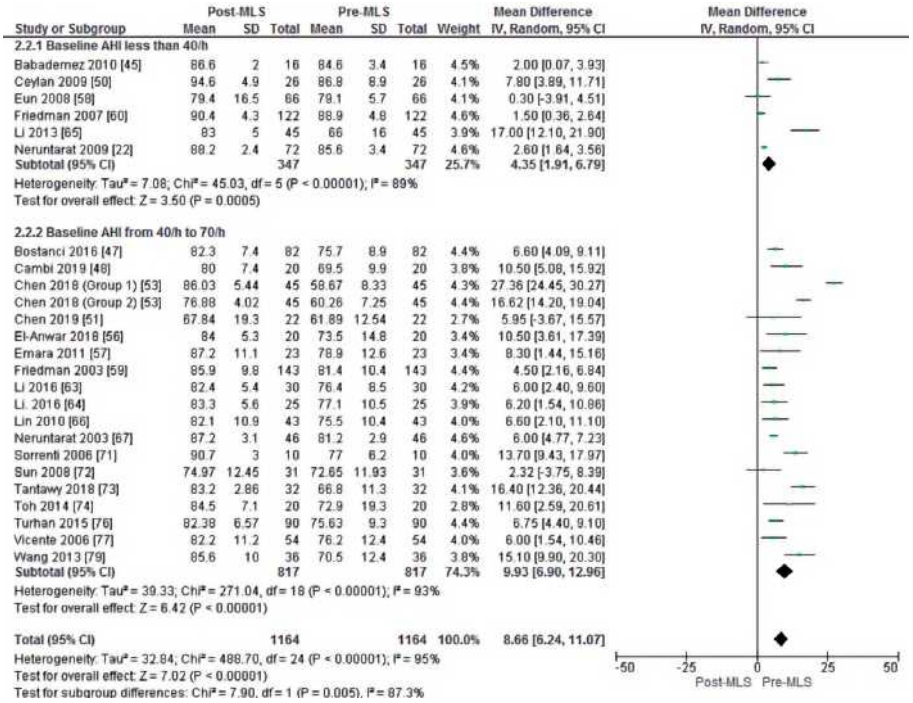


Fig. S3. Pre- and post-MMA mean difference for apnea-hypopnea index (a), lowest oxygen saturation (b), oxygen desaturation index (c), and Epworth sleepiness scale (d). CI, confidence interval; MMA, maxillomandibular advancement; SD, standard deviation.

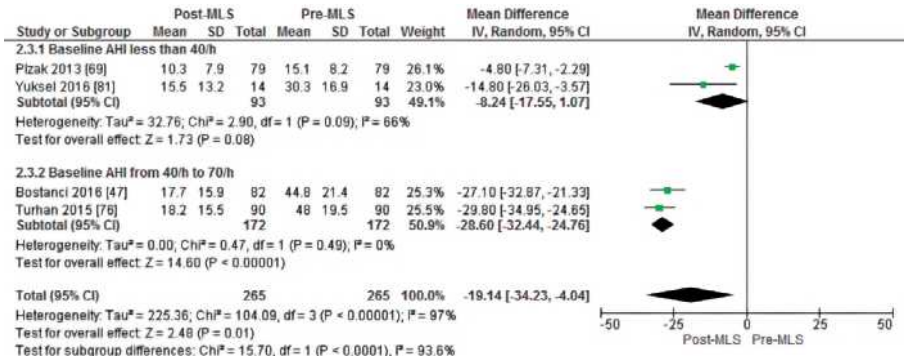
a


Post-MLS
Pre-MLS
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
2.1.1 Baseline AHI less than 40/h
Babademez 2010 [45] 8.9 6.5 16 20.1 10.5 16 2.6% -11.20 [-17.25, -5.15]
Benazzo 2008 [46] 18.7 16 109 37 19.1 109 2.7% -18.30 [-22.98, -13.62]
Camnmaroto 2017 (Group 1) [49] 22.92 13.3 10 34.04 14.03 10 2.1% -11.12 [-23.10, 0.86]
Camnmaroto 2017 (Group 2) [49] 9.63 9.25 10 35.59 13.87 10 2.2% -25.96 [-38.29, -15.63]
Camnmaroto 2017 (Group 3) [49] 13.53 7.76 10 37.84 21.6 10 1.9% -24.31 [-38.54, -10.08]
Ceylan 2009 [50] 16.1 3.9 26 29.6 7.8 26 2.7% -13.50 [-16.85, -10.15]
Cillo 2013 [55] 12.1 8.2 13 28.3 13.2 13 2.4% -16.20 [-24.65, -7.75]
Eun 2008 [58] 13.9 18.7 66 22.9 14.7 66 2.6% -9.00 [-14.74, -3.26]
Friedman 2007 [60] 14.5 10.2 122 23.2 7.6 122 2.8% -8.70 [-10.96, -6.44]
Gunbey 2015 [61] 15.3 9.8 42 35.8 12.1 42 2.7% -20.50 [-25.21, -15.79]
Li 2013 [65] 8.91 5.9 45 39.42 17.82 45 2.6% -30.51 [-35.99, -25.03]
Neruntarat 2009 [22] 16.8 3.2 72 35.6 9.2 72 2.8% -18.80 [-21.05, -16.55]
Plzak 2013 [69] 14.1 18.2 79 28.7 17.1 79 2.6% -14.60 [-20.11, -9.09]
Sezen 2011 [70] 15.34 11.06 12 28.78 10.69 12 2.4% -13.44 [-22.14, -4.74]
Tsou 2018 [75] 17.51 18.92 36 25.14 17.53 36 2.4% -7.63 [-16.06, 0.80]
Vicini 2014 (Group 1) [78] 19.8 14.1 12 38.4 19.7 12 1.9% -18.60 [-32.31, -4.89]
Vicini 2014 (Group 2) [78] 9.9 8.6 12 38.5 14.3 12 2.3% -28.60 [-38.04, -19.16]
Yuksel 2016 [81] 18 11.3 14 33.2 18.9 14 2.1% -15.20 [-26.73, -3.67]
Subtotal (95% CI) 706 706 43.5% -16.65 [-19.85, -13.44]
Heterogeneity: Tau² = 33.67; Chi² = 102.85, df = 17 (P < 0.00001); I² = 83%
Test for overall effect: Z = 10.17 (P < 0.00001)
2.1.2 Baseline AHI from 40/h to 70/h
Bostanci 2016 [47] 19.9 17.4 82 47.3 18.7 82 2.6% -27.40 [-32.93, -21.87]
Cambi 2019 [48] 19.4 10.1 20 49.3 18.5 20 2.3% -29.90 [-39.14, -20.66]
Chen 2014 (Group 1) [52] 35.08 18.5 22 66.38 17.03 22 2.2% -31.30 [-41.81, -20.79]
Chen 2014 (Group 2) [52] 26.17 18.85 24 46.1 13.26 24 2.3% -19.93 [-29.15, -10.71]
Chen 2018 (Group 1) [53] 25.21 7.85 26 51.78 14.65 26 2.5% -26.57 [-32.96, -20.18]
Chen 2018 (Group 2) [53] 14.87 2.17 45 52.34 6.29 45 2.8% -37.47 [-39.41, -35.53]
Chen 2019 [51] 27.03 4.01 45 49.67 7.43 45 2.8% -22.64 [-25.11, -20.17]
Chiffer 2015 [54] 19.8 22.1 18 53.9 25.4 18 1.7% -34.10 [-49.65, -18.55]
El-Anwar 2018 [56] 24.5 10.9 20 48.8 31.6 20 1.8% -24.30 [-38.95, -9.65]
Emara 2011 [57] 15.4 10.7 23 40.7 17.4 23 2.4% -25.30 [-33.65, -16.95]
Friedman 2003 [59] 28.1 20.6 143 43.9 23.7 143 2.6% -15.80 [-20.95, -10.65]
Li 2016 [63] 16.5 11.2 30 48.4 16.9 30 2.5% -31.90 [-39.15, -24.65]
Li 2016 [64] 12.8 8.2 25 45.7 21.7 25 2.3% -32.90 [-41.99, -23.81]
Lin 2010 [66] 23.4 24.7 43 51.5 25.4 43 2.2% -28.10 [-38.69, -17.51]
Neruntarat 2003 [67] 18.6 4.1 46 47.9 8.4 46 2.8% -29.30 [-32.00, -26.60]
Omur 2005 [68] 17.31 14.17 22 47.5 15.74 22 2.3% -30.19 [-39.04, -21.34]
Sorrenti 2006 [71] 9.4 5.4 10 54.7 11.5 10 2.4% -45.30 [-53.17, -37.43]
Sun 2008 [72] 28.58 29.11 31 65.93 23.83 31 1.9% -37.35 [-50.59, -24.11]
Tantawy 2018 [73] 25.6 9.52 32 68.4 25.3 32 2.3% -42.80 [-52.17, -33.43]
Toh 2014 [74] 13.5 17.1 20 41.3 22.1 20 2.0% -27.80 [-40.05, -15.55]
Turhan 2015 [76] 20.46 17.73 90 51.81 18.84 90 2.6% -31.35 [-36.69, -26.01]
Vicente 2006 [77] 14.1 23.5 54 52.8 14.9 54 2.5% -38.70 [-46.12, -31.28]
Wang 2013 [79] 23.2 18.4 36 59.8 20.5 36 2.3% -36.60 [-45.60, -27.60]
Yi 2011 [80] 30.1 23.1 26 65.6 17.6 26 2.1% -35.50 [-46.66, -24.34]
Subtotal (95% CI) 933 933 56.5% -30.72 [-33.99, -27.46]
Heterogeneity: Tau² = 47.88; Chi² = 159.86, df = 23 (P < 0.00001); I² = 86%
Test for overall effect: Z = 18.45 (P < 0.00001)
Total (95% CI) 1639 1639 100.0% -24.74 [-28.06, -21.42]
Heterogeneity: Tau² = 101.91; Chi² = 642.67, df = 41 (P < 0.00001); I² = 94%
Test for overall effect: Z = 14.61 (P < 0.00001)
Test for subgroup differences: Chi² = 36.37, df = 1 (P < 0.00001), I² = 97.3%
-50 -25 0 25 50
Post-MLS Pre-MLS

b


Post-MLS
Pre-MLS
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
2.2.1 Baseline AHI less than 40/h
Babademez 2010 [45] 86.6 2 16 84.6 3.4 16 4.5% 2.00 [0.07, 3.93]
Ceylan 2009 [50] 94.6 4.9 26 86.8 8.9 26 4.1% 7.80 [3.89, 11.71]
Eun 2008 [58] 79.4 16.5 66 79.1 5.7 66 4.1% 0.30 [-3.91, 4.51]
Friedman 2007 [60] 90.4 4.3 122 88.9 4.8 122 4.6% 1.50 [0.36, 2.64]
Li 2013 [65] 83 5 45 66 16 45 3.9% 17.00 [12.10, 21.90]
Neruntarat 2009 [22] 88.2 2.4 72 85.6 3.4 72 4.6% 2.60 [1.64, 3.56]
Subtotal (95% CI) 347 347 25.7% 4.35 [1.91, 6.79]
Heterogeneity: Tau² = 7.08; Chi² = 45.03, df = 5 (P < 0.00001); I² = 89%
Test for overall effect: Z = 3.50 (P = 0.0005)
2.2.2 Baseline AHI from 40/h to 70/h
Bostanci 2016 [47] 82.3 7.4 82 75.7 8.9 82 4.4% 6.60 [4.09, 9.11]
Cambi 2019 [48] 80 7.4 20 69.5 9.9 20 3.8% 10.50 [5.08, 15.92]
Chen 2018 (Group 1) [53] 86.03 5.44 45 58.67 8.33 45 4.3% 27.36 [24.45, 30.27]
Chen 2018 (Group 2) [53] 76.88 4.02 45 60.26 7.25 45 4.4% 16.62 [14.20, 19.04]
Chen 2019 [51] 67.84 19.3 22 61.89 12.54 22 2.7% 5.95 [-3.67, 15.57]
El-Anwar 2018 [56] 84 5.3 20 73.5 14.8 20 3.4% 10.50 [3.61, 17.39]
Emara 2011 [57] 87.2 11.1 23 78.9 12.6 23 3.4% 8.30 [1.44, 15.16]
Friedman 2003 [59] 85.9 9.8 143 81.4 10.4 143 4.4% 4.50 [2.16, 6.84]
Li 2016 [63] 82.4 5.4 30 76.4 8.5 30 4.2% 6.00 [2.40, 9.60]
Li. 2016 [64] 83.3 5.6 25 77.1 10.5 25 3.9% 6.20 [1.54, 10.86]
Lin 2010 [66] 82.1 10.9 43 75.5 10.4 43 4.0% 6.60 [2.10, 11.10]
Neruntarat 2003 [67] 87.2 3.1 46 81.2 2.9 46 4.6% 6.00 [4.77, 7.23]
Sorrenti 2006 [71] 90.7 3 10 77 6.2 10 4.0% 13.70 [9.43, 17.97]
Sun 2008 [72] 74.97 12.45 31 72.65 11.93 31 3.6% 2.32 [-3.75, 8.39]
Tantawy 2018 [73] 83.2 2.86 32 66.8 11.3 32 4.1% 16.40 [12.36, 20.44]
Toh 2014 [74] 84.5 7.1 20 72.9 19.3 20 2.8% 11.60 [2.59, 20.61]
Turhan 2015 [76] 82.38 6.57 90 75.63 9.3 90 4.4% 6.75 [4.40, 9.10]
Vicente 2006 [77] 82.2 11.2 54 76.2 12.4 54 4.0% 6.00 [1.54, 10.46]
Wang 2013 [79] 85.6 10 36 70.5 12.4 36 3.8% 15.10 [9.90, 20.30]
Subtotal (95% CI) 817 817 74.3% 9.93 [6.90, 12.96]
Heterogeneity: Tau² = 39.33; Chi² = 271.04, df = 18 (P < 0.00001); I² = 93%
Test for overall effect: Z = 6.42 (P < 0.00001)
Total (95% CI) 1164 1164 100.0% 8.66 [6.24, 11.07]
Heterogeneity: Tau² = 32.84; Chi² = 488.70, df = 24 (P < 0.00001); I² = 95%
Test for overall effect: Z = 7.02 (P < 0.00001)
Test for subgroup differences: Chi² = 7.90, df = 1 (P = 0.005), I² = 87.3%
-50 -25 0 25 50
Post-MLS Pre-MLS

c


Post-MLS
Pre-MLS
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
2.3.1 Baseline AHI less than 40/h
Pizak 2013 [69] 10.3 7.9 79 15.1 8.2 79 26.1% -4.80 [-7.31, -2.29]
Yuksel 2016 [81] 15.5 13.2 14 30.3 16.9 14 23.0% -14.80 [-26.03, -3.57]
Subtotal (95% CI) 93 93 49.1% -8.24 [-17.55, 1.07]
Heterogeneity: Tau² = 32.76; Chi² = 2.90, df = 1 (P = 0.09); I² = 66%
Test for overall effect: Z = 1.73 (P = 0.08)
2.3.2 Baseline AHI from 40/h to 70/h
Bostanci 2016 [47] 17.7 15.9 82 44.8 21.4 82 25.3% -27.10 [-32.87, -21.33]
Turhan 2015 [76] 18.2 15.5 90 48 19.5 90 25.5% -29.80 [-34.95, -24.65]
Subtotal (95% CI) 172 172 50.9% -28.60 [-32.44, -24.76]
Heterogeneity: Tau² = 0.00; Chi² = 0.47, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 14.60 (P < 0.00001)
Total (95% CI) 265 265 100.0% -19.14 [-34.23, -4.04]
Heterogeneity: Tau² = 225.36; Chi² = 104.09, df = 3 (P < 0.00001); I² = 97%
Test for overall effect: Z = 2.48 (P = 0.01)
Test for subgroup differences: Chi² = 15.70, df = 1 (P < 0.0001), I² = 93.6%
-50 -25 0 25 50
Post-MLS Pre-MLS

d

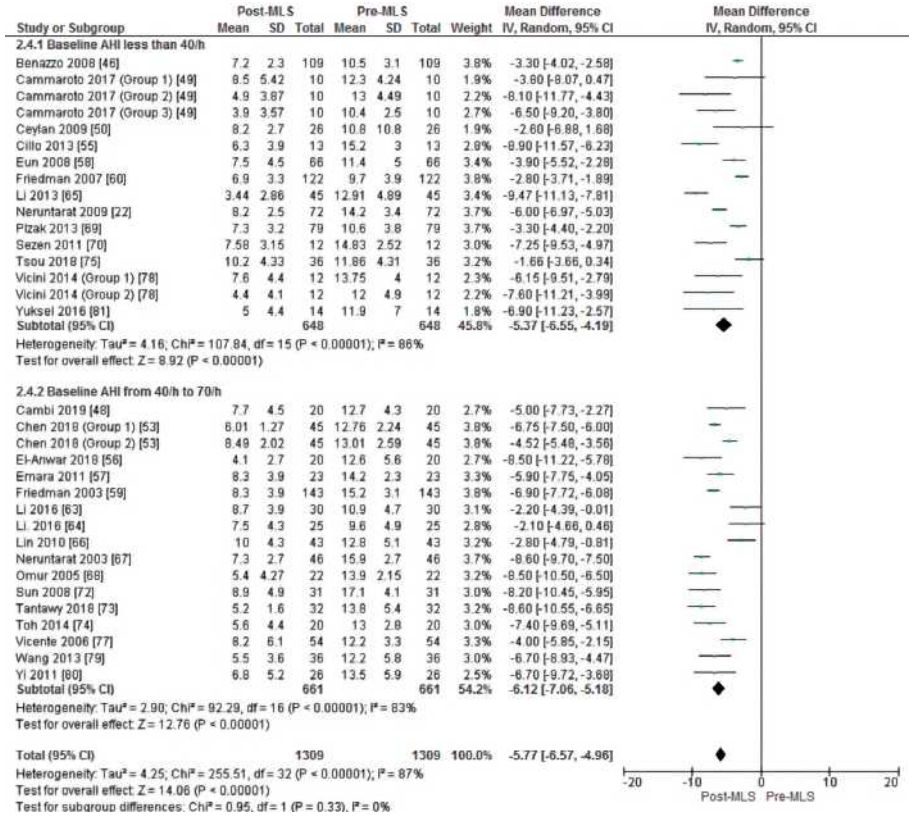
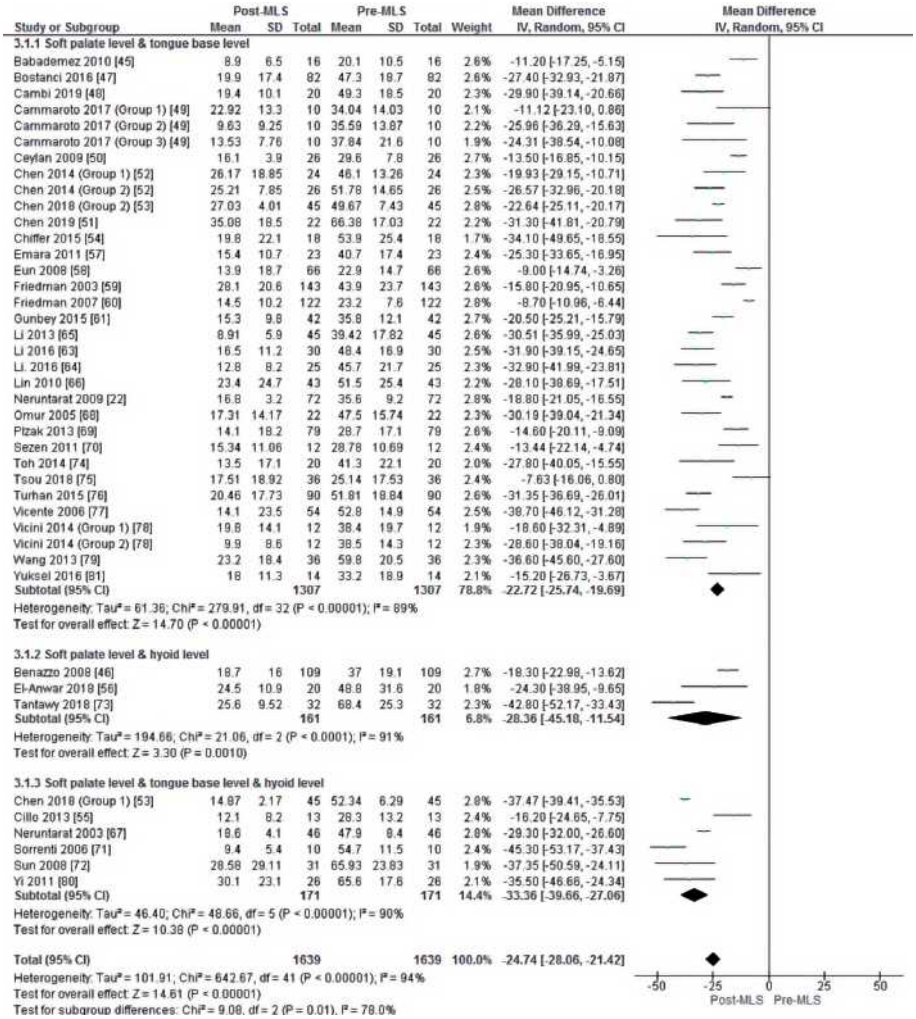
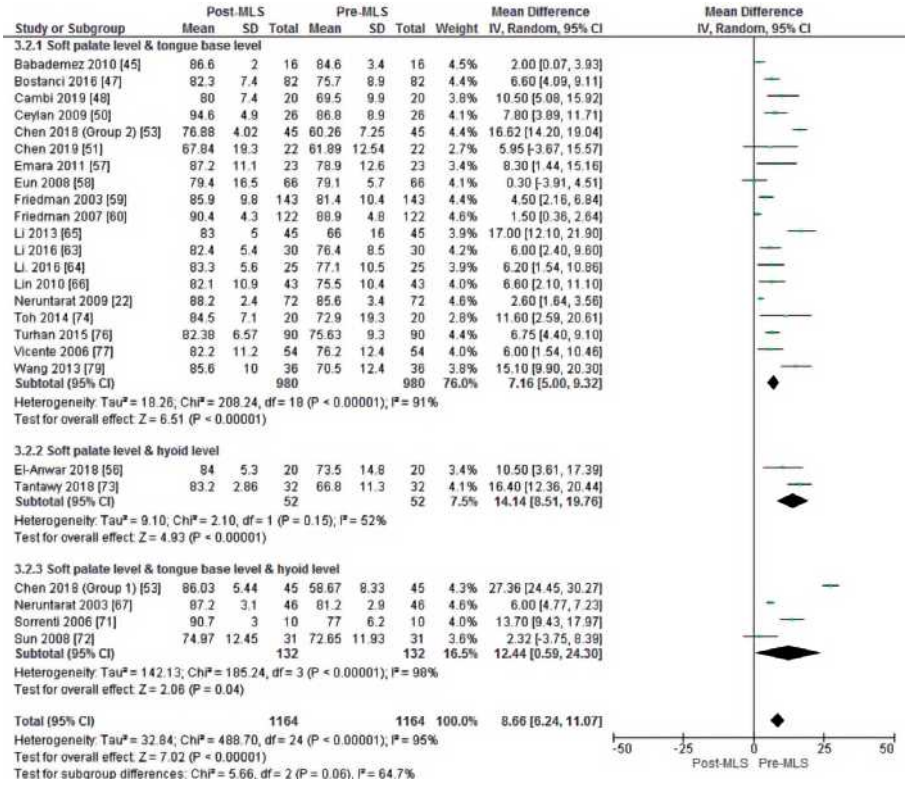


Fig. S4. Pre- and post-MLS mean difference for apnea-hypopnea index (a), lowest oxygen saturation (b), oxygen desaturation index (c), and Epworth sleepiness scale (d). CI, confidence interval; MLS, multilevel surgery; SD, standard deviation.

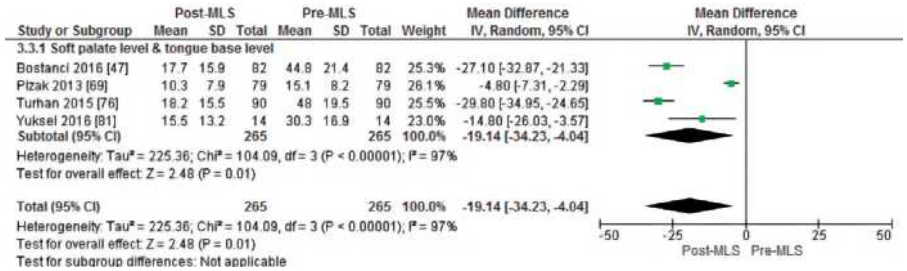
a


Post-MLS
Pre-MLS
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
3.1.1 Soft palate level & tongue base level
Babademez 2010 [45] 8.9 6.5 16 20.1 10.5 16 2.6% -11.20 [-17.25, -5.15]
Bostanci 2016 [47] 19.9 17.4 82 47.3 18.7 82 2.6% -27.40 [-32.93, -21.87]
Cambi 2019 [48] 19.4 10.1 20 49.3 18.5 20 2.3% -29.90 [-39.14, -20.66]
Carnmaroto 2017 (Group 1) [49] 22.92 13.3 10 34.04 14.03 10 2.1% -11.12 [-23.10, 0.86]
Carnmaroto 2017 (Group 2) [49] 9.63 9.25 10 35.59 13.87 10 2.2% -25.96 [-36.29, -15.63]
Carnmaroto 2017 (Group 3) [49] 13.53 7.76 10 37.84 21.6 10 1.9% -24.31 [-38.54, -10.08]
Ceylan 2009 [50] 16.1 3.9 26 29.6 7.8 26 2.7% -13.50 [-16.85, -10.15]
Chen 2014 (Group 1) [52] 26.17 18.85 24 46.1 13.26 24 2.3% -19.93 [-29.15, -10.71]
Chen 2014 (Group 2) [52] 25.21 7.85 26 51.78 14.65 26 2.5% -26.57 [-32.96, -20.18]
Chen 2018 (Group 2) [53] 27.03 4.01 45 49.67 7.43 45 2.8% -22.64 [-25.11, -20.17]
Chen 2019 [51] 35.08 18.5 22 66.38 17.03 22 2.2% -31.30 [-41.81, -20.79]
Chiffer 2015 [54] 19.8 22.1 18 53.9 25.4 18 1.7% -34.10 [-49.65, -18.55]
Emara 2011 [57] 15.4 10.7 23 40.7 17.4 23 2.4% -25.30 [-33.65, -16.95]
Eun 2008 [58] 13.9 18.7 66 22.9 14.7 66 2.6% -9.00 [-14.74, -3.26]
Friedman 2003 [59] 28.1 20.6 143 43.9 23.7 143 2.6% -15.80 [-20.95, -10.65]
Friedman 2007 [60] 14.5 10.2 122 23.2 7.6 122 2.8% -8.70 [-10.96, -6.44]
Gunbey 2015 [61] 15.3 9.8 42 35.8 12.1 42 2.7% -20.50 [-25.21, -15.79]
Li 2013 [65] 8.91 5.9 45 39.42 17.82 45 2.6% -30.51 [-35.99, -25.03]
Li 2016 [63] 16.5 11.2 30 48.4 16.9 30 2.5% -31.90 [-39.15, -24.65]
Li. 2016 [64] 12.8 8.2 25 45.7 21.7 25 2.3% -32.90 [-41.99, -23.81]
Lin 2010 [66] 23.4 24.7 43 51.5 25.4 43 2.2% -28.10 [-38.69, -17.51]
Neruntarat 2009 [22] 16.8 3.2 72 35.6 9.2 72 2.8% -18.80 [-21.05, -16.55]
Omur 2005 [68] 17.31 14.17 22 47.5 15.74 22 2.3% -30.19 [-39.04, -21.34]
Ptzak 2013 [69] 14.1 18.2 79 28.7 17.1 79 2.6% -14.60 [-20.11, -9.09]
Sezen 2011 [70] 15.34 11.06 12 28.78 10.69 12 2.4% -13.44 [-22.14, -4.74]
Toh 2014 [74] 13.5 17.1 20 41.3 22.1 20 2.0% -27.80 [-40.05, -15.55]
Tsou 2018 [75] 17.51 18.92 36 25.14 17.53 36 2.4% -7.63 [-16.06, 0.80]
Turhan 2015 [76] 20.46 17.73 90 51.81 18.84 90 2.6% -31.35 [-36.69, -26.01]
Vicente 2006 [77] 14.1 23.5 54 52.8 14.9 54 2.5% -38.70 [-46.12, -31.28]
Vicini 2014 (Group 1) [78] 19.8 14.1 12 38.4 19.7 12 1.9% -18.60 [-32.31, -4.89]
Vicini 2014 (Group 2) [78] 9.9 8.6 12 38.5 14.3 12 2.3% -28.60 [-38.04, -19.16]
Wang 2013 [79] 23.2 18.4 36 59.8 20.5 36 2.3% -36.60 [-45.60, -27.60]
Yuksel 2016 [81] 18 11.3 14 33.2 18.9 14 2.1% -15.20 [-26.73, -3.67]
Subtotal (95% CI) 1307 1307 78.8% -22.72 [-25.74, -19.69]
Heterogeneity: Tau² = 61.36; Chi² = 279.91, df = 32 (P < 0.00001); I² = 89%
Test for overall effect: Z = 14.70 (P < 0.00001)
3.1.2 Soft palate level & hyoid level
Benazzo 2008 [46] 18.7 16 109 37 19.1 109 2.7% -18.30 [-22.98, -13.62]
El-Anwar 2018 [56] 24.5 10.9 20 48.8 31.6 20 1.8% -24.30 [-39.95, -8.65]
Tantawy 2018 [73] 25.6 9.52 32 68.4 25.3 32 2.3% -42.80 [-52.17, -33.43]
Subtotal (95% CI) 161 161 6.8% -28.36 [-45.18, -11.54]
Heterogeneity: Tau² = 194.66; Chi² = 21.06, df = 2 (P < 0.0001); I² = 91%
Test for overall effect: Z = 3.30 (P = 0.0010)
3.1.3 Soft palate level & tongue base level & hyoid level
Chen 2018 (Group 1) [53] 14.97 2.17 45 52.34 6.29 45 2.8% -37.47 [-39.41, -35.53]
Cillo 2013 [55] 12.1 8.2 13 28.3 13.2 13 2.4% -16.20 [-24.65, -7.75]
Neruntarat 2003 [67] 18.6 4.1 46 47.9 8.4 46 2.8% -29.30 [-32.00, -26.60]
Sorrenti 2006 [71] 9.4 5.4 10 54.7 11.5 10 2.4% -45.30 [-53.17, -37.43]
Sun 2008 [72] 28.58 29.11 31 65.93 23.83 31 1.9% -37.35 [-50.59, -24.11]
Yi 2011 [80] 30.1 23.1 26 65.6 17.6 26 2.1% -35.50 [-46.66, -24.34]
Subtotal (95% CI) 171 171 14.4% -33.36 [-39.66, -27.06]
Heterogeneity: Tau² = 46.40; Chi² = 48.66, df = 5 (P < 0.00001); I² = 90%
Test for overall effect: Z = 10.38 (P < 0.00001)
Total (95% CI) 1639 1639 100.0% -24.74 [-28.06, -21.42]
Heterogeneity: Tau² = 101.91; Chi² = 642.67, df = 41 (P < 0.00001); I² = 94%
Test for overall effect: Z = 14.61 (P < 0.00001)
Test for subgroup differences: Chi² = 9.08, df = 2 (P = 0.01), I² = 78.0%
-50 -25 0 25 50
Post-MLS Pre-MLS

b


Post-MLS
Pre-MLS
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
3.2.1 Soft palate level & tongue base level
Bademez 2010 [45] 86.6 2 16 84.6 3.4 16 4.5% 2.00 [0.07, 3.93]
Bostanci 2016 [47] 82.3 7.4 82 75.7 8.9 82 4.4% 6.60 [4.09, 9.11]
Cambi 2019 [48] 80 7.4 20 69.5 9.9 20 3.8% 10.50 [5.08, 15.92]
Ceylan 2009 [50] 94.6 4.9 26 86.8 8.9 26 4.1% 7.80 [3.89, 11.71]
Chen 2018 (Group 2) [53] 76.88 4.02 45 60.26 7.25 45 4.4% 16.62 [14.20, 19.04]
Chen 2019 [51] 67.84 19.3 22 61.89 12.54 22 2.7% 5.95 [-3.67, 15.57]
Emara 2011 [57] 87.2 11.1 23 78.9 12.6 23 3.4% 8.30 [1.44, 15.16]
Eun 2008 [58] 79.4 16.5 66 79.1 5.7 66 4.1% 0.30 [-3.91, 4.51]
Friedman 2003 [59] 85.9 9.8 143 81.4 10.4 143 4.4% 4.50 [2.16, 6.84]
Friedman 2007 [60] 90.4 4.3 122 88.9 4.8 122 4.6% 1.50 [0.36, 2.64]
Li 2013 [65] 83 5 45 66 16 45 3.9% 17.00 [12.10, 21.90]
Li 2016 [63] 82.4 5.4 30 76.4 8.5 30 4.2% 6.00 [2.40, 9.60]
Li. 2016 [64] 83.3 5.6 25 77.1 10.5 25 3.9% 6.20 [1.54, 10.86]
Lin 2010 [66] 82.1 10.9 43 75.5 10.4 43 4.0% 6.60 [2.10, 11.10]
Neruntarat 2009 [22] 88.2 2.4 72 85.6 3.4 72 4.6% 2.60 [1.64, 3.56]
Toh 2014 [74] 84.5 7.1 20 72.9 19.3 20 2.8% 11.60 [2.59, 20.61]
Turhan 2015 [76] 82.38 6.57 90 75.63 9.3 90 4.4% 6.75 [4.40, 9.10]
Vicente 2006 [77] 82.2 11.2 54 76.2 12.4 54 4.0% 6.00 [1.54, 10.46]
Wang 2013 [79] 85.6 10 36 70.5 12.4 36 3.8% 15.10 [9.90, 20.30]
Subtotal (95% CI) 980 980 76.0% 7.16 [5.00, 9.32]
Heterogeneity: Tau² = 18.26; Chi² = 208.24, df = 18 (P < 0.00001); I² = 91%
Test for overall effect: Z = 6.51 (P < 0.00001)
3.2.2 Soft palate level & hyoid level
El-Anwar 2018 [56] 84 5.3 20 73.5 14.8 20 3.4% 10.50 [3.61, 17.39]
Tantawy 2018 [73] 83.2 2.86 32 66.8 11.3 32 4.1% 16.40 [12.36, 20.44]
Subtotal (95% CI) 52 52 7.5% 14.14 [8.51, 19.76]
Heterogeneity: Tau² = 9.10; Chi² = 2.10, df = 1 (P = 0.15); I² = 52%
Test for overall effect: Z = 4.93 (P < 0.00001)
3.2.3 Soft palate level & tongue base level & hyoid level
Chen 2018 (Group 1) [53] 86.03 5.44 45 58.67 8.33 45 4.3% 27.36 [24.45, 30.27]
Neruntarat 2003 [67] 87.2 3.1 46 81.2 2.9 46 4.6% 6.00 [4.77, 7.23]
Sorrenti 2006 [71] 90.7 3 10 77 6.2 10 4.0% 13.70 [9.43, 17.97]
Sun 2008 [72] 74.97 12.45 31 72.65 11.93 31 3.6% 2.32 [-3.75, 8.39]
Subtotal (95% CI) 132 132 16.5% 12.44 [0.59, 24.30]
Heterogeneity: Tau² = 142.13; Chi² = 185.24, df = 3 (P < 0.00001); I² = 98%
Test for overall effect: Z = 2.06 (P = 0.04)
Total (95% CI) 1164 1164 100.0% 8.66 [6.24, 11.07]
Heterogeneity: Tau² = 32.84; Chi² = 488.70, df = 24 (P < 0.00001); I² = 95%
Test for overall effect: Z = 7.02 (P < 0.00001)
Test for subgroup differences: Chi² = 5.66, df = 2 (P = 0.06), I² = 64.7%
-50 -25 0 25 50
Post-MLS Pre-MLS

c


Post-MLS
Pre-MLS
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
3.3.1 Soft palate level & tongue base level
Bostanci 2016 [47] 17.7 15.9 82 44.8 21.4 82 25.3% -27.10 [-32.87, -21.33]
Pizak 2013 [69] 10.3 7.9 79 15.1 8.2 79 26.1% -4.80 [-7.31, -2.29]
Turhan 2015 [76] 18.2 15.5 90 48 19.5 90 25.5% -29.80 [-34.95, -24.65]
Yuksel 2016 [81] 15.5 13.2 14 30.3 16.9 14 23.0% -14.80 [-26.03, -3.57]
Subtotal (95% CI) 265 265 100.0% -19.14 [-34.23, -4.04]
Heterogeneity: Tau² = 225.36; Chi² = 104.09, df = 3 (P < 0.00001); I² = 97%
Test for overall effect: Z = 2.48 (P = 0.01)
Total (95% CI) 265 265 100.0% -19.14 [-34.23, -4.04]
Heterogeneity: Tau² = 225.36; Chi² = 104.09, df = 3 (P < 0.00001); I² = 97%
Test for overall effect: Z = 2.48 (P = 0.01)
Test for subgroup differences: Not applicable
-50 -25 0 25 50
Post-MLS Pre-MLS

d

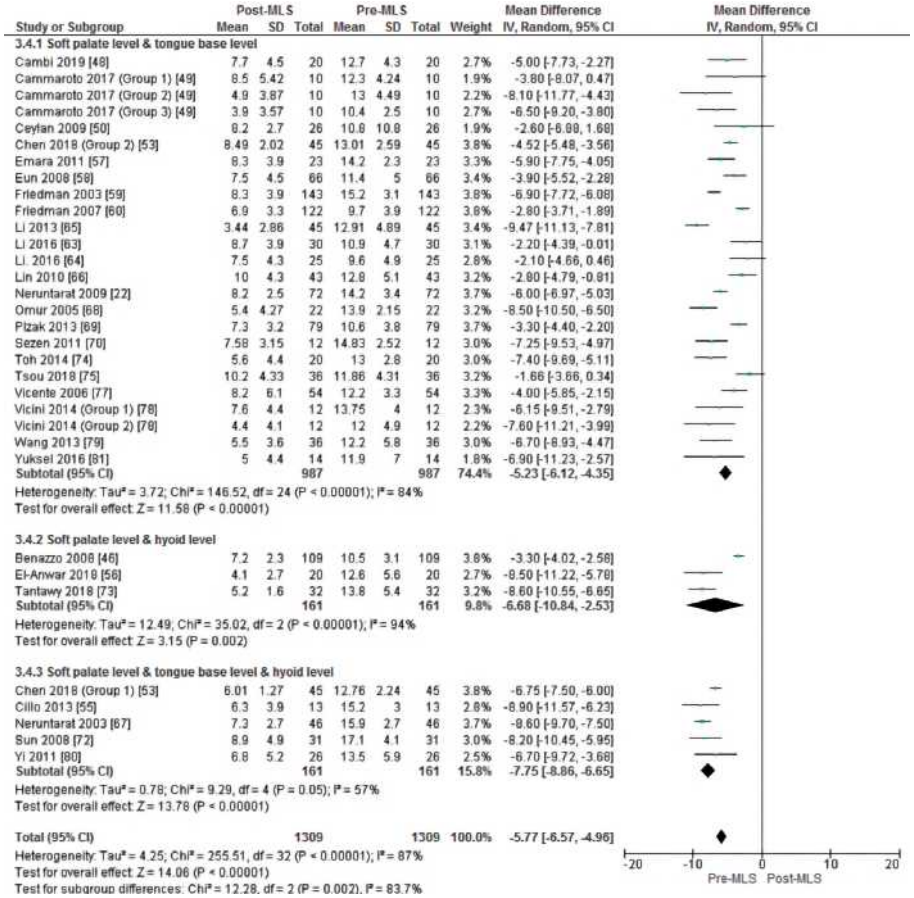
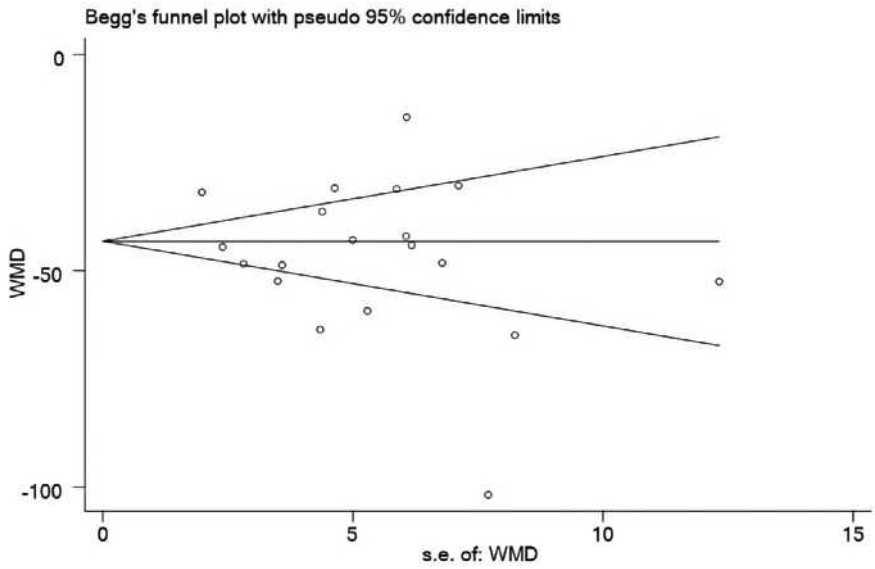


Fig. S5. Pre- and post-MLS mean difference for apnea-hypopnea index (a), lowest oxygen saturation (b), oxygen desaturation index (c), and Epworth sleepiness scale (d) – three subgroups according to the different target levels of obstructive sites addressed by surgery. CI, confidence interval; MLS, multilevel surgery; SD, standard deviation.

a



b

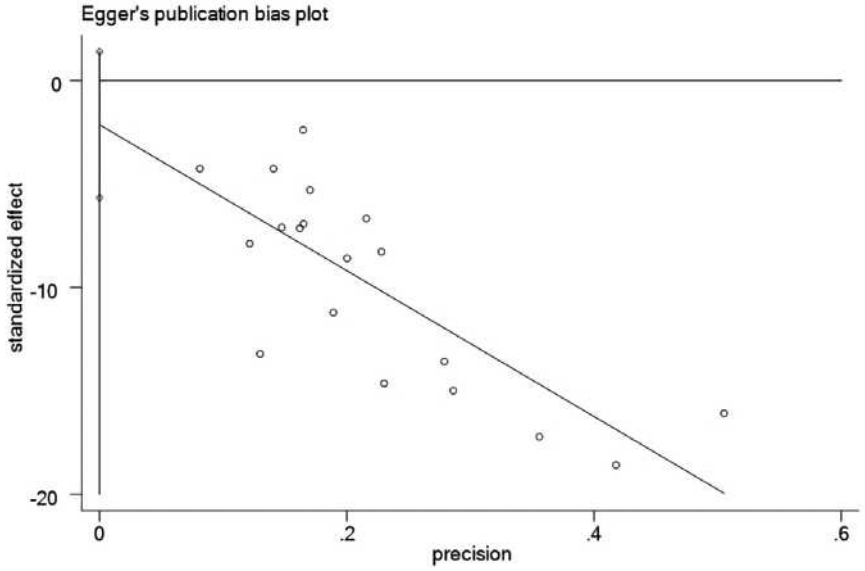
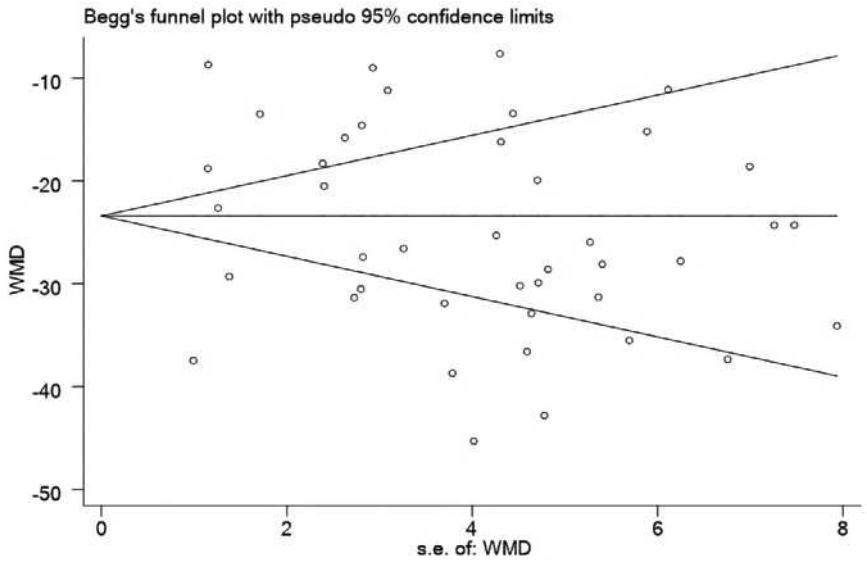


Fig. S6. Begg's funnel plot (a) and Egger's publication bias plot (b) for all maxillomandibular advancement surgery studies in meta-analysis. s.e., standard error; WMD, weighted mean difference.

a



b

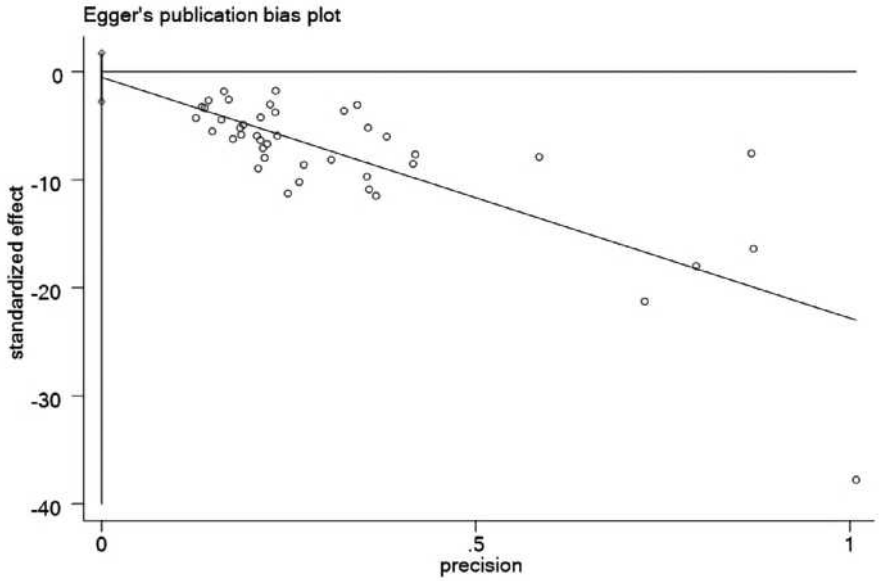


Fig. S7. Begg's funnel plot (a) and Egger's publication bias plot (b) for all multilevel surgery studies in meta-analysis. s.e., standard error; WMD, weighted mean difference.

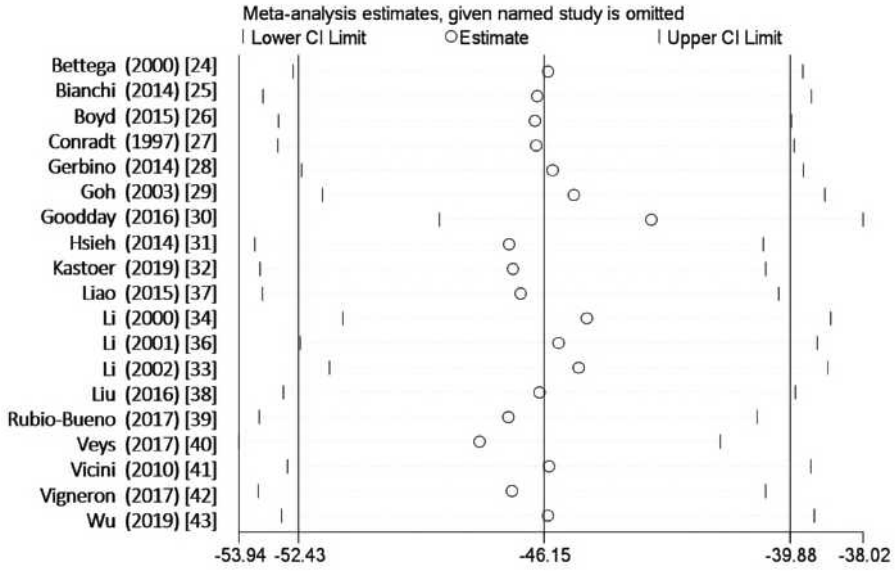


Fig. S8. Sensitivity analysis of AHI in meta-analysis for maxillomandibular advancement surgery studies. CI, confidence interval.

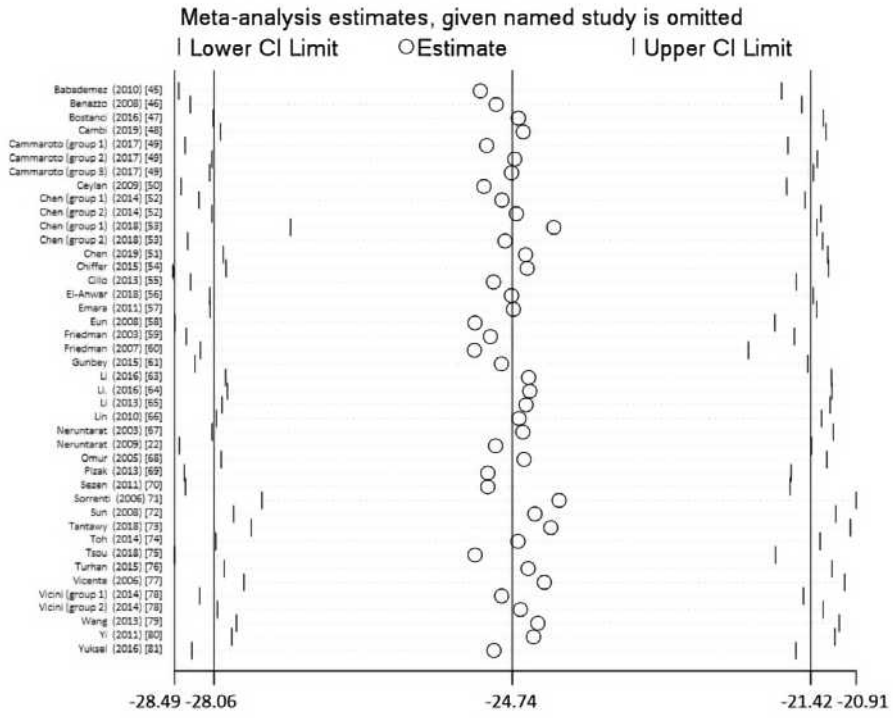


Fig. S9. Sensitivity analysis of AHI in meta-analysis for multilevel surgery studies. CI, confidence interval.

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CHAPTER 6

Maxillomandibular advancement and upper airway stimulation for treatment of obstructive sleep apnea: A systematic review

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ABSTRACT

This systematic review aimed to comparatively evaluate the efficacy and safety of maxillomandibular advancement (MMA) and upper airway stimulation (UAS) in obstructive sleep apnea (OSA) treatment. A MEDLINE and Embase databases search of articles on MMA and/or UAS for OSA was conducted. Twenty-one MMA studies and nine UAS studies were included. All the MMA studies demonstrated a reduction in apnea hypopnea index (AHI) postoperatively and success rates ranged from 41.1% to 100%. Ten MMA studies reported pre- and postoperative Epworth sleepiness scale (ESS), and all but one studies demonstrated a reduction in ESS. In the UAS studies, all but one demonstrated a reduction in AHI and success rates ranged from 26.7% to 77.8%. In the eight UAS studies reporting pre- and postoperative ESS, an ESS reduction was demonstrated. No studies reported any deaths related to MMA or UAS. The most common postoperative complication after MMA and UAS was facial paresthesia in mandibular area and discomfort due to electrical stimulation, respectively. This systematic review suggests that both MMA and UAS are effective and generally safe therapies for OSA. However, due to the limitations of the included studies, there is no evidence yet to directly compare these two procedures in OSA treatment.

Keywords: Obstructive sleep apnea; Therapy; Maxillo-mandibular surgery; Hypoglossal nerve; Systematic review

INTRODUCTION

Obstructive sleep apnea (OSA) is a prevalent sleep-related breathing disorder characterized by recurrent upper airway obstruction during sleep[1], and its overall prevalence ranges from 9% to 38% in the general adult population[2]. OSA is associated with considerable health risks, such as cardiovascular and cerebrovascular disease[3, 4]. Continuous positive airway pressure (CPAP) is accepted as the first-line therapy for moderate to severe OSA, but poor compliance and suboptimal use of CPAP drive OSA patients to seek alternative therapies, including other non-invasive therapies and surgical treatment[5, 6].

Moderate to severe OSA is usually caused by multilevel obstructions of the upper airway, which highlights the need for surgical therapies able to resolve multilevel upper airway collapse[7]. One such therapy that has existed for many decades is maxillomandibular advancement (MMA)[8, 9]. MMA is a multilevel skeletal surgery in which the maxilla and mandible are advanced by a combination of a Le Fort I osteotomy of the maxilla and a bilateral sagittal split osteotomy of the mandible[8, 9]. By expanding the skeletal framework attached with the pharyngeal soft tissues, MMA enlarges the velo-orohypopharyngeal airway[10] and increases the tension of the pharyngeal soft tissues, decreasing the collapsibility of the upper airway[11]. MMA is currently considered as the most effective surgical treatment modality for moderate to severe OSA in adults aside from tracheostomy.

A more contemporary therapy is hypoglossal nerve stimulation (HNS), which works by electrically stimulating the branches of the hypoglossal nerve that innervate muscles responsible for protruding the tongue and thus maintaining upper airway patency during sleep[12]. Currently, there are three different systems for HNS therapy, including the Aura6000 Targeted Hypoglossal Neurostimulation system (LivaNova PLC, London, England, UK), the GenioTM system (Nyxoah SA, Mont-Saint-Guibert, Belgium), and the Inspire II upper airway stimulation (UAS) system (Inspire Medical Systems, Maple Grove, MN, USA)[13]. Given that the Inspire UAS system is the most widely used system having Food and Drug Administration (FDA) approval for clinical use[14], this review only focused on the UAS therapy (Inspire® system). Over the past decade, UAS has emerged as an effective therapy and therefore has become an increasingly popular treatment option for moderate to severe OSA[15, 16].

Currently, the main indications for MMA are moderate to severe OSA, and mild OSA in patients presenting with a dentofacial deformity[17]. UAS therapy is generally indicated for patients with the following characteristics: moderate to severe OSA (apnea hypopnea index [AHI] 15-65 events/h with <25% central or mixed apneas), positive airway pressure (PAP) therapy failure, and absence of complete concentric velum collapse (CCCp) on drug-induced sleep endoscopy (DISE)[18]. When no generally accepted indicative results are found during clinical, laboratory, or endoscopic examinations (e.g., significant skeletal-dental deformity, AHI > 65 events/h, CCCp on DISE), patients with moderate to severe OSA may be expected to benefit from MMA as well as UAS therapy. Although MMA and UAS have both demonstrated efficacy and safety for patients, there is a paucity of evidence on comparison of these two treatment options[17].

Therefore, the purpose of this systematic review was to comprehensively evaluate and compare the efficacy of MMA and UAS for moderate to severe OSA, through the assessment of AHI and Epworth sleepiness score (ESS) as primary outcomes. Secondly, the postoperative complications of these two therapies were investigated.

METHODS

This systematic review was performed in accordance with the preferred reporting items for systematic review and meta-analysis (PRISMA) statement[19]. The protocol for this system-atic review was registered at PROSPERO (PROSPERO ID: CRD42021261394; https://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42021261394).

Selection criteria

The inclusion criteria were as follows: (1) adult patients (> 18 years old) with moderate to severe OSA diagnosed by polysomnography (PSG; AHI ≥ 15 events/h); (2) patients who underwent MMA or UAS for OSA; (3) studies that reported pre- and postoperative PSG data; (4) studies with a follow-up ≥ 6 months; (5) study designs: randomized controlled trials (RCTs), quasi-experimental studies, and cohort studies; and (6) English language.

The exclusion criteria were the following: (1) sample size < 10 patients; (2) patients who underwent other adjunctive surgical procedures (e.g., uvulopalatopharyngoplasty) at the time of MMA or UAS; and (3) preliminary studies in which the findings had been nested in other studies with larger sample size and/or longer follow-up.

Literature search

A literature search was performed with the help of an information specialist (RS) using MEDLINE and Embase databases on Dec 14, 2021. Search terms and search strategies used for each database are available in supplementary materials (**Table S1a**).

Study selection

After removal of duplicate articles, the remaining results were screened based on title and abstract by two independent reviewers (NZ and JH). The full texts of potentially relevant articles were retrieved and further evaluated by NZ and JH independently for compliance of studies with the eligibility criteria. Discrepancies were resolved by discussion. Reference lists of eligible studies were checked for additional studies.

Data extraction

The extracted data included: article title, year of publication, first author, study design, specific surgical technique, length of follow-up, sample size, age, gender, body mass index (BMI), preoperative and postoperative PSG data (AHI, respiratory disturbance index [RDI], and oxygen desaturation index [ODI]), preoperative and postoperative ESS score, preoperative and postoperative data on quality of life (QoL), surgical success rate and cure rate, and postoperative complications. According to the accordion severity grading system of surgical complications[20], the postoperative complications were classified as major and minor, depending on the needs for endoscopic or interventional radiologic procedures or re-operation as well as failure of one or more organ systems.

Data were extracted by NZ and JH independently. Discrepancies were resolved through discussion. If RDI is reported by a study, it would be extracted as AHI, since these two respiratory parameters have been consolidated based on the 2013 American Academy of Sleep Medicine's manual for the scoring of sleep and associated events[21]. If there were multiple follow-up data in a study, the data with longest follow-up time were included. Surgical success was defined as "a postoperative AHI < 20 events/h

and at least 50% reduction in AHI after surgery"[22], and surgical cure was defined as "a postoperative AHI < 5 events/h"[23].

Quality assessment

Methodologic quality assessment of each study was performed by NZ and JH independently, and any discrepancies were resolved by discussion.

The Methodological Index for Non-Randomized Studies (MINORS) quality assessment tool, a validated tool for the methodological assessment of non-randomized surgical studies[24], was used to assess the methodological quality of the included studies. The MINORS tool is composed of eight items applicable to all non-randomized studies and four additional items specifically for comparative studies. Each item was scored as 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate), giving a global ideal score of 24 for comparative studies and 16 for non-comparative studies. For comparative studies, the categorizations are as follows: 0-6, very low quality; 7-10, low quality; 11-15 fair quality; and ≥ 16, high quality. For non-comparative studies, the categorizations are as follows: 0-4, very low quality; 5-7, low quality; 8-12, fair quality; and ≥ 13, high quality[25].

Statistical analysis

The collected parameters (age, BMI, AHI, ODI, and ESS) were pooled by weighted average and weighted standard deviation[26]. When there were RCTs or comparative studies between MMA and UAS, meta-analyses were performed to compare the overall effect of MMA and UAS in treating OSA. Heterogeneity of the studies was assessed by I^2 statistic with cut-off of 25% (low), 50% (moderate) and 75% (high)[27]. When moderate to high heterogeneity was present, a random-effects model was adopted; otherwise, a fixed-effects model was used. Because some patients may report multiple complications, the complication rate of each study was calculated by dividing the number of events by the number of patients.

RESULTS

Search results

The flow diagram of study selection progress is summarized in **Figure 1**. A total of 2952 studies were screened after deduplication, 212 were retrieved for full-text review.

MMA group Twenty-one studies[11, 28-47] were identified, producing a pooled data set of 581 patients (male 78.5%) with weighted age of 42.2 ± 11.5 years and weighted BMI of 28.1 ± 6.4 kg/m^2. The mean follow-up period from surgery to final postoperative PSG was 25.9 months (range, 6 months-12.5 years). One study[39] was excluded from the analyses for clinical efficacy, because the data of a subset of the patients with longer follow-up period were nested in another included study[38]. The characteristics of these studies are shown in **Table 1**.

UAS group Nine studies[15, 48-55] were identified, yielding a total of 1029 patients (male 96.2%) with weighted age of 55.1 ± 10.1 years and weighted BMI of 29.1 ± 4.2 kg/m^2. The mean follow-up period was 18.8 months (range, 6 months-5 years). The characteristics are summarized in **Table 2**.

Because there was no RCT or comparative study of MMA and UAS in treating OSA, a meta-analysis could not be performed to compare their overall effect sizes on OSA.

Quality assessment

MMA group One of the included studies was an RCT of MMA and autotitrating positive airway pressure (APAP), one was a retrospective quasi-experimental study, ten were prospective cohort studies, and nine were retrospective cohort studies. As only MMA cohort of the RCT was included in the analyses, after omitting the unrequired APAP cohort, this study was regarded as a single-arm trial. The quality of the RCT was therefore assessed using MINORS tool as per the other included studies. Of these studies, three studies were classified as "high quality", and the others were classified as "fair quality" (Supplementary **Table S2a**).

UAS group Six prospective studies and three retrospective studies were included. Of these, one study was classified as "high quality", and eight studies as "fair quality" (Supplementary **Table S2b**).

Respiratory parameters

MMA group Fifteen MMA studies[11, 28-31, 33-37, 41, 42, 44, 45, 47] reported a significant reduction in AHI postoperatively ($P < 0.05$), the others[32, 38, 40, 43, 46] reported an AHI reduction but did not report a *P*-value. All the studies[11, 28-38, 40-47] totaling 446 patients demonstrated a weighted baseline AHI of 54.6 ± 27.4 events/h and a weighted postoperative AHI of 10.1 ± 10.8 events/h.

In four studies[11, 32, 36, 43] (n = 78) reporting pre- and postoperative ODI, two demonstrated a significant reduction in ODI after MMA ($P < 0.05$), and the other two also reported a ODI reduction but without a *P*-value. The weighted pre- and postoperative ODI was 35.1 ± 22.8 events/h and 6.3 ± 6.4 events/h, respectively.

UAS group Of the selected studies, the study form Bachour et al.[55] did not show a significant reduction in AHI postoperatively, five studies[48-51, 54] demonstrated a significant reduction in AHI postoperatively ($P < 0.05$), and three studies[15, 52, 53] showed a AHI reduction but did not report a *P*-value. The weighted pre- and postoperative AHI in 1003 patients was 35.2 ± 14.7 events/h and 15.0 ± 16.1 events/h, respectively.

Of six studies[15, 49-52, 55] reporting pre- and postoperative ODI, the study from Bachour et al. [55] did not found a significant improvement in ODI postoperatively, while the others[15, 49-52] reported a reduction in ODI after surgery, of which two studies did not report a *P*-value. The weighted pre- and postoperative ODI was 26.5 ± 16.0 events/h and 14.6 ± 18.5 events/h (n = 180), respectively.

Subjective parameters

MMA group Of nine studies[11, 34, 36, 41-45, 47] (n = 217) reporting pre- and postoperative ESS, the study from Lin et al. did not show an improvement in ESS after MMA, one study demonstrated a reduction in ESS but without a *P*-value, and the others reported a significant reduction in ESS ($P < 0.05$). The weighted pre- and postoperative ESS was 13.1 ± 5.5 and 6.7 ± 4.8, respectively.

Three studies[30, 42, 44] assessed pre- and postoperative QoL. Boyd et al. found that after MMA there was a significant improvement in Functional Outcomes of Sleep Questionnaire (FOSQ) ($P < 0.05$)[30]. Veys et al. assessed subjective outcome of MMA using OSA QoL questionnaire. They found that there was an improvement in all of the following six symptoms after MMA: daytime sleepiness, snoring, concentration, waking up at night, headache, and high blood pressure, while the influence of MMA on nocturia and sexual activity was variable[44]. Lin et al. found that there was no significant improvement in Short-Form 36 Quality of Life (SF-36) after MMA[42].

UAS group Of eight studies[15, 49-55] reporting pre- and postoperative ESS, seven demonstrated a significant reduction in ESS postoperatively ($P < 0.05$), and one reported a ESS reduction but did not report a *P*-value. The weighted pre- and postoperative ESS was 11.4 ± 5.4 (n = 1006) and 7.0 ± 4.6 (n = 1001), respectively.

Two studies reported pre- and post-UAS FOSQ score. The STAR trial cohort demonstrated an increase of FOSQ score five years after surgery (14.3 ± 3.3 to 18.0 ± 2.2). Van de Heyning et al. also found a significant improvement in FOSQ score postoperatively (89.1 ± 23.5 to 100.8 ± 16.9, $P < 0.05$).

Surgical success and cure

MMA group Surgical success rate of MMA was available in 15 studies[11, 28, 32-35, 37, 38, 40, 41, 43-47], which ranged from 41.1% to 100%. Surgical cure rate of MMA was reported in seven studies[11, 34, 42-45, 47], which ranged from 36% to 67.9%.

UAS group Surgical success rate of UAS was available in six studies[15, 50-52, 54, 55], ranging from 26.5% to 77.8%. Surgical cure rate was reported in four studies[15, 50, 51, 55], which ranged from 6.7% to 44%.

Long-term follow-up outcomes

MMA group Five studies[30, 31, 38, 42, 46] reported long-term follow-up (≥ 2 years) data in 151 patients with weighted baseline AHI of 51.7 ± 28.2 events/h. At a mean follow-up of 5.0 years, the weighted postoperative AHI was 11.1 ± 13.0 events/h. Only one study[42] with 53 patients reported long-term follow-up ESS (10.8 ± 5.0 to 10.2 ± 5.1, $P > 0.05$). Boyd et al.[30] reported a long-term improvement in FOSQ score after MMA. Surgical success rate was reported in two studies[38, 46] (90% and 41.4%, respectively), and surgical cure rate was only available in one study[42] (67.9%).

UAS group Three studies[15, 50, 51] reported long-term follow-up (≥ 2 years) data in 127 patients with weighted baseline AHI of 29.7 ± 11.0 events/h. At a mean follow-up of 4.2 years, the weighted postoperative AHI was 12.3 ± 14.8 events/h. These three studies[15, 50, 51] also reported a long-term improvement in ODI and ESS after UAS therapy. One study[15] reported a long-term (five years follow-up) improvement in FOSQ score. Surgical success and cure rates were reported in all three studies[15, 50, 51] (success rate: 77.8%, 71.1%, and 74.6%, respectively; cure rate: 33.3%, 35%, and 44%, respectively).

Safety

There were no studies reporting any deaths related to MMA or UAS surgery.

MMA group Of the included studies, ten reported participants' complications after MMA (n = 428)[28, 30, 33, 39, 42-47]. The rate of major complication ranged from 0 to 18%. Five

studies reported the major compilations after MMA, which included reoperations for removal of osteosynthesis screws and plates (n = 8)[30, 33, 46], reoperations for maxillary non-union (n = 2)[28, 46], and acute dyspnea (n = 1)[45].

The most common minor complication reported was facial paresthesia caused by the impairment of inferior alveolar nerve[30, 33, 39, 43, 45-47]. Four studies[39, 45-47] reported both the rates of transient and persistent paresthesia in mandibular area, which were 100% and 13% (n = 175), 100% and 28% (n = 25), 90% and 60% (n = 34), and 32% and 0% (n = 28), respectively. Besides, one study[43] (n = 34) reported only the rate of transient paresthesia in mandibular area – 75%; one study[33] (n = 11) reported only the rate of the persistent symptom – 27%. In the long-term follow-up study from Boyd et al.[30] (n = 30), although no patients exhibited such facial anesthesia as measured objectively, 40% of patients perceived a decrease in sensation subjectively. Facial paresthesia in infraorbital area was reported by two studies[45, 46]. In the study by Vicini et al.[45] (n = 25), the rates of transient and persistent paresthesia in infraorbital area were 100% and 4%, respectively; in the study by Vigneron et al.[46] (n = 34), they were 37% and 30%, respectively.

Excluding facial paresthesia, the other reported minor complications consisted of developed malocclusion[30, 45-47] (n = 13), temporomandibular disorders[46, 47] (n = 11), local infection[28, 30, 47] (n = 6), minor postoperative wound pain[33] (n = 2), and others (n = 5)[28, 44, 47]. Of ten studies[28, 30, 32, 41-47] that investigated patients' perception of their facial appearance after MMA, two studies[30, 46] reported that there were 13% (4/30) and 15% (5/34) patients who perceived worsening of their facial appearance after MMA, respectively; the others[28, 32, 41-45, 47] reported that the perception of facial appearance was positive or neutral in all the patients after MMA.

UAS group Of the five studies reporting patients' complications (n = 2051)[15, 49, 51, 52, 54], the rate of serious device-related adverse events range from 0 to 7%. Four studies[15, 51, 52, 54] reported a total of 50 serious device-related adverse events requiring surgical repositioning or replacement of the neurostimulator or implanted leads. In addition, in the study from Suurna et al.[54] (n = 1849), 0.4% of the patients reported intraoperative serious adverse events including but not limited to hematoma (n = 8), infection (n = 2), extra implant procedure (n = 1), intraoperative arrest (n = 1), and pneumothorax (n = 1).

Since one study[54] did not report the count of minor complications, the safety outcomes of a subset of the study population (ADHERE cohort) reported in a previous study[56] were used for analyzing the minor complication rate. In that study[56], the rates of minor surgery-related and device-related complication 137 ± 77 days after UAS implant were 6% (18/313) and 22% (69/313), respectively; 386 ± 136 days after UAS implant were 4% (8/217) and 24% (53/217), respectively. In STAR trial cohort[15] consisting of 126 participants, the rates of minor surgery-related and device-related complication were both 136% (171/126) at the first year; at the fifth year, they were decreased to 1% (1/126) and 16% (20/126), respectively. Van de Heyning et al.[52] reported only minor surgery-related adverse events in their population, which yielded a minor complication rate of 57% (16/28). Philip et al.[49] and Steffen et al.[51] did not report any minor complications in their study populations. The most common minor surgery-related and device-related complication was incision discomfort[15, 51, 56] and discomfort due to electrical stimulation[15, 56], respectively.

DISCUSSION

This is the first systematic review aiming to comparatively evaluate MMA and UAS therapy in treating OSA. We reviewed 21 studies on MMA and nine studies on UAS in treating OSA. Due to the fact that there is no RCT or comparative study of MMA and UAS, a meta-analysis cannot be performed to directly compare these two interventions. Separate analyses of studies on MMA and UAS were utilized for this review. It should be noted that UAS therapy has stricter inclusion criteria (e.g., 15 ≤ AHI ≤ 65 events/h, absence of CCCp during DISE)[14, 17] for patients than MMA. There is therefore discrepancy of patients' baseline characteristics between the MMA cohort and UAS cohort. In this review, MMA cohort has younger age and higher baseline AHI compared to UAS cohort. To obtain definitive results on the comparison of MMA and UAS, future studies should include comparative studies of these two therapies where participants would have comparable baseline characteristics and be qualified for both therapies.

Objective outcomes

Based on the separate analysis of studies on MMA and UAS, we reported that these two procedures are both effective treatment modalities for OSA. However, compared to UAS, MMA seems to be more effective in treating OSA with a more significant decrease

in AHI and higher success rate. Through different mechanisms, MMA and UAS have been proven to be able to address multiple sites of collapse simultaneously[11, 36]. MMA enlarges the entire pharynx and reduces the collapsibility of the upper airway by advancing the maxillomandibular complex and anterior pharyngeal tissues attached to the maxilla, mandible, and hyoid bone[39]. The mechanism by which UAS resolves multilevel collapse, is enlargement of the retropalatal airway associated with tongue protrusion, which is so called "palatoglossus coupling" phenomenon[48]. Safiruddin et al. found that the retropalatal enlargement in response to UAS was statistically significant only in the responders, while the responders and non-responders had similar degrees of retro-lingual opening to stimulation[57]. Therefore, we are of opinion that the superiority of MMA over UAS in OSA treatment may be associated with the ability of MMA to enlarge the retropalatal airway more significantly. To improve patient selection for MMA and UAS, the mechanism of action of these two surgical procedure and the role of pathogenesis of OSA on the outcome of both surgeries need to be further clarified in future studies.

Subjective outcomes

It is interesting to note that several studies[42, 55] reported a discordance between objective outcome measures (e.g., AHI) and patient-reported outcome measures, which highlights the importance of subjective outcomes evaluation for OSA patients. In contrast to published ESS data, there is a scarcity of evidence related to other subjective outcomes of surgical treatment for OSA. Boyd et al.[30] evaluated the impact of MMA on quality of life (QoL) by Functional Outcomes of Sleep Questionnaire (FOSQ). At two years after MMA, a significant improvement in mean FOSQ scores of 4.7 was observed. In a study by Woodson et al.[15], the improvements in mean FOSQ scores following UAS were 3.0 at 1 year and 3.7 at 5 years, respectively. In addition to the daytime sleepiness and QoL, patient satisfaction – an important measure of therapy quality – should be noted when evaluating treatment options for OSA. Currently only a few studies have evaluated the patient satisfaction with MMA or UAS for the management of OSA[56, 58-62]. In a study by Butterfield et al.[59], 95.5% of patients were satisfied with MMA surgery for OSA, 90.9% would repeat the procedure, and 86.4% would recommend MMA to others for OSA treatment. In the ADHERE registry, 94% of patients reported that they were satisfied with UAS therapy and would undergo UAS again, and 93% reported that they would recommend UAS to others[56]. According to the available evidence, both MMA and UAS could significantly improve the perception for OSA patients, with high level of patient satisfaction. However,

the comparison of improvement in patient-perceived measures between the two therapies needs to be addressed in future studies.

Long-term outcomes

The long-term follow-up period of the included MMA studies ranges from 2 years to 12.5 years. Because of the small sample size, one study by Pottel et al.[63] reporting the longest follow-up result of MMA was excluded. In that study, the short term (within 2 years) success rate was 66.67% (8/12), and the long-term (range 14-20 years) success rate of MMA was 44.44% (4/9). In a study of 29 OSA patients treated by MMA, Vigneron et al.[46] concluded that the success rate was 85.7% in the immediate postoperative period and 41.1% at 12.5 years. Besides, they concluded that the good candidates for long-term success of MMA were the young patients (< 45 years old), with BMI < 25kg/m^2, AHI < 45 events/h, SNB angle < 75°, narrow retrolingual space (< 8 mm), and preoperative orthodontics, and without co-morbidity. It has been suggested that long-term failure of MMA might be attributed to weight gain[38, 63, 64], skeletal relapse[64], and ageing[63]. Given that UAS is an innovative therapy for OSA during the last decade, the longest follow-up period of the UAS studies was 5 years from STAR trial[15]. The success rates of UAS in STAR trial cohort were 66% (83/126), 74% (73/98), 75% (53/71) at 1, 3, and 5 years, respectively. In UAS therapy for OSA treatment, patients' adherence is necessary to guarantee the clinical efficacy[65]. The STAR trial revealed a high adherence to UAS therapy in long-term, with the patient self-reported nightly device use of 80% at 5 years, which might partially explain the stability of treatment effect. In addition, lower baseline ODI was found to be predictive of 5-year response to UAS therapy. It is therefore concluded that both MMA and UAS were relatively stable treatment for patients with moderate to severe OSA. In order to maintain the clinical efficacy, more effort is needed to provide continuous follow-up for OSA patients and to ascertain the factors associated with long-term stability of outcomes.

Safety

In terms of treatment safety, this systematic review revealed that both MMA and UAS were generally safe surgical procedure for OSA, with a relatively low rate of major complication. In the included MMA studies, all but one of the major complications were reoperation for removal of hardware. Age has been shown to be a risk factor for increased need for hardware removal[66]. In addition, Passeri et al. found that patients who were active smokers or have a history of smoking had higher risk of

complications, among which included removal of hardware[67]. The most common minor complication of MMA detailed in literatures was paresthesia of the lower lip and chin. It has been suggested that age at the time of surgery and addition of a genioplasty increase the risk of facial paresthesia, and large degree of advancement further increase the risk in older patients[68, 69]. In the STAR cohort (n = 126), the rates of major complication requiring device explanation, reposition or replacement were 4% at 4 years and 9.5% at 5 years, indicating that the reoperations after UAS may occur more often during the late time frame. The STAR cohort also suggested that the majority of minor complications after UAS were gradually resolved. Of note, Withrow et al. evaluated the impact of age on safety of UAS and found no significant difference between younger and older cohorts in complication rates[70]. The current evidence suggests that both MMA and UAS appear to be a safe approach in OSA treatment, while compared to MMA treating OSA with UAS may lead to less complications for older patients.

Clinical relevance

In patients with moderate to severe OSA and failure of CPAP treatment, a portion of them could qualify for both MMA and UAS therapy. The current evidence shows that MMA may have superior efficacy in OSA treatment. However, MMA is a more invasive intervention exposing patients to longer recovery time and higher risk of postoperative complications. An overnight admission of intensive care unit is required for OSA patients following MMA surgery, and the length of hospitalization after MMA reported previously ranged from <2 days to 5-8 days[69]. Additionally, MMA surgery often involves time-consuming preoperative and/or postoperative orthodontic work. One notable potential problem with MMA has been the accompanying alteration in facial appearance; however, most of patients undergoing MMA for OSA view the change in facial appearance as neutral even positive[30, 32, 46]. In comparison to MMA, UAS surgery is less invasive and more patient-friendly and does not require extended recovery. The majority of patients are discharged the same day or one day after UAS surgery[71]. In addition to the information regarding treatment efficacy and safety, cost of treatment options is important in assisting decision-making in OSA treatment. It has been indicated that UAS is cost effective, with a lifetime incremental cost effectiveness ratio (ICER) of USD 39,471 per quality-adjusted life year (QALY) in the United States healthcare system[72] and EUR 44,446 per QALY in a European setting[73], respectively. However, to our knowledge, no study has assessed the cost-effectiveness of MMA, which precludes the comparison of cost-effectiveness between these two

therapies. Hence, to further assist decision making in OSA treatment, there is a need to assess and compare the costs and cost-effectiveness of each intervention.

While the primary target patient population differs between MMA and UAS, it has been proposed that these two procedures might be considered as complementary therapies[17]. For example, the UAS may be considered when a patient fails to respond to MMA. It is interesting to note that in a recent study[74], Sarber et al. evaluated the efficacy of UAS therapy in 18 OSA patients who did not meet all FDA criteria for UAS and found a promising treatment outcome. They suggested that future studies need to consider the expansion of current FDA criteria for UAS, particularly in BMI and AHI criteria. Thus, to optimize surgical outcome, reduce rate of mortality and morbidity, and improve quality of life and other subjective outcomes, further investigation is essential to clarify indications of each therapy for OSA.

Limitations

There are several limitations of the present review. Firstly, because of the inherent difficulty of randomizing patients to different surgical interventions or sham surgery[75], except for one RCT and one quasi-experimental trail, all the included studies were cohort studies, the majority of which demonstrated fair quality according to the MINORS tool. Due to the lack of RCT and comparative studies of MMA and UAS for OSA, a meta-analysis cannot be performed to directly compare these two procedures. Besides, meta-analyses were not conducted to separately assess overall effect sizes of MMA and UAS therapy on OSA, as mean and SD of the difference between pre- and postoperative measures were absent in majority of the selected studies. In this review we performed separate analyses for MMA and UAS studies, combined with noticeable differences between the two cohorts in age and OSA severity, which prevented us from generating a solid conclusion on the comparison of these two procedures. Due to the fact that some patients may fall between two stools, comparison of the two procedures is important. Future studies should include quasi-experimental trial and comparative cohort study comparing MMA and UAS to better clarify which modality is superior in OSA treatment. These studies can be part of a future large international consortium, which is more likely to generate solid conclusions. Secondly, due to the implemented inclusion criteria, which included the presence of both preoperative and postoperative PSG data, some well-conducted studies reporting on only subjective outcomes and/or safety were excluded for this study. Therefore, the present analysis of subjective outcomes and

safety may not be entirely representative of the population undergoing MMA or UAS in current literature. Lastly, our review is exclusively based on studies published in English, which can introduce a language bias[76].

CONCLUSION

The results presented in this review suggest that both MMA and UAS are effective and generally safe surgical treatment modalities for patients with moderate to severe OSA. However, within the limitation of the selected studies, there is currently no evidence on the comparison of MMA and UAS in the treatment of OSA.

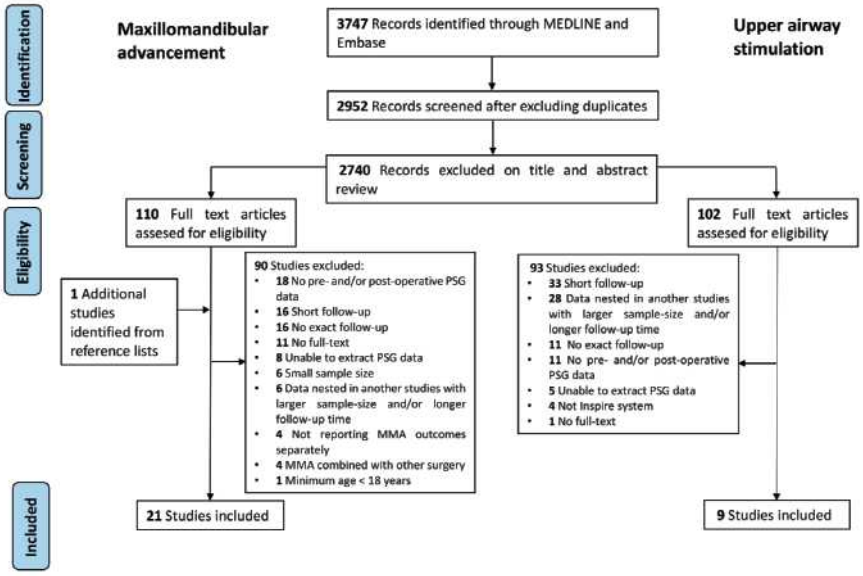

Figure 1. PRISMA flow diagram of the study selection process

Table 1. Characteristics of studies on maxillomandibular advancement

Study	Design	N	Age (years) (mean±SD)	% Male	Degree of advancement (mm) (mean±SD)		Follow-up (mean±SD)
					Max	Mand	
Bettega et al. 2000	Retro	20	44.4±10.6	90	11.8±0.5	11.8±0.5	6m
Bianchi et al. 2014	Retro	10	45±14	100	10	10	6m
Boyd et al. 2015	Pro	14			7.0±2.3	9.2±3.3	6.6±2.8y
Conradt et al. 1997	Retro	15	44±12	93.3			>2y
Gerbino et al. 2014	Pro	10	44.9		9.2±1.2	10.4±2.2	6m
Goh et al. 2003	Pro	11	42.8±8.2	100	10	10	7.7m
Goodday et al. 2016	Retro	13	37.8±8.6	84.6			9.6m
Hsieh et al. 2014	Pro	16	33±7.9	75			12±8m
Kastoer et al. 2019	Pro	14	51.1±7.3	57.1			6m
Li et al. 1999	Retro	175	43.5±11.5	83			6m
Li et al. 2000	Retro	40	45.6±20.7	82.5	10.8±2.7	10.8±2.7	4.2±2.7y
Li et al. 2001	Retro	52	46.6±6.7	82.7	10.5±1.5		6m
Li et al. 2002	Pro	12	47.3±9.8	75	10.5±1.2	10.5±1.2	6m
Liao et al. 2015	Pro	20	33.4±6.5	85			14±9.3m
Lin et al. 2020	Pro	53	35.7±11.7	75.7	4.3±2.9	13.3±3.8	24m
Liu et al. 2016	Retro	20	44±12	85	7±1.4		6m
Rubio-Bueno et al. 2017	Pro	34	40.8±13.9	41.2	4.9±3.2	10.4±3.9	6m
Veys et al. 2017	Pro	10	44.7±9.5	80	4.8±2.8	8.3±2.3	6m
Vicini et al. 2010	RCT	25	49.1±9.1	92		11	13±2.5m
Vigneron et al. 2017	Retro	29	40.7±12.6		8.4±4.1	11.7±5.1	12.5±3.5y
Wu et al. 2019	Retro	28	37.2±11.8	53.6	2.0±3.1	8.8±3.7	>1y

AHI, apnea-hypopnea index (events/h); BMI, body mass index (kg/m^2); ESS, Epworth sleepiness scale; m, months; Max, maxilla; Mand, mandible; N, number of patients; ODI, oxygen desaturation index (events/h); Post-op, postoperative; Pre-op, preoperative; Pro, prospective; RCT, randomized controlled trial; Retro, retrospective; y, years.

[a] Respiratory disturbance index (RDI) in this study was extracted as AHI.

[b] The number of patients was 9.

[c] This study defined surgical success as an AHI < 15 events/h with ≥ 50% reduction in postoperative AHI.

[d] This study did not define the criteria of surgical success.

[e] This study defined surgical success as a RDI < 15 events/h with ≥ 50% reduction in postoperative RDI.

[f] This study defined surgical success as a postoperative RDI < 20 events/h.

BMI (mean±SD)		AHI (mean±SD)		ODI (mean±SD)		ESS (mean±SD)		% Success	% Cure
Pre-op	Post- op	Pre-op	Post- op	Pre-op	Post- op	Pre-op	Post- op		
26.9±4.3	25.4±3.3	59.3±29.0	11.1±8.9					75[c]	
		56.8±5.2	12.3±5.5						
		50.0±20.0	8.0±10.7						
28.3±3.4		51.4±16.9	8.5±9.4						
31.6±5.5	28±1.4	69.8±35.2	17.3±16.7	59.5±5.3	9.1±8			80[d]	
29.4±4.6	27.2±3.3	70.7±15.9	11.4±7.4					81.8	
38.8±10.9	37.3±8.0	117.9±9.2	16.1±26.2			12.9±5.5[b]	5.0±4.1[b]	76.9	46.2
22±3.3		35.7±18	4.8±4.4					100	
25.7±3.7		40.2±25.6	9.9±7.2	13.5±18.6	4.0±3.5	13±6	9±7		
		72.3±26.7[a]	7.2±7.5[a]					95[e]	
31.4±6.7	32.2±6.3	71.2±27.0[a]	7.6±5.1[a]					90[e]	
32.0±6.0		61.6±23.9[a]	9.2±8[a]					90[f]	
33.5±6.2	32.3±4.1	75.3±26.4[a]	10.4±10.8[a]					83.3[f]	
22.4±3.4		41.6±19.2	5.3±4			11.9±7.3	7±3	100[c]	
24.8±3.3	23.9±4.7	34.8±26.0	7.4±6.7			10.8±5	10.2±5.1		67.9
27±4.6	27.4±4.6	53.6±26.6	9.5±7.4	38.7±30.3	8.1±9.2	17.0±4.8	5.7±2.7	90	50
27.6±4.5	25.5±4.3	38.3±10.7	6.5±4.3	34.7±12.5	5.4±4.1	17.4±5.4	0.8±1.4	100	52.9
		26.8±12.7	12.3±14.4			14.1±5.9	5.7±3.0	70	40
32.7±5.8	31.4±6.5	56.8±16.5	8.1±7			11.6±2.8	7.7±1.3	88	36
24.6±4		56.6±24	25.5±20.6				7.5±4.7	41.4	
24.2±5.1		59.3±14.5	10.9±3.3			12.8±2.8	6.9±2.5	85.7	46.4

Table 2. Characteristics of studies on upper airway stimulation

Study	Design	N	Age (years) (mean±SD)	% Male	Follow-up (month)	BMI (mean±SD)	
						Pre-op	Post-op
Bachour et al. 2021	Retro	15	52.9±6.6	86.7	18±9.6	29.1±3.3	30.1±4.5
Heiser et al. 2017	Pro	20	57±12	100	12	28.1±13.1	
Philip et al. 2018	Pro	10	52.0±9.4	100	6	28.8±3.3	
Steffen et al. 2019	Retro	18	51.5		24	27.9±4.5	28.0±4.7
Steffen et al. 2020	Pro	38	58.0±10.0	97.4	36	29.1±3.9	28.6±3.3
Suurna et al. 2021	Pro	782			14.3±7.0	29.2±4	
Van de Heyning et al. 2012	Pro	28	55.1±9.2	96.4	6	29.5±2.5	
Vanderveken et al. 2013	Retro	21	55±11	95.2	6	28±2	
Woodson et al. 2018	Pro	97	54.4±10.3		60	28.6±2.5	

AHI, apnea-hypopnea index (events/h); BMI, body mass index (kg/m^2); ESS, Epworth sleepiness scale; N, number of patients; ODI, oxygen desaturation index (events/h); Post-op, postoperative; Pre-op, preoperative; Pro, prospective; Retro, retrospective.

[a] The number of patients was 18.

[b] The number of patients was 71.

[c] The number of patients was 92.

AHI (mean±SD)		ODI (mean±SD)		ESS (mean±SD)		% Success	% Cure
Pre-op	Post- op	Pre-op	Post-op	Pre-op	Post-op		
33.0±16.5	36.5±23.8	25.3±18.3	30.3±21.1	11.5±3.8	8.1±4.5	26.7	6.7
28.9±7.6	6.6±5.1						
46.7±12.2	14.5±8.9	38.1±21.1	10.5±9.9	15.9±3.5	10.0±6.1		
26.3±10.6	10.4±10.1	12.8±10.2	10.1±12.0	12.7±5.2	5.1±3.8	77.8	33.3
30.0±13.7	13.1±14.1	25.8±16.7	11.6±14.0	12.1±5.8	6.0±3.2	62	35
35.8±15.0	14.5±14.9			11.4±5.5	7.1±4.6	69.7	
42.3±16.4	32.6±29.1	30.7±21.6	26.7±27.0	11.0±5.0	7.6±4.3	50	
38.5±11.8	20.3±20.6			8.2 ± 5.0[a]	6.4 ± 4.3[a]	62	
30.4±9.4[b]	12.4±16.3	27.2±10.0[b]	9.9±14.5	11.3±5.2	6.9±4.7[c]	74.6[b]	44

SUPPLEMENTARY MATERIAL

Table S1a. Search strategy in MEDLINE database

Ovid MEDLINE(R) ALL <1946 to Dec 14, 2021>		
Step	**Search**	**Result**
1	exp Sleep Apnea Syndromes/ or Snoring/ or ((sleep adj3 (apnea or apnoea or hypopnea or hypopnoea)) or (upper adj airway adj resistance) or (sleep adj disordered adj breathing) or snore or snoring).ti,ab,kf,ot.	54852
2	(mma or ((maxillomandibular or mandibular) adj2 advancement) or ((bimaxillar or orthognathic) adj2 surgery) or maxillary-osteomy or (multilevel or multi-level)).ti,ab,kf.	51520
3	'Electric Stimulation Therapy'/ or 'Electric Stimulation'/ or 'implantable Neurostimulators'/ or (((hypoglossal-nerve* or nervus-hypoglossus or cranial-nerve* or (XII adj nerve*)) adj2 (stimulat* or surgery or therap*)) or (upper-airway adj stimulat*) or Neurostimulat* or (implantable-nerve adj stimulat*) or electrical-stimulat*).ti,ab,kf.	52389
4	2 or 3	103811
5	1 and 4	1972

Table S1b. Search strategy in Embase database

Embase Classic+Embase <1947 to Dec 14, 2021>		
Step	**Search**	**Result**
1	exp 'snoring'/ or exp 'sleep disordered breathing'/ or (sleep adj3 (apnea or apnoea or hypopnea or hypopnoea)).ti,ab. or 'upper airway resistance'.ti,ab. or 'sleep disordered breathing'.ti,ab. or snor*.ti,ab.	97390
2	(mma or ((maxillomandibular or mandibula) adj2 advancement) or bimaxillar-surgery or maxillary-osteomy or orthognathic-surgery).ti,ab,kw.	8129
3	(multilevel or multi-level).ti,ab,kw.	49506
4	exp electrostimulation/ or exp 'nerve stimulator'/	101629
5	(((hypoglossal-nerve* or nervus-hypoglossus or cranial-nerve* or (XII adj nerve*)) adj2 (stimulat* or surgery or therap*)) or (upper-airway adj stimulat*) or Neurostimulat* or (implantable-nerve adj stimulat*) or electrical-stimulat*).ti,ab,kw.	71405
6	2 or 3 or 4 or 5	190441
7	1 and 6	2037
8	(exp experimental organism/ or animal tissue/ or animal cell/ or exp animal disease/ or exp carnivore disease/ or exp bird/ or exp experimental animal welfare/ or exp animal husbandry/ or animal behavior/ or exp animal cell culture/ or exp mammalian disease/ or exp mammal/ or exp marine species/ or nonhuman/ or animal.hw.) not human/	7698484
9	7 not 8	1960
10	limit 9 to (conference abstracts or embase)	1775

Table S2a. Methodological appraisal of the individual studies according to MINORS assessment tool – maxillomandibular advancement surgery

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Total score	Quality
Bettega et al. 2000	2	2	0	2	1	2	2	0					11	Fair
Bianchi et al. 2014	2	2	0	2	1	2	0	0					9	Fair
Boyd et al. 2015	2	2	2	2	1	2	0	2					13	High
Conradt et al. 1997	2	2	0	2	1	2	2	0					11	Fair
Gerbino et al. 2013	2	2	2	2	1	2	2	0					13	High
Goh et al. 2013	2	2	2	2	0	2	2	0					12	Fair
Goodday et al. 2016	2	2	0	2	0	2	0	0					8	Fair
Hsieh et al. 2014	2	0	2	2	1	2	0	0					9	Fair
Kastoer et al. 2019	2	0	2	2	1	2	2	0					11	Fair
Li et al. 1999	0	2	0	2	0	2	2	0					8	Fair
Li et al. 2000	2	2	0	2	0	2	0	0					8	Fair
Li et al. 2001	2	2	0	2	0	2	0	0					8	Fair
Li et al. 2002	2	1	2	2	0	2	0	0					9	Fair
Liao et al. 2015	2	2	2	2	1	2	0	0					11	Fair
Lin et al. 2020	2	2	2	2	1	2	0	0					11	Fair
Liu et al. 2016	2	2	0	2	1	2	0	0					9	Fair
Rubio-Bueno et al. 2017	2	2	2	2	1	2	0	0					11	Fair
Veys et al. 2017	2	2	2	2	0	2	0	0					10	Fair
Vicini et al. 2010	2	2	2	2	1	2	2	0					13	High
Vigneron et al. 2017	2	2	0	2	1	2	0	0					9	Fair
Wu et al. 2019	2	2	0	2	1	2	0	0	0	2	0	2	13	Fair

Q1, a clear study aim; Q2, inclusion of consecutive patients; Q3, prospective collection of data; Q4, endpoint appropriate to the aim of the study; Q5, unbiased assessment of the study; Q6, follow-up period appropriate to the aim of the study endpoint; Q7, loss of follow-up less than 5%; Q8, prospective calculation of the study size; Q9, an adequate control group; Q10, contemporary group; Q11, baseline equivalent of groups; Q12, adequate statistical analysis.

Table S2b. Methodological appraisal of the individual studies according to MINORS assessment tool – upper airway stimulation

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Total score	Quality
Bachour et al. 2021	2	2	0	2	0	2	2	0	10	Fair
Heiser et al. 2017	2	2	2	2	0	2	0	0	10	Fair
Philip et al. 2018	2	0	2	2	1	2	0	0	9	Fair
Steffen et al. 2019	2	2	0	2	0	2	0	0	8	Fair
Steffen et al. 2020	2	2	2	2	0	2	0	0	8	Fair
Suurna et al. 2021	2	2	2	2	0	2	0	0	10	Fair
Van de Heyning et al. 2012	2	2	2	2	1	2	2	0	13	High
Vanderveken et al. 2013	2	0	2	2	1	2	0	0	9	Fair
Woodson et al. 2018	2	0	2	2	1	2	0	0	9	Fair

Q1, a clear study aim; Q2, inclusion of consecutive patients; Q3, prospective collection of data; Q4, endpoint appropriate to the aim of the study; Q5, unbiased assessment of the study; Q6, follow-up period appropriate to the aim of the study endpoint; Q7, loss of follow-up less than 5%; Q8, prospective calculation of the study size.

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CHAPTER 7

Intra-individual variation of upper airway measurements based on computed tomography

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ABSTRACT

The aims of this study were (1) to quantify the intra-individual variation in the upper airway measurements on supine computed tomography (CT) scans at two different time points; and (2) to identify the most stable parameters of the upper airway measurements over time. Ten subjects with paired CT datasets (3-6 months interval) were studied, using computer software to segment and measure the upper airway. The minimum cross-sectional area of the total airway and all its segments (velopharynx, oropharynx, tongue base, and epiglottis) generally had the largest variation, while the length of the total airway had the lowest variation. Sphericity was the only parameter that was stable over time (relative difference < 15%), both in the total airway and each subregion. There was considerable intra-individual variation in CT measurements of the upper airway, with the same patient instruction protocol for image acquisitions. The length of the total airway, and the sphericity of the total upper airway and each segment were stable over time. Hence, such intra-individual variation should be taken into account when interpreting and comparing upper airway evaluation parameters on CT in order to quantify treatment results or disease progress.

Keywords: Intra-individual variation; Repeatability; Upper airway; Computed tomography; Measurement

INTRODUCTION

Over the past decades growing awareness of the detrimental effects of obstructive sleep apnea (OSA) has increasingly raised interest in morphometric evaluation of the upper airway[1-3]. Traditionally, upper airway morphology imaging consisted of a two-dimensional (2D) lateral cephalogram[4, 5]. However, due to the technical advancement of computed tomography (CT), this imaging modality has gained increasing popularity[5, 6]. Compared with a 2D lateral cephalogram, CT exhibits the capacity to analyze the upper airway three-dimensionally[7, 8]. Three-dimensional (3D) analysis has been widely used to assess the upper airway, which has given rise to the proposal and usage of multiple methods[3, 9, 10]. Volumetric, areal, and linear measurements, the parameters commonly used for upper airway evaluation, have been shown to have good to excellent inter-operator and intra-operator reliability in previous studies[9-12].

The rationale behind upper airway measurements may be to compare results of an individual to a reference group, or, more likely, to quantify changes within the airway between different time points. While the previous studies quantify the variation and precision of the measurement method itself, measurement on different time points could yield variation in repeated airway measurements as well. It has been proven that the upper airway dimension is influenced by an individual's body position, head and neck posture, mandibular movement, tongue position, and breathing stage[5, 13-16]. It is a challenge to standardize all these interfering factors during CT scan acquisition[11, 14]. Therefore, even if no airway-influencing intervention has been performed, it is suspected that considerable intra-individual variation in CT volumetric, areal and linear measurements of the upper airway at different time points exists. This variation between time points may hamper adequate evaluation of upper airway changes after surgical and orthodontic procedures, even if a validated measurement method is used. Understanding the degree of intra-individual variation in the upper airway measurements is thus imperative for clinical evaluation and research.

The intra-individual variation of the upper airway measurements has been studied only scarcely. In the study by Obelenis Ryan et al.[11], different volumetric readings of the upper airway were found in the context of different CBCT examinations with identical scanning and patient positioning protocols. However, in their study, the CBCT scans were taken in an upright position. It is well known that upper airway dimension is different between the upright and supine positions[17, 18]. For this reason, a new study under controlled conditions with the patient in supine position during the image acquisition is relevant.

Hence, the primary aim of this study was to quantify the natural intra-individual variation in the upper airway measurements on supine CT scans at two different time points. The secondary aim was to identify the most stable parameters of the upper airway measurements over time, by which accurate evaluation and comparison of the upper airway before and after intervention may be achieved in the future.

METHODS

Due to the retrospective nature of the study and de-identifying patient data prior to conducting the study, the Medical Ethical Committee of the Amsterdam UMC decided that the Medical Research Human Subjects Act was not applicable to this study (Ref. NoW20_261).

Study population

The population consisted of 10 subjects selected from a patient database of the Department of Oral and Maxillofacial Surgery (5 males and 5 females; mean age 50.3 ± 10.3 years, range 34-68 years), which had two CT datasets (T0 and T1) of the head and neck region acquired in the Amsterdam UMC. They were scanned for various indications, viz., maxillary/mandibular granuloma and palatal fistula, with a 3-6 months' time interval between scans (mean 4.8 ± 1.2 months). The inclusion criteria were the following: (1) adequate scan quality; (2) sufficient field of view (sella/nasion to epiglottis base); and (3) time interval between the scans of 3 to 6 months. The exclusion criteria were as follows: (1) patients younger than 18 years; (2) cases with intubation or other potential airway-influencing interventions during or between scans; (3) patients with previous upper airway surgery; and (4) patients with suspected or diagnosed OSA, of whom the upper airway may alter during the progression of OSA disease.

CT image acquisition

The included spiral CT scans of head and neck were acquired between 2018 and 2019 using the following scanning protocol (SOMATOM Force, Siemens Medical Solutions, Erlangen, Germany): 120 kV, 380 mAs, max. FOV 300 mm, pitch 0.85, slice thickness 1.0 mm, slice increment 1.0 mm, image matrix 512×512, window W1600/L400, hard-tissue kernel H60s. During the imaging procedure, the patients were in supine position and were instructed to remain still with maximum intercuspation, to breathe gently, and not to swallow.

CT measurements

Reference frame The Digital Imaging and Communications in Medicine (DICOM) files of the CT were imported in Maxilim software (version 2.3.0, Medicim NV, Mechelen, Belgium) for measurements. A hard-tissue reconstruction was created at 300 Hounsfield units (HU) and a soft-tissue reconstruction at -400 HU. To standardize the measurements and minimize the measurement error, the Frankfort Horizontal (FH) plane was constructed for reorientation of the 3D images at T0[19]. The T1 dataset was superimposed on the T0 dataset, using voxel-based matching on the structures of the cranial base[20, 21].

Landmarks After re-orientation and superimposition of the paired CT scans, four anatomical landmarks (**Figure 1**) were identified for segmentation of the regions of interest: posterior nasal spine (PNS), tip of uvula (TUV), tip of epiglottis (TEP), and base of epiglottis (BEP). The reliability of these landmarks has been validated in a previous study[9]. Based on TUV and TEP, the midpoint between them (MUE) was then calculated and localized (**Figure 1**). Because PNS is a bony landmark and thus an unaltered position between scans, it was localized only once for the T0 scan and re-used for the T1 scan; the other four landmarks were identified on both scans.

Boundary The soft-tissue model was imported into Blender software (version 2.81, Blender Foundation, Amsterdam, The Netherlands) for further analysis. The superior boundary of the upper airway was defined as the plane through the PNS parallel to the FH plane[9, 22]. The inferior boundary was the plane through the BEP parallel to the FH plane[9, 22]. The lateral and posterior boundaries consisted of the pharyngeal walls and the anterior boundary was composed of the soft palate, base of tongue, and anterior wall of the pharynx, with a cut-off at PNS point[10, 23].

Segmentation Based on the identified landmarks, the upper airway was segmented into four distinct regions (**Figure 1**): velopharynx region (between PNS and TUV), oropharynx region (between TUV and MUE), tongue base region (between MUE and TEP), and epiglottis region (between TEP and BEP). Cutting planes were parallel to the FH plane.

Upper airway parameters One operator (CK), with extensive experience with Blender, performed the measurements in all 20 datasets. The operator was blinded to the measurement results of T0 scans during the measurement for T1 scans. To quantify the inter-operator reliability, a second operator (RS) repeated the entire

measurement protocol in five randomly selected datasets. The operators were blinded to each other's results. The upper airway parameters of interest were volume, length, surface area, minimum cross-sectional area (MCA), and lateral dimension (LAT) and anteroposterior dimension (AP) of the MCA. These parameters were measured for the total airway and for the individual segments (**Table 1**). Before measuring the MCA, the "islands" (loose air parts) and "dead space" (space in mouth and space between tongue base and epiglottis) were removed from the upper airway model (**Figure 2**).

Derived airway parameters Based on these parameters, the following derived parameters were calculated: mean cross-sectional area (meanCSA)[24] for the size of the total airway and each segment; LAT/AP ratio in MCA, airway uniformity[10], and sphericity[10] for the shape of the total airway and of each segment separately (**Table 1**).

Outcome variables The following outcome variables were derived in this study:

- Intra-individual variation (number of patients = 10; number of CT datasets = 20): the relative difference in the measurements between two scans (T0 and T1) of an individual by operator 1.
- Intra-individual repeatability (number of patients = 10; number of CT datasets = 20): the intra-class correlation coefficient (ICC) for the measurements between two scans (T0 and T1) of an individual by operator 1.
- Inter-operator variation (number of CT datasets = 5): the relative difference between the measurements by operator 1 and operator 2 at T0/T1.
- Inter-operator reliability (number of CT datasets = 5): the ICC for the measurements by operator 1 and operator 2 at T0/T1.
- Agreement and smallest detectable difference (SDD) in the measurements between two scans (T0 and T1) of an individual (number of patients = 10; number of CT datasets = 20) by operator 1.

Statistical analysis

All data were analyzed using SPSS software (version 26, IBM Corp., Armonk, NY, USA). Descriptive statistical analysis was performed for all demographic and outcome variables.

The intra-individual repeatability and inter-operator reliability of upper airway measurements were evaluated using ICC[25]. Values of ICC less than 0.40, between 0.40 and 0.75, and greater than 0.75 are indicative of poor, fair to good, and excellent reliability, respectively[25]. The relative difference was used to estimate the intra-individual variation and inter-operator variation, which was calculated with the formula: (absolute difference/mean)*100%. Bland-Altman analysis was used to determine the agreement of the airway measurements between two different scans and to obtain the precise confidence interval for paired difference[26]. Based on Bland-Altman's method, SDD in the airway measurements between two scans of an individual was calculated with the formula: $(1.96*SD_{T0-T1})$.

RESULTS

Descriptive statistics of all measurements, intra-individual variation estimated by relative difference, intra-individual repeatability estimated by ICC, inter-operator variation estimated by relative difference, and inter-operator reliability estimated by ICC are presented in **Table 2**. Of the 50 upper airway parameters, the ICC values of intra-individual repeatability were greater than 0.75 for 26, between 0.40 to 0.75 for 19, and less than 0.40 for 5. For the inter-operator reliability estimated by the ICC, all the parameters showed excellent reliability (ICC 0.832-0.999). As for the intra-individual variation in the total airway, the mean relative difference was maximum in MCA (35.5%) and minimum in length (4.9%). Regarding the different airway subregions, the mean relative differences between two scans were exceedingly large (> 25%) in: volume at the oropharynx (34.4%), tongue base (29.8%), and epiglottis (25.4%); LAT of MCA at the epiglottis (25.4%); AP of MCA at the velopharynx (28.4%) and tongue base (26.5%); meanCSA at the oropharynx (25.3%), tongue base (26.9%), and epiglottis (25.1%); LAT/AP ratio of MCA at the tongue base (26.3%); and MCA at all levels. The relative differences of the sphericity between two scans in the total airway and each segment were all below 15%.

Table 3 shows the results of Bland-Altman analysis of differences between the paired scans (T0-T1; mean, SD, and 95% limits of agreement), as well as the absolute value of differences (|T0-T1|; mean and SD) and SDD values.

DISCUSSION

This is the first study to evaluate the intra-individual variation of linear, areal, and volumetric measurements of the upper airway in CT scans acquired at two different time points. Because of the short time interval between T0 and T1 (3-6 months), the absence of airway-influencing intervention during or between scans, no airway-influencing pathology or disease present in the patient, and the same position protocol between CT acquisitions, no airway alteration was expected within the scan pairs in our study population. Nevertheless, our findings suggest that different degree of variation exists in each segment of the upper airway between T0 and T1. Although patients with an airway-altering disease (i.e., OSA) or intervention were excluded, this finding may be especially important for evaluating change in these patients as a method to quantify diseases progress or treatment effects.

Regarding the intra-individual variation of the upper airway measurements between T0 and T1 (see **Table 2**), we found that the MCA of the total airway and of each segment separately generally showed the largest variation, with a relative difference of approximately 30%. Such variation could have two causes. Firstly, the location of MCA is not always constant during the dynamic upper airway movement due to breathing. Secondly, errors or variation in determining the location of the MCA may exist. Although several studies have found that MCA is the most important characteristic of the upper airway that may contribute to distinguishing OSA cases from non-OSA cases[27, 28], caution is thus warranted in interpreting this finding or applying it in clinical practice due to the natural variation found for MCA in the present study.

A significant limitation in CT analysis of the upper airway is differentiating the boundaries of soft tissues and empty spaces (air) by using limited difference in grey levels between them. However, the measurement of upper airway length is not affected by this as it is determined by a user-generated plane. Increased airway length has been suggested to be correlated with the presence and severity of OSA[10]. For consistency and reproducibility, we used a bony landmark having shown excellent reliability in previous studies – PNS – to define the superior boundary of the upper airway[9, 29]. In our study, the length of the total upper airway showed the least variation (relative difference: 4.9%) and it may therefore be regarded as a stable evaluation parameter for the upper airway.

Airway shape may contribute to the development of OSA[1, 10]. Recently, a derived variable, that is sphericity of the upper airway, was suggested and investigated[10, 30].

Klazen et al. found that less sphericity was the main predictor for OSA in patients with craniofacial macrosomia[30]. It is interesting to note that sphericity had low ICC values for intra-individual repeatability; however, it also showed low variation between T0 and T1 in both the total airway and each segment, all the relative differences being below 15%. This may be explained by the fact that ICC is a ratio between inter-unit variability and total variability (intra-unit and inter-unit)[31]. In this study, minor inter-unit variabilities of the sphericity measurements were indicated by the extremely low SDs, which could explain the low ICC values. Therefore, this parameter should not be disregarded based on ICC value alone.

The mean relative differences between two CT scans of the volumes of the total airway, velopharynx, oropharynx, tongue base, and epiglottis were 21.3%, 15.9%, 34.4%, 29.8%, and 25.4%, respectively. Obelenis Ryan et al.[11] evaluated CBCT scans of 27 patients obtained at two time points and reported that the mean relative differences of the volumes of the nasopharynx, oropharynx, and hypopharynx were 9.8%, 17.8%, and 12.0%, respectively. However, care should be taken in comparing the results between the two studies because of the different methodology in the upper airway segmentation. Moreover, differences between CT and CBCT evaluation of the upper airway should be noted. CT are performed when the patient is in the supine position, while most CBCT units acquire images with the patient in the upright position[32]. Soft tissue contrast resolution on CBCT imaging is inferior to CT imaging and therefore segmentation results are different[33].

There are several studies describing the morphometric evaluation of the upper airway[23, 24]. To date, however, there is no methodological standardization in 3D analysis of the upper airway[34]. Chen et al.[9] proposed a method of landmark localization for 3D upper airway measurements, which showed excellent intra- and inter-operator reliability. In the present study, four of the six landmarks proposed by Chen et al. were utilized: PNS, TUV, TEP, and BEP. Additionally, a derived landmark, MUE, was localized at the midpoint between TUV and TEP. Through the experience of over 8,000 drug-induced sleep endoscopy (DISE) examinations, Kezirian et al.[35] found four structures, namely velum, oropharyngeal lateral wall, tongue base, and epiglottis, which play a prominent role in upper airway obstruction. Accordingly, they proposed the VOTE classification system, which has been widely used for characterizing DISE findings. In 3D evaluation of the upper airway, various subregion definitions of the airway have been used in previous studies[11, 22, 23]. However, structure-based assessment for the upper airway cannot be achieved in

these methods. Therefore, based on the work by Kezirian et al.[35], the upper airway was divided into four subregions corresponding to the VOTE classification system. Because PNS, TUV, TEP, and BEP demonstrated excellent intra- and inter-operator reliability in the study of Chen et al.[9], the segmentation of the upper airway based on these landmarks may be considered reliable.

In the current study, all the parameters showed excellent inter-operator reliability. Zimmerman et al. conducted a study to assess the reliability of upper airway analysis with CBCT[34]. Interestingly, in contrast to our results, they found that the MCA and total airway volume showed poor inter-operator reliability. It needs to be noted that in Zimmerman et al.' study, six examiners of varying levels of education and clinical experience separately performed the upper airway analysis, and the reliability improved with the examiner education and experience. In our study, the measurement protocol was conducted by two experienced examiners, which may explain the discrepancy of reliability between the two studies. In addition, unlike their study, we used a fixed threshold for the selection of the upper airway. In this way, the operator's subjectivity in the threshold sensitivity selection was eliminated. Since it is generally accepted that the inter-operator reliability of the airway measurements is lower than the intra-operator reliability[34], it was decided to evaluate only the inter-operator reliability. Given that the measurement method of the upper airway used in this study is considered to be reliable, it was possible to evaluate the variation of upper airway measurements between repeated CT scans.

For the upper airway analysis, the primary confounding factors during 3D radiographic image acquisition include the individual's body, head, jaw, and tongue position, as well as the respiratory phase[5, 14, 15]. A systematic review on the effect of head and tongue posture on the dimensions and morphology of the pharyngeal airway concluded that altered head, body, and jaw position had a significant effect on the upper airway dimensions, particularly on the retro-palatal and retro-glossal regions of the oropharynx[14]. In another study by Gurani et al.[5], five sagittal MRI scans from ten subjects in different head and tongue positions were measured. They found that with the head in supine neutral position, the retropalatal, oropharyngeal, and total volumes increased significantly when the tongue was altered from a resting position to the tip of the tongue in contact with the posterior edge of the hard palate ($P \leq 0.05$). Schwab et al.[15] investigated the effects of respiration on the upper airway size using cine-CT in 15 normal subjects, 14 snorer/mildly apneic subjects, and 13 patients with OSA, all of whom were scanned in the supine position during awake

nasal breathing. In all three groups, there were significant dimensional changes at all anatomic levels of the upper airway during the respiratory cycle, especially in the OSA groups. Therefore, 3D assessment of the upper airway cannot be considered reliable unless all the above confounding factors are controlled during image acquisition. In this study, even with the same patient instruction during CT acquisition, different upper airway readings were found between two repeated CT scans within the same individual, which emphasizes the need for a more standardized patient instruction in terms of posture and breathing phase during image acquisition for evaluation. This needs to be developed and validated in future studies. As recommended by the American Association of Orthodontists White Paper[36], three-dimensional imaging of the airway is a snapshot of a specific moment of the breathing cycle and such technique currently does not represent a proper and reliable risk assessment tool for OSA. The results of the current study reinforce this recommendation.

This study can provide better insight into the real effects of potentially airway-altering procedures on airway size and morphology, such as orthognathic surgery and orthodontics treatment. The differences in the upper airway measurements caused by orthognathic surgery, such as maxillomandibular advancement for OSA treatment, are probably larger than those between two distinct CT scans in our study. However, minor differences in the upper airway measurements should be interpreted cautiously, in particular when quantifying the effect of treatment on the upper airway parameters in a single individual. The SDD provides the amount of potential variation that should be taken into account when interpreting the measurement changes over time at individual level (see **Table 3**). For example, a SDD of the MCA at the total airway of 61.3 mm^2 was found in the present study. This suggests that a change in MCA can only be considered to represent a real change if it is larger than 61.3 mm^2.

Our study has several limitations. First, the sample size might be considered limited. However, it should be mentioned that the sample size is sufficient to demonstrate the considerable intra-individual variation in upper airway measurements. This variation is not expected to decrease with a larger sample size; only its estimate will be more precise[37]. Second, although patients were provided with standardized instructions during CT acquisition, the retrospective nature of the data collection makes it impossible to verify this. While in theory this study could have been performed prospectively, using an enlarged field-of-view, this would have exposed patients who do not need imaging of the complete airway to a larger radiation dose, including vital structures, raising ethical objections to a prospective set-up. This is the reason why we

tried to make use of this set of existing radiographic examinations. The fact that most of published studies on 3D evaluation of the upper airway are retrospective studies with various patient instruction protocols, emphasize the difficulty of this issue. Our study highlights that caution should be taken when interpreting the results of upper airway comparison and evaluation using CT, and that a strict protocol is required for repeated measurements and subsequent imaging sessions. Further studies with a larger sample size should be performed to re-determine the natural intra-individual variation of the airway between two CT scans acquired at different time points, using a standardized patient instruction protocol.

CONCLUSION

Our study demonstrates that the dimensions and morphology of the upper airway in CT scans can vary considerably within an individual at different time points, even if the same patient instruction protocol for image acquisition is used. The MCA of the total airway and all its segments generally had the largest intra-individual variation, with relative differences of approximately 30%. The length of the total airway had the lowest intra-individual variation, with relative difference of 4.9%. The relative differences of the sphericity between two scans in the total airway and each segment were all below 15%. The length of the total upper airway, and the sphericity of the total airway and each segment were stable over time. Therefore, such intra-individual variation should be considered when interpreting the results of upper airway comparison and evaluation using CT, and the smallest detectable difference is necessary to detect true differences in upper airway measurements over time at individual level.

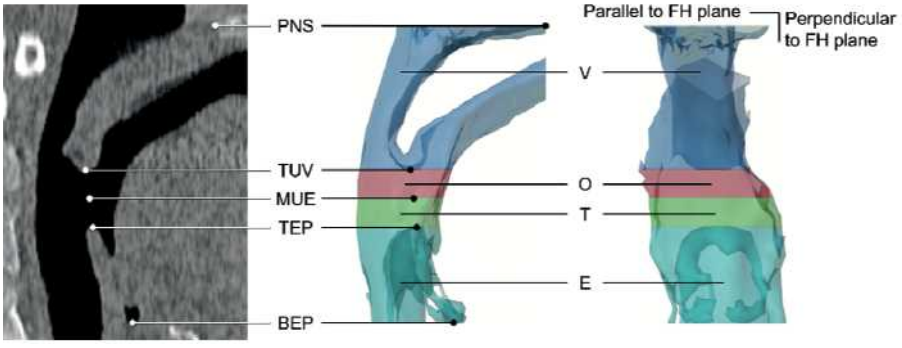

Figure 1. Location of the anatomic landmarks on the midsagittal plane and upper airway subregions of interest defined according to the landmarks. Landmarks: PNS, posterior nasal spine; TUV, tip of the uvula; MUE, midpoint between tip of the uvula and tip of the epiglottis; TEP, tip of the epiglottis; and BEP, base of epiglottis. Subregions: V, velopharynx region; O, oropharynx region; T, tongue base region; and E, epiglottis region.

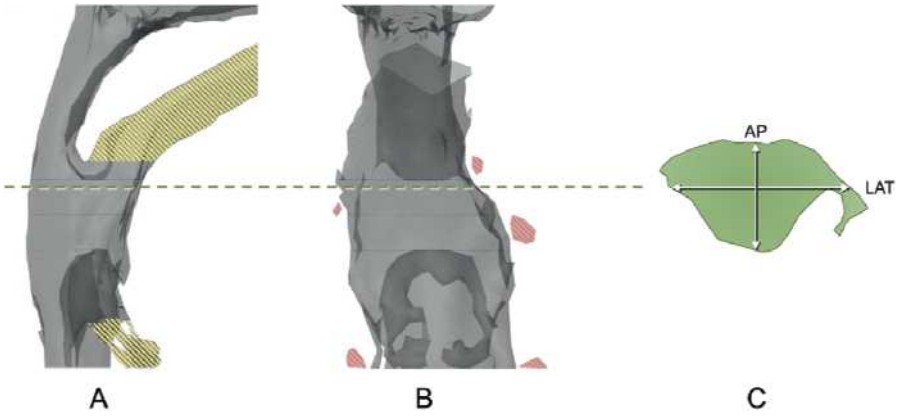

Figure 2. Measurement of minimum cross-sectional area (MCA), using Blender software. (A) "Dead space" (yellow shadow) of the evaluated airway. (B) "Islands" (red shadow) of the evaluated airway. (C) Anteroposterior dimension (AP) and lateral dimension (LAT) of MCA.

Table 1. Definition of airway parameters

Airway parameter	Unit	Definition
Volume	mm^3	Volume of upper airway
Length	mm	Length perpendicular to Frankfort Horizontal (FH) plane of upper airway
Surface area	mm^2	Surface area of upper airway without the top and bottom
Minimum cross-sectional area (MCA)	mm^2	At axial view, the minimum cross-sectional area of upper airway after removal of "islands" and "dead space"
Lateral dimension of MCA (LAT of MCA)	mm	At MCA, the maximum lateral dimension in an orientation perpendicular to the midsagittal plane
Anteroposterior dimension of MCA (AP of MCA)	mm	At MCA, the anteroposterior dimension on the midsagittal plane
Mean cross-sectional area (meanCSA)	mm^2	Equal to the ratio of volume to length (V/L)
LAT/AP of MCA	dimensionless (ratio)	Ratio of LAT to AP of MCA
Airway uniformity	dimensionless (ratio)	Uniformity of upper airway, equal to the ratio of MCA to meanCSA (MCA/meanCSA)
Airway sphericity	dimensionless (ratio)	Mathematical measure of sphericity (how round an object is). A flat object has a sphericity of 0, and a sphere has a sphericity of 1[9]. Sphericity = $[\pi^{1/3} (6 \times V)^{2/3}]/SA'$ Note: the closed surface area with top and bottom (SA') was used for calculating the airway sphericity.

Table 2. Descriptive statistics of variables (N = 10), intra-individual variation and repeatability (N = 10), and inter-operator variation and reliability (n = 5)

	To		T1		Intra-individual				
					Variation				ICC
	Mean	SD	Mean	SD	Mean	SD	Min	Max	
Volume (mm³) in the region of									
Total airway	12603.3	5057.8	12455.9	5553.7	21.3	15.8	3.1	52.5	0.836
Velopharynx	5795.6	2122.3	5720.0	2337.1	15.9	15.0	0.8	47.7	0.913
Oropharynx	1707.3	1301.1	1679.7	1512.3	34.4	16.4	11.8	65.8	0.895
Tongue base	1613.3	1089.1	1572.6	1218.2	29.8	17.9	8.5	67.9	0.878
Epiglottis	3487.1	1650.2	3483.6	1514.9	25.4	29.4	2.6	82.6	0.665
Length (mm) in the region of									
Total airway	66.3	12.4	66.0	12.4	4.9	4.3	0.3	14.1	0.944
Velopharynx	33.5	6.3	32.4	4.6	6.9	6.2	1.8	18.8	0.850
Oropharynx	8.4	3.8	8.5	3.9	16.9	13.3	0.0	46.8	0.905
Tongue base	8.4	3.8	8.5	3.9	16.9	13.3	0.0	46.8	0.905
Epiglottis	16.0	3.0	16.5	2.6	10.2	14.1	2.9	49.4	0.668
Surface area (mm²) in the region of									
Total airway	5572.1	1865.1	5512.9	1916.7	16.0	13.2	3.1	36.6	0.829
Velopharynx	2661.5	695.2	2558.2	730.0	16.6	15.5	0.9	42.0	0.669
Oropharynx	607.0	471.9	617.5	487.2	22.5	12.6	6.4	47.2	0.966
Tongue base	525.3	287.6	538.6	303.5	19.0	14.2	2.2	43.4	0.913
Epiglottis	1778.3	707.0	1798.6	710.0	19.6	14.0	3.4	44.3	0.832
minCSA (mm²) in the region of									
Total airway	80.6	54.1	81.1	47.3	35.5	20.3	8.0	69.0	0.845
Velopharynx	97.5	75.4	96.6	62.4	30.2	22.4	5.7	69.0	0.912
Oropharynx	176.6	83.6	163.8	74.6	31.0	21.2	3.1	73.1	0.740
Tongue base	176.0	88.3	156.4	65.6	30.2	18.2	11.2	58.2	0.788
Epiglottis	126.0	63.1	108.2	53.6	36.9	26.1	8.0	81.2	0.669
LAT of minCSA (mm) in the region of									
Total airway	15.7	6.7	16.3	7.4	22.4	17.2	2.9	44.2	0.845
Velopharynx	16.7	6.3	17.2	6.5	17.6	14.7	5.1	44.2	0.864
Oropharynx	21.9	8.2	23.1	7.2	19.1	19.3	0.5	51.6	0.809
Tongue base	21.7	6.7	21.2	5.6	12.5	15.4	1.2	49.4	0.822
Epiglottis	19.7	6.2	18.6	6.1	25.4	22.9	6.2	63.2	0.499
AP of minCSA (mm) in the region of									
Total airway	6.5	3.3	6.1	2.1	27.7	13.3	9.4	51.7	0.781
Velopharynx	5.5	2.8	6.0	3.3	28.4	14.0	8.0	52.4	0.852
Oropharynx	10.9	2.6	10.4	2.6	16.9	10.3	2.7	30.9	0.713
Tongue base	11.5	3.1	10.6	2.9	26.5	20.1	3.7	69.4	0.552
Epiglottis	8.3	3.2	6.9	2.1	23.2	23.3	5.0	75.0	0.658
meanCSA (mm²) in the region of									
Total airway	194.3	79.5	188.0	69.5	24.4	19.8	2.0	59.4	0.728
Velopharynx	181.4	72.7	180.5	82.8	22.5	17.5	2.7	59.1	0.861

Inter-operator				
Variation				ICC
Mean	SD	Min	Max	
2.8	2.1	1.4	6.5	0.997
7.4	4.5	2.8	15.0	0.959
1.8	1.3	0.1	3.4	0.999
2.7	0.9	1.9	3.9	0.999
4.9	4.0	1.1	11.0	0.989
1.3	0.9	0.5	2.9	0.997
3.2	2.1	0.7	6.6	0.980
4.8	6.0	0	15.2	0.994
4.8	6.0	0	15.2	0.994
4.5	2.3	2.0	8.1	0.949
3.8	3.9	0.2	9.7	0.993
5.4	4.1	1.1	12.2	0.968
2.8	2.0	1.3	6.0	0.999
3.3	1.7	1.7	5.4	0.998
6.9	10.9	0.6	26.3	0.979
3.3	7.0	0	16.0	0.980
3.3	7.1	0	16.0	0.980
1.0	1.0	0	2.7	0.999
2.9	3.5	0	7.2	0.996
1.4	1.6	0.2	3.6	0.999
1.2	1.9	0	4.5	0.996
2.3	2.8	0	6.1	0.990
3.2	2.9	0	6.9	0.988
1.8	1.0	0.6	3.2	0.995
2.3	3.9	0.4	9.3	0.982
3.2	4.5	0	10.9	0.929
3.2	4.5	0	10.9	0.960
3.6	3.7	1.4	10.2	0.962
3.5	3.2	0	7.6	0.893
6.9	10.3	0	25.2	0.948
2.2	1.5	0.2	3.6	0.998
4.2	3.0	0.3	8.5	0.986

Table 2. continued

	T0		T1		Intra-individual				
					Variation				ICC
	Mean	SD	Mean	SD	Mean	SD	Min	Max	
Oropharynx	196.0	87.4	181.9	72.3	30.3	21.3	2.4	59.3	0.712
Tongue base	193.6	89.4	175.3	61.1	26.9	18.3	1.0	57.0	0.757
Epiglottis	214.9	91.3	208.8	82.4	25.1	28.0	2.0	86.7	0.605
LAT/AP of MCA in the region of									
Total airway	2.64	0.85	2.62	0.79	22.7	17.9	2.4	65.4	0.540
Velopharynx	3.29	1.08	3.40	2.03	24.2	10.9	12.5	40.9	0.734
Oropharynx	2.00	0.56	2.22	0.51	18.3	17.7	0	62.4	0.614
Tongue base	2.01	0.83	2.18	1.03	26.3	29.5	6.7	94.7	0.126
Epiglottis	2.46	0.46	2.87	1.09	18.0	18.6	0.5	57.0	0.569
Airway uniformity in the region of									
Total airway	0.41	0.16	0.43	0.15	17.8	15.8	0.1	44.3	0.819
Velopharynx	0.51	0.20	0.52	0.18	18.9	15.2	0.8	41.6	0.809
Oropharynx	0.90	0.07	0.89	0.11	8.3	6.4	1.5	19.8	0.533
Tongue base	0.90	0.06	0.88	0.10	5.0	4.2	0.4	12.2	0.775
Epiglottis	0.58	0.13	0.52	0.14	21.9	17.1	5.8	59.9	0.372
Sphericity in the region of									
Total airway	0.42	0.04	0.41	0.05	11.1	7.5	2.6	24.9	0.128
Velopharynx	0.47	0.05	0.48	0.07	11.4	8.7	1.3	28.8	0.279
Oropharynx	0.69	0.08	0.68	0.06	7.0	5.1	0.2	16.6	0.633
Tongue base	0.70	0.06	0.70	0.06	5.0	4.3	0.3	11.1	0.691
Epiglottis	0.49	0.04	0.49	0.05	8.2	6.5	1.6	18.6	0.304

AP, anteroposterior dimension; LAT, lateral dimension; Max, maximum; MCA, minimum cross-sectional area; meanCSA, mean cross-sectional area; Min, minimum; N, number of patients; n; number of CT datasets; SD, standard deviation.

Inter-operator				
Variation				ICC
Mean	SD	Min	Max	
3.0	6.3	0	14.2	0.986
3.3	5.7	0.2	13.3	0.975
6.9	10.3	0	25.2	0.997
4.3	6.3	0	15.3	0.983
5.5	6.5	0	15.3	0.984
5.4	7.1	0.6	17.0	0.919
4.8	3.2	0.6	9.6	0.862
5.2	6.2	0.7	16.0	0.940
4.8	6.0	0.2	15.3	0.970
5.7	4.3	0.2	10.9	0.978
3.4	5.7	0.1	13.5	0.950
5.4	5.0	0.2	13.1	0.869
4.5	4.3	0.2	10.3	0.832
3.2	3.6	0	7.9	0.929
3.0	1.8	0.2	4.6	0.945
0.3	0.3	0.1	0.8	0.999
0.5	0.3	0.1	0.9	0.991
3.4	5.8	0.1	13.8	0.851

Table 3. Bland-Altman analysis of difference between two scans (T0 and T1) (N = 10)

	To-T1		|To-T1|		95% CI		SDD
	Mean	SD	Mean	SD	Upper	Lower	
Volume (mm³) in the region of							
Total airway	147.5	3037.6	2379.9	1719.9	6101.2	-5806.3	5953.8
Velopharynx	75.6	928.9	703.0	565.7	1896.1	-1744.9	1820.5
Oropharynx	27.7	645.0	514.0	351.3	1291.9	-1236.6	1264.3
Tongue base	40.7	570.3	445.6	326.4	1158.5	-1077.1	1117.8
Epiglottis	3.5	1296.8	857.5	929.8	2545.2	-2538.1	2541.7
Length (mm) in the region of							
Total airway	0.3	4.2	3.1	2.6	8.4	-7.8	8.1
Velopharynx	1.2	3.0	2.3	2.2	7.1	-4.8	5.9
Oropharynx	-0.1	1.7	1.3	1.0	3.1	-3.4	3.3
Tongue base	-0.1	1.7	1.3	1.0	3.1	-3.4	3.3
Epiglottis	-0.6	2.3	1.5	1.8	4.0	-5.1	4.5
Surface area (mm²) in the region of							
Total airway	59.2	1105.8	847.9	654.2	2226.7	-2108.3	2167.5
Velopharynx	103.3	579.6	415.7	394.6	1239.2	-1032.6	1135.9
Oropharynx	-10.5	126.0	111.0	48.0	236.4	-257.4	246.9
Tongue base	-13.3	123.0	96.7	70.3	227.8	-254.4	241.1
Epiglottis	-20.3	399.4	323.1	209.8	762.5	-803.2	782.8
MCA (mm²) in the region of							
Total airway	-0.6	28.3	24.3	12.1	54.9	-56	55.4
Velopharynx	0.9	29.1	23.2	15.8	57.8	-56.1	57.0
Oropharynx	12.8	57.1	48.1	29.6	124.8	-99.2	112.0
Tongue base	19.6	50.6	45.7	26	118.9	-79.6	99.2
Epiglottis	17.8	47.7	40.2	28.8	111.2	-75.7	93.5
LAT of MCA (mm) in the region of							
Total airway	-0.6	3.9	3.1	2.2	7.1	-8.3	7.7
Velopharynx	-0.5	3.3	2.6	1.9	6.0	-7.0	6.5
Oropharynx	-1.2	4.8	3.6	3.2	8.2	-10.6	9.4
Tongue base	0.5	3.7	2.5	2.7	7.8	-6.7	7.2
Epiglottis	1.1	6.2	4.6	4.0	13.2	-11.0	12.1
AP of MCA (mm) in the region of							
Total airway	0.3	1.8	1.6	0.7	3.9	-3.2	3.6
Velopharynx	-0.5	1.7	1.5	0.8	2.8	-3.7	3.3
Oropharynx	0.6	2.0	1.7	1.0	4.4	-3.3	3.9
Tongue base	0.9	2.8	2.6	1.4	6.5	-4.6	5.6
Epiglottis	1.4	2.2	1.8	1.9	5.8	-3.0	4.4
meanCSA (mm²) in the region of							
Total airway	6.3	55.0	41.9	33.5	114.1	-101.5	107.8
Velopharynx	0.9	43.5	33.3	25.8	86.3	-84.4	85.3
Oropharynx	14.2	60.9	52.3	29.8	133.5	-105.2	119.3
Tongue base	18.3	53.4	46.4	28.9	123.0	-86.3	104.7
Epiglottis	6.1	77.3	52.1	54.8	157.6	-145.4	151.5

Table 3. continued

	To-T1		|To-T1|		95% CI		SDD
	Mean	SD	Mean	SD	Upper	Lower	
LAT/AP of MCA in the region of							
Total airway	0.02	0.78	0.60	0.47	1.55	-1.51	1.53
Velopharynx	-0.11	1.18	0.87	0.76	2.20	-2.42	2.32
Oropharynx	-0.22	0.47	0.38	0.35	0.70	-1.14	0.92
Tongue base	-0.17	1.24	0.70	1.01	2.26	-2.60	2.42
Epiglottis	-0.41	0.78	0.54	0.68	1.12	-1.94	1.52
Airway uniformity in the region of							
Total airway	-0.01	0.09	0.07	0.06	0.18	-0.19	0.18
Velopharynx	-0.01	0.12	0.09	0.08	0.22	-0.24	0.23
Oropharynx	0.01	0.09	0.07	0.05	0.18	-0.16	0.17
Tongue base	0.01	0.05	0.04	0.03	0.12	-0.09	0.10
Epiglottis	0.07	0.15	0.12	0.10	0.36	-0.23	0.29
Sphericity in the region of							
Total airway	0.01	0.06	0.05	0.03	0.12	-0.10	0.11
Velopharynx	-0.01	0.07	0.06	0.05	0.13	-0.16	0.15
Oropharynx	0.01	0.06	0.05	0.03	0.12	-0.11	0.12
Tongue base	0	0.05	0.03	0.03	0.09	-0.09	0.09
Epiglottis	0	0.06	0.04	0.03	0.11	-0.11	0.11

AP, anteroposterior dimension; CI, confidence interval; LAT, lateral dimension; MCA, minimum cross-sectional area; meanCSA, mean cross-sectional area; N, number of patients; SD, standard deviation; SDD, smallest detectable difference.

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CHAPTER 8

Obstructive sleep apnea caused by acromegaly: Case report

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ABSTRACT

Background: Acromegaly is an uncommon syndrome caused by growth hormone-producing pituitary adenoma or pituitary gland hypertrophy. Acromegaly is known to be characterized by progressive somatic disfigurement and a wide range of systematic manifestations. This case study describes a rare case of severe obstructive sleep apnea (OSA) caused by acromegaly.

Clinical presentation: A female patient presented to the consultant clinic with the chief complaint of progressively worsening sleep and was diagnosed with severe OSA. Because of a peculiar facial appearance of the patient, acromegaly was suspected and confirmed by the findings of hormonal analysis and magnetic resonance imaging (MRI). After transsphenoidal resection of the pituitary adenoma, her OSA was almost cured, with residual apnea-hypopnea index of 5.5 events/h.

Conclusion: This case highlights the importance of a comprehensive clinical examination of OSA patients. In every sleep-related breathing disorder case, sleep clinicians should be aware of alternate problems that could cause upper airway obstruction.

Keywords: Obstructive sleep apnea; Acromegaly; Pituitary adenoma

INTRODUCTION

Acromegaly is a rare syndrome which affects both sexes equally, with an estimated annual incidence of three to four cases per million[1]. It is characterized by excessive secretion of growth hormone (GH) and insulin-like growth factor type 1 (IGF-1), largely owing to a hyperfunctioning pituitary adenoma[2]. It may present with a variety of clinical manifestations, the most common being acral and soft tissue overgrowth, diabetes mellitus, hypertension, and heart and respiratory comorbidities[3]. Currently, there is considerable evidence that acromegaly is associated with an increased risk of sleep apnea (SA), given that acromegaly alters the structure, elasticity, and function of the entire respiratory system[4].

This paper reported a rare case of severe OSA caused by acromegaly. The patient's OSA was almost cured following transsphenoidal resection of the pituitary adenoma.

CASE PRESENTATION

In April 2013, a 50-year old woman who complained of poor sleep was diagnosed with moderately severe OSA at the Department of Otorhinolaryngology (ENT) and Head and Neck Surgery. Her polysomnogram (PSG) showed an apnea-hypopnea index (AHI) of 23.8 events/h (**Table 1**). A mandibular advancement device (MAD) was prescribed. As shown in **Table 1,** a follow-up PSG 15 months later, performed with the MAD in situ, revealed a residual mild positional OSA with an AHI of 8.7 events/h and an AHI supine of 14.3 events/h.

In November 2017, she presented to the Department of ENT and Head and Neck Surgery again, due to increasing complaints of poor sleep, snoring, apneas, choking and not being refreshed after a night's rest, in spite of compliant use of the MAD. On physical examination, she weighed 71 kg, height was 168 cm, BMI was 25.2 kg/m^2, and neck circumference was 34 cm. A PSG, the results of which were shown in **Table 1**, confirmed severe OSA (AHI = 74.1 events/h). A drug-induced sleep endoscopy (DISE) exhibited a total obstruction at velum and oropharynx levels, together with partial obstruction at tongue base and epiglottis levels. When the jaw thrust maneuver was applied, only the obstruction at tongue base level disappeared. Continuous positive airway pressure (CPAP) therapy was proposed and advocated by the ENT surgeon. However, the patient refused CPAP therapy.

The patient was referred to the Department of Oral and Maxillofacial Surgery (OMFS) for a maxillomandibular advancement (MMA). At this point, both the ENT surgeon and the maxillofacial surgeon noticed a peculiar facial appearance, e.g. thickened skin, widened nose and pronounced chin. The patient was therefore also referred to the Department of Internal Medicine.

A thorough workup at the Department of Internal Medicine, including hormonal analysis and magnetic resonance imaging (MRI) (**Figure 1**), revealed the diagnosis "acromegaly" due to a pituitary macroadenoma. Thereafter the patient was referred to the Department of Neurosurgery for resection of the pituitary macroadenoma.

In September 2018, the patient underwent an endoscopic transsphenoidal resection of the pituitary macroadenoma. The histopathology confirmed a plurihormonal pituitary adenoma. The postoperative course was uneventful.

A follow-up PSG 7 months after surgery demonstrated a dramatic improvement of OSA (AHI = 5.5 events/h), as shown in **Table 1**. The patient reported significant improvement of sleep quality and did not show any symptoms of residual OSA. Her IGF-1 level remained normal in hormonal analysis at 13 months after surgery (81 nmol/L pre-surgery vs 25 nmol/L post-surgery; reference range: 10–27 nmol/L).

However, at 13 months after surgery, the clinical examination showed a malocclusion which had not been present at the initial consult at the Department of OMFS. A cone-beam computed tomography (CBCT) scan showed a significant condylar hyperplasia on the right side and a skeletal asymmetry. Different treatment options were discussed with the patient for creating an optimal occlusion and skeletal symmetry. However, the patient declined orthodontic treatment and/or orthognathic surgery, due to the fact that she did not want to have another operation. She was prescribed an Essix retainer to prevent further malocclusion and she had regular checkups to evaluate possible further progression of asymmetry.

DISCUSSION

Acromegaly is a rare disease which can lead to multi-systemic disorder. Patients with acromegaly are at a high risk of developing SA, specifically OSA. In a review by Attal et al., PSG-diagnosed OSA was found in an average of 69% of patients with active acromegaly in 11 studies (n = 239)[5].

The pathophysiology of nocturnal airway obstruction in acromegaly is not yet understood, but it is thought to be multifactorial[4, 6]. The persistent excessive GH and IGF-1 in acromegaly could cause anatomical changes, affecting the craniofacial bones and soft tissues, respiratory mucosa and cartilage, as well as the activity of the respiratory muscles, thus facilitating collapse or obstruction of the upper and middle oropharyngeal space during sleep.

This case, to the authors' knowledge, is the first reported acromegalic case where DISE was performed, by means of which dynamic evaluation of the upper airway during sleep was obtained. DISE revealed total obstruction during inspiration at the level of the soft palate and oropharynx with partial narrowing at the base of the tongue and epiglottis, which was similar to the outcome of the Muller maneuver in the study of Pelttari et al.[7]. In that study, significant narrowing during forced inspiration at the level of the soft palate was observed in 11 patients with acromegaly, while little if any narrowing occurred at the base of the tongue.

The effect of treated acromegaly on OSA is inconsistent. Tasbakan et al. found that OSA commonly persisted in well-controlled acromegaly patients, despite normal levels of IGF-1 and GH after adenomectomy[6]. In another study, it was demonstrated that surgical treatment of acromegaly had no significant effect on OSA[8]. In contrast, Buyse et al. reported the cases of three acromegalic patients with severe OSA who demonstrated a manifest improvement in apnea after treatment of acromegaly[9].

In this case, after adenomectomy, severe OSA was dramatically reduced, as was proved by the postoperative PSG. Therefore, the cure or control of acromegaly could be associated with alleviation of OSA, although further studies are needed to investigate this relationship. Swelling of soft tissue, owing to direct stimulation of the epithelial sodium channel by the high GH and IGF-1 levels, is considered to play a major role in the onset of OSA for patients with acromegaly. Therefore, the reduction of soft tissue swelling after the treatment of acromegaly, possibly leading to better upper airway patency, may be the main explanation for the patient's relief from OSA[5, 10].

This patient was satisfied with the final treatment outcome and believed that all her concerns about sleep quality and daily energy had been addressed. She did not want any further orthodontic and/or orthognathic treatment for her facial asymmetry and malocclusion. Long-time follow-up is therefore needed to monitor the possible progression of her facial abnormalities and malocclusion, together with her OSA status.

CONCLUSION

Acromegaly, as a rare risk factor for OSA, is often detected late owing to its insidious onset and slow progression. This case highlights the importance of clinical examination and diagnostic suspicion in OSA. Given the complex interplay of multiple etiologies in OSA, the assessment of patients with suspected OSA should take into consideration all the possible risk factors.

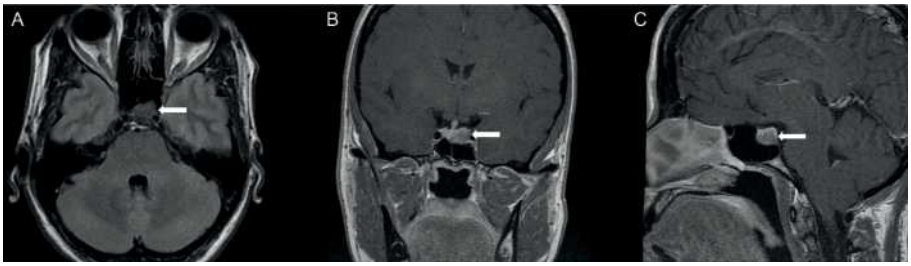

Figure 1. Preoperative magnetic resonance imaging in the axial (A), coronal (B) and sagittal (C) planes demonstrated the large pituitary mass (indicated by arrows)

Table 1. Results of polysomnogram

	1st PSG	2nd PSG with MAD	3rd PSG	4th PSG
Parameters	**April 2013**	**August 2014**	**February 2018**	**April 2019**
AHI, events/h	23.8	8.7	74.1	5.5
AI, events/h	14.8	5.7	55.5	2.4
HI, events/h	9	2.9	18.6	3.2
AHI supine, events/h	43.5	14.3	62.2	5.4
AHI non-supine, events/h	17.6	3.5	81.6	5.9
Mean O^2 saturation, %	95	96	93	95
Minimum O^2 saturation, %	80	77	67	86
3% ODI, events/h	18.6	14.8	75.9	16
REM sleep rate, % TST	21.2	20.6	15.7	27.2

PSG, polysomnogram; MAD, mandibular advancement device; AHI, apnea-hypopnea index; AI, apnea index; HI, hypopnea index; ODI, oxygen desaturation index; REM, rapid eye movement; TST, total sleep time.

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CHAPTER 9

General discussion

The studies presented in this thesis aim to extend knowledge on the role of maxillomandibular advancement (MMA) for the treatment of obstructive sleep apnea (OSA), and more specifically the effects of MMA in OSA patients with and without anteroposterior maxillomandibular deficiency; predictors of surgical response/non-response to MMA; and comparison between MMA and other surgical interventions for OSA (i.e., multilevel surgery [MLS], upper airway stimulation [UAS]). Furthermore, the thesis aims to examine the intra-individual variation of upper airway measurements using computed tomography (CT). Additionally, a rare case with severe OSA caused by acromegaly is presented.

In this chapter, the main findings of the studies included in this thesis are presented and discussed. Where appropriate, suggestions for future research are made. This chapter ends by giving a general conclusion.

MAIN FINDINGS

Indications for MMA

Recognizing that maxillary and/or mandibular deficiency contribute to the development of OSA, MMA has been advocated in the management of OSA since the mid-1980s[1]. In the early stage, MMA was the second phase of a two-phase airway reconstructive protocol for the treatment of OSA, where patients underwent MMA for persistent OSA in cases of incomplete response to phase I surgery (e.g., palatal surgery, genioglossus advancement, and/or hyoid myotomy)[2]. As investigators have gained more insight into the role of MMA in OSA management, various surgical protocols for MMA have been proposed. However, to date, there has been no consistent indication for MMA. In the most current American Academy of Sleep Medicine (AASM) practice guidelines, it is recommended that "MMA is indicated for surgical treatment of severe OSA in patients who cannot tolerate or who are unwilling to adhere to positive airway pressure therapy, or in whom oral appliances, which are more often appropriate in mild and moderate OSA patients, have been considered and found ineffective or undesirable (Option)"[3]. Of note, this recommendation is given as an "Option" as it is drawn from low-quality evidence. Currently, the general indications for MMA are: moderate to severe OSA, and OSA patients with concomitant dentofacial deformity[4]. While the advancement of both jaws is functionally and esthetically beneficial to OSA patients with anteroposterior maxillomandibular deficiency (maxillary and

mandibular retrognathia), there is a concern about the effect of MMA for OSA patients without such deficiency. In this thesis, we found no significant difference in the effects of MMA on respiratory function and facial esthetics between OSA patients with and without maxillomandibular deficiency, which supports the notion that MMA can be considered as an appropriate treatment for OSA patients without such deficiency (**chapter 2**).

Both complete concentric collapse at the palate (CCCp) and complete collapse at lateral pharyngeal wall observed during drug induced sleep endoscopy (DISE) have been suggested to be a negative predictor of treatment success of some non-continuous positive airway pressure (non-CPAP) therapies, such as upper airway surgery, and mandibular advancement device (MAD)[5-7]. CCCp is also defined as an absolute contraindication to unilateral UAS[8]. Most recently, Liu et al. suggested that MMA could be considered as a first-line treatment in OSA patients with those two specific airway collapse patterns[9]. However, limited evidence is available on this topic[10,11]. The finding in **chapter 4**, that those two DISE phenotypes are not associated with surgical response to MMA, further supports this indication for MMA.

To conclude, current evidence supports that the indications for MMA could be expanded, which include OSA patients with coexisting dentofacial deformity; moderate to severe OSA patients who do not accept or have failed other forms of therapy, either with or without coexisting dentofacial deformity; presence of complete concentric collapse at the palate; and presence of complete collapse at lateral pharyngeal wall. In addition, especially younger people gain from a MMA procedure because earlier intervention could enhance life expectancy and besides that, MMA shows better results in younger patients[12]. Nevertheless, since the precise indications and staging protocols for MMA remain undefined, large-scale prospective studies are necessary to further explore the role of MMA in OSA management and define the indications for MMA.

Predictors of response and non-response to MMA

MMA has been proven to be a highly effective surgical procedure for OSA, with a success rate of approximately 85% (**chapter 5**)[12], but there is still room for improvement. Identifying predictors of MMA surgical response can help offer adequate treatment plans upfront based on predicted therapeutic response. A meta-analysis by Holty et al. showed that younger age, lower preoperative weight and

apnea hypopnea index, as well as greater degree of maxillary advancement were predictive of increased surgical success[12]. Several other potential predictors were also identified previously, such as a smaller neck circumference[13] and mandibular retrognathia[14].

In this thesis, we further surveyed the potential predictors from the most common clinically available data (patient-related, polysomnographic, cephalometric, and surgical data) and DISE findings, respectively (**chapter 3** and **4**). In **chapter 3**, we found that the existence of cardiovascular disease, higher central apnea index, and larger superior posterior airway space were the independent predictors of non-response to MMA (**chapter 3**).

In terms of the pattern of upper airway collapse during DISE, we found that complete anteroposterior epiglottic collapse was a negative predictor of response to MMA (**chapter 4**). It should be noted that **chapter 4** did not distinguish primary and secondary epiglottis collapse. Future prospective studies with larger study groups are necessary to investigate if the predictive value of primary and secondary epiglottic collapses in surgical response to MMA is different. In addition, multilevel collapse of the upper airway is prevalent in patients with moderate to severe OSA (**chapter 4**)[15]. It may be the case that certain combinations of collapse levels are associated with the surgical response to MMA. Future research is needed to answer this question.

Taken together, given the absence of consistent findings and limited evidence, it is still a challenge for clinicians to precisely identify responders or nonresponders to MMA. More research is necessary to investigate which parameters can reliably predict the surgical outcome and thus should be taken into consideration in the patient selection procedure. In addition, because patients' satisfaction is also an important outcome measurement in the management of OSA, the predictors of patients' satisfaction in MMA surgery should be identified in future studies.

MMA versus other surgical approaches

Moderate to severe OSA is usually characterized by multilevel collapse of the upper airway[15], which highlights the need for surgical therapies able to resolve multilevel collapse. MMA, MLS, and UAS are all multilevel approaches[8, 11, 16]. MMA, as stated above, is generally indicated for patients with moderate to severe OSA, and OSA patients with concomitant dentofacial deformity[4]. In terms of MLS, AASM practice

guidelines suggest that it is acceptable in patients with narrowing of multiple sites in the upper airway, particularly if they have failed UPPP as a sole treatment[3]. In contrast to MMA and MLS, UAS therapy has stricter indication criteria, viz., moderate to severe OSA (AHI 15-65 events/h) with less than 25% central and/or mixed apneas, intolerance or failure of PAP treatment, and absence of CCCp during DISE[17].

Despite that the indications for the three types of surgery are not exactly same, a subset of patients may be expected to benefit from all of them when no generally accepted indicative factors for treatment failure are found (e.g., significant dentofacial deformity, CCCp during DISE). These approaches have shown favorable treatment outcomes for OSA[12, 17-19], but there is a paucity of evidence on the comparison between them. Consequently, there is no adequate evidence for final decision-making regarding the choice of surgery types. On the basis of the meta-analyses in **chapter 5,** it was concluded that MMA might offer greater improvements in AHI compared to MLS, but the complication rate of MMA is higher. It should be noted that the conclusion of **chapter 5** is drawn from the comparison between MMA and MLS by separately pooling results from studies on each type of surgery. To compare the efficacy and safety of MMA and UAS in the treatment of OSA, a systematic review was performed including 21 studies on MMA and 9 studies on UAS (**chapter 6**). Due to the noticeable differences between the MMA cohort and UAS cohort in age and baseline AHI, it is not feasible to generate a solid conclusion on the comparison of efficacy and safety of these two procedures. Notably, in addition to treatment efficacy and safety, cost of the therapy option is important in assisting decision-making in OSA management. To our knowledge, few studies have assessed the cost-effectiveness of MLS[20] or UAS[21, 22], but no study has assessed the such information about MMA. This precludes the comparison of cost-effectiveness among MMA, MLS, and UAS.

Future research should entail well designed comparative studies among MMA, MLS, and UAS with larger sample size and long-term follow-up, in which thorough assessment of objective respiratory and sleep parameters, subjective outcomes, quality of life, morbidity and mortality, and cost-effectiveness is performed. Such findings will help optimize shared decision-making between clinicians and patients for OSA treatment.

Three-dimensional evaluation of the upper airway

Three-dimensional (3D) evaluation of the upper airway has been widely used to investigate the role of upper airway anatomy in the pathogenesis of OSA and in the treatment outcome of therapies for OSA (e.g., MMA, MAD)[23-26]. It has been suggested that upper airway dimension is affected by multiple factors, such as body position, mandibular movement, tongue position, breathing stage, wakefulness versus sleep, and sleep stage[27-30]. In the clinic, it is still a challenge to standardize all these interfering factors during imaging acquisition[31]. This may result in considerable intra-individual variation in 3D upper airway measurements, which hampers accurate upper airway assessment.

Obelenis Ryan et al. evaluated the differences in upper airway volume in the same patients from their consecutive cone-beam computed tomography (CBCT) scans. They found that volumetric measurements of the upper airway differed between different CBCT scans with identical scanning and patient positioning protocols[31]. In addition to volumetric parameters of the upper airway, our study in **chapter 7** also quantified the intra-individual variation in the areal and linear parameters on the supine CT scans at two different time points (3 to 6 months interval). It was found that there was considerable intra-individual variation in CT volumetric, areal, and linear measurements of the upper airway, even if a same patient instruction protocol for image acquisition was used. As recommended by the American Association of Orthodontists White Paper, 3D imaging of the airway is a snapshot of a specific moment of the breathing cycle, and such technique currently does not represent a proper and reliable risk assessment tool for OSA[32]. The finding in **chapter 7** reinforces this recommendation. Such intra-individual variation should be taken into account when interpreting and comparing upper airway measurements on CT, which may also apply to other 3D imaging techniques (e.g., CBCT, magnetic resonance imaging [MRI]). Despite the many advantages of CT, the main downside is the inevitable radiation exposure. Future research should be performed to evaluate such variation on different airway imaging techniques. Moreover, a standardized and validated patient instruction protocol in imaging acquisition should be developed in future research.

Personalized treatment for OSA

The heterogeneity of OSA is reflected by various risk factors[33, 34], pathophysiological causes[35], clinical presentations[36-38], and consequences[38, 39]. Recognition of this heterogeneity is imperative, because the treatment for OSA can be personalized based on individual characteristics.

Risk factors

In addition to the most common risk factors, such as obesity, increased age, and male gender, some endocrine and metabolic disorders are also associated with OSA[33, 34]. This thesis presented a patient who was referred for consultation of MMA for severe OSA but was subsequently diagnosed with acromegaly. The patient's OSA was almost completely resolved after transsphenoidal resection of a pituitary adenoma (**chapter 8**). Current evidence has shown a variable response of OSA to the treatment of acromegaly[40, 41], hence clinicians who treat patients with acromegaly should not assume that OSA will recover by curing the underlying endocrine disorder. Nevertheless, our case still highlights that the assessment of patients with suspected OSA should involve all possible risk factors for the purpose of personalized and effective treatment.

Pathophysiologic phenotypes

Available evidence has indicated that phenotyping is the prerequisite for developing personalized medicine in OSA[42-44]. Eckert et al. proposed a three-point (Passive critical closing pressure of the upper airway, Arousal threshold, Loop gain, and Muscle responsiveness [PALM]) scale to categorize OSA patients according to pathophysiologic phenotypes and thus select the appropriate therapy for the individual patient[45]. Briefly, in patients who had severe and moderate pharyngeal anatomical impairment (i.e., category 1 and 2a), there is an indication for CPAP or other anatomic intervention (e.g., MAD, upper airway surgery, positional therapy). In the category 2b and 3, nonanatomic traits are likely to contribute importantly to OSA pathogenesis, and single or combined therapy that targets on nonanatomic traits may be required[45]. For example, for the patients with impaired muscle function, hypoglossal nerve simulation[18], muscle training[46], and pharmacologic therapy[47] may be helpful, while oxygen therapy[48] and carbonic anhydrase inhibitors[49] may be beneficial in the patients with high loop gain. However, it should be highlighted that implementing this concept into the clinical setting is difficult now, as it is complicated to measure the PALM variables. A simplified phenotyping tool should therefore be developed for routine clinical use.

Clinical phenotypes

In addition to the pathophysiologic phenotypes, different OSA phenotypes based on clinical features and polysomnographic data have been proposed as well, in order to assess disease severity, OSA consequence, and predict treatment outcome[50-52]. Ye et

al. firstly applied cluster analysis to identify clinical phenotypes in an Icelandic Sleep Apnea Cohort (822 patients with moderate to severe OSA). Three main clusters were identified, which were "disturbed sleep group", "minimally symptomatic group", and "excessive daytime sleepiness group"[51]. Among these three clusters, the probabilities of having comorbid hypertension, diabetes, and cardiovascular disease were highest in the "minimally symptomatic group" and lowest in the "excessive daytime sleepiness group"[51]. Currently, there is accumulating evidence on the association between clinical phenotypes and response to treatment for OSA such as CPAP[53], MAD[54], and MMA (**chapter 3** and **4**). This thesis revealed that the presence of cardiovascular disease, higher baseline central apnea index, larger superior posterior airway space (**chapter 3**), and the presence of complete anteroposterior epiglottic collapse on DISE (**chapter 4**) might be unfavorable clinical phenotypes for surgical response to MMA.

Genotypes

Assessment of differences in molecular signatures between individuals now plays an important role in developing personalized medicine. However, neither biomarkers nor "-omics" analyses (e.g., genomics, proteomics) have been extensively used in the study on OSA[55, 56]. To truly achieve a personalized OSA treatment, a combination of physiological phenotypes, clinical phenotypes, and genotypes, integrated with patients' preference, may be necessary in the future.

CONCLUSION

The following can be concluded from this thesis:

1. There is no significant difference in the effect of MMA on respiratory function and facial esthetics between OSA patients with and without maxillomandibular deficiency (**chapter 2**).

2. The presence of cardiovascular disease, higher preoperative central apnea index, and larger preoperative superior posterior airway space are independently associated with non-response to MMA for OSA (**chapter 3**).

3. DISE can be a promising tool in order to identify patients who will or will not respond to MMA for treating OSA. Patients with complete anteroposterior epiglottic collapse may be less suitable candidates for MMA (**chapter 4**).

4. Based on a systematic review and meta-analysis, it was concluded that both MMA and MLS are effective treatment options for OSA to improve respiratory parameters and patient-reported outcomes. Compared to MLS, MMA may be more effective in improving OSA. However, the complication rate of MMA is higher (**chapter 5**).

5. Based on a systematic review, it was concluded that both MMA and UAS are effective and generally safe therapies for OSA. However, due to the limitations of the included studies, there is no evidence yet to directly compare these two procedures (**chapter 6**).

6. The dimensions and morphology of the upper airway in CT scans may vary considerably within an individual at different time points, even if the same patient instruction protocol for image acquisition is used. Such intra-individual variation should be considered when interpreting the results of upper airway comparison and evaluation using CT, and the smallest detectable difference is necessary to detect true differences in upper airway measurements over time at the individual level (**chapter 7**).

7. A comprehensive clinical examination of OSA patients is important. Given the complex interplay of multiple etiologies in OSA, the assessment of patients with suspected OSA should take into consideration all possible risk factors (**chapter 8**).

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CHAPTER 10

Summary in English and Dutch

SUMMARY

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder, which is characterized by repetitive episodes of complete or partial upper airway collapse during sleep. Undiagnosed and untreated OSA can potentially lead to serious medical issues and substantial economic costs. Although continuous positive airway pressure (CPAP) is the gold standard treatment for OSA, there is a need for other treatment modalities as the efficacy of CPAP is often hampered by low tolerance and poor compliance.

Maxillomandibular advancement (MMA) has been considered as a highly effective surgical therapy for moderate to severe OSA. The position of MMA within the arsenal of treatment options for OSA, however, is still not fully understood. The main purpose of this thesis was to expand the body of knowledge concerning the role of MMA in OSA treatment, which may contribute to optimizing surgical management of OSA. Furthermore, intra-individual variation of upper airway measurements using computed tomography (CT) was studied. Additionally, treatment of a severe OSA case caused by acromegaly was described.

In **chapter 2,** we compared the effect of MMA on respiratory function between OSA patients with and without anteroposterior maxillomandibular deficiency based on respiratory parameters measured by polysomnography (PSG) and patient satisfaction with postoperative breathing. Also, the effect of MMA on facial esthetics was compared between the two groups based on cephalometric measurements and patient satisfaction with postoperative esthetics. We found that there was no significant difference in the effects of MMA on respiratory function and facial esthetics between OSA patients with and without such deficiency. This supports the view that MMA can also be considered as an appropriate treatment for OSA patients without maxillomandibular deficiency.

In **chapter 3**, the potential predictors of surgical response to MMA were explored from the most common clinically available data, i.e., patient-related, polysomnographic, cephalometric, and surgical variables. In this retrospective study, one hundred patients were included. Surgical response was achieved in 66 patients (66%). Multivariate logistic regression revealed that the presence of cardiovascular disease, higher baseline central apnea index, and larger superior posterior airway space

were independently associated with non-response to MMA. If confirmed in future research, these predictors may guide patient selection for MMA.

Drug induced sleep endoscopy (DISE) is a unique tool for dynamic visualization of upper airway collapse. **Chapter 4** presents a retrospective study aiming to investigate if DISE findings were predictive of surgical response to MMA. Furthermore, the predictive value of jaw thrust maneuver during DISE in terms of MMA outcome was explored. A total of 64 patients were included. Thirty-nine patients were responders, and 25 were nonresponders. After adjusting for baseline characteristics and surgical characteristics, the presence of complete anteroposterior epiglottic collapse was independently associated with non-response to MMA. No significant association was found between the effect of jaw thrust maneuver during DISE on upper airway patency and response to MMA. It was concluded that DISE could be a promising tool for predicting MMA surgical outcome, and patients with complete anteroposterior epiglottic collapse might be less suitable candidates for MMA.

Chapter 5 describes a systematic review and meta-analysis on the comparison of clinical efficacy and safety between MMA and multilevel surgery (MLS) for OSA. In total, twenty studies on MMA and 39 studies on MLS were included. We found that regardless of disease severity (i.e., baseline apnea hypopnea index [AHI]), MMA might be a more effective therapy compared to MLS in improving OSA, demonstrating a significantly higher AHI reduction and success rate. However, the rates of major and minor complications of MMA are higher than those of MLS.

Chapter 6 presents a systematic review aiming to compare the clinical efficacy and safety of MMA and upper airway stimulation (UAS) in the treatment of OSA. Twenty-one studies on MMA and nine studies on UAS were included. Current evidence suggests that both MMA and UAS are effective and generally safe therapies for OSA. However, due to the noticeable differences between MMA cohort and UAS cohort in age and baseline AHI, a solid conclusion cannot be drawn about the comparison between these two therapies.

Chapter 7 focuses on the intra-individual variation in the upper airway measurements on supine computed tomography (CT) scans at two different time points. This is relevant, due to the fact that three-dimensional upper airway measurements are commonly used to evaluate the role of upper airway anatomy in pathogenesis of

OSA and to assess the treatment effect or disease progress. In addition to a reliable measurement method, understanding the degree of intra-individual variation of the upper airway on different scans is imperative to achieve accurate evaluation and comparison of the upper airway. Therefore, ten subjects with paired CT datasets (3-6 months interval) were studied. There was considerable intra-individual variation in CT measurements of the upper airway, with the same patient instruction protocol for image acquisition. The minimum cross-sectional area of the total airway and all its segments generally had the largest variation, while the length of the total airway had the lowest variation. Sphericity was the only parameter that was stable over time both in the total airway and each segment. Our results suggested that such variation should be considered when interpreting the results of upper airway evaluation and comparison using CT.

Chapter 8 presents a female patient of middle age whose severe OSA was caused by an uncommon syndrome – acromegaly. The patient presented to the Department of Otorhinolaryngology due to her progressively worsening sleep and was diagnosed with severe OSA (AHI = 74.1 events/h). She was referred to the Department of Oral and Maxillofacial Surgery for consultation of MMA surgery for OSA. Due to her peculiar facial appearance, acromegaly was suspected and then confirmed by hormonal analysis and magnetic resonance imaging. After transsphenoidal resection of her pituitary adenoma, the patient's OSA was almost resolved (AHI = 5.5 events/h). This case highlights the importance of a comprehensive clinical examination for OSA patients.

SAMENVATTING

Obstructief Slaap Apneu (OSA) is een veel voorkomende slaap gerelateerde ademhalingsstoornis, die wordt gekenmerkt door herhaalde episodes van volledige of gedeeltelijke collaps van de bovenste luchtwegen tijdens het slapen. Niet-gediagnosticeerde en onbehandelde OSA kan leiden tot potentieel ernstige medische en economisch kostbare gevolgen. Hoewel continue positieve luchtwegdruk (CPAP) de gouden standaardbehandeling voor OSA is, is er behoefte aan andere behandelingsmodaliteiten, aangezien de werkzaamheid van CPAP vaak wordt belemmerd door lage tolerantie en slechte therapietrouw.

Maxillomandibular advancement (MMA) wordt beschouwd als een zeer effectieve chirurgische therapie voor matige tot ernstige OSA. De positie van MMA binnen het arsenaal aan behandelingsopties voor OSA is echter nog steeds niet volledig begrepen. Het belangrijkste doel van dit proefschrift was het uitbreiden van de kennis over de rol van MMA in de behandeling van OSA, wat kan bijdragen aan de optimalisatie van de chirurgische behandeling van OSA. Verder werd de intra-individuele variatie van metingen van de bovenste luchtwegen met behulp van computertomografie (CT) bestudeerd. Daarnaast werd de behandeling van een ernstig geval van OSA, veroorzaakt door acromegalie, beschreven.

In **hoofdstuk 2** vergeleken we het effect van MMA op de ademhalingsfunctie tussen OSA-patiënten met en zonder anteroposterieure maxillomandibulaire deficiëntie op basis van respiratoire parameters gemeten door polysomnografie (PSG) en patiënttevredenheid voor wat betreft postoperatieve ademhaling. Ook werd het effect van MMA op de esthetiek van het gezicht vergeleken tussen de twee groepen op basis van cephalometrische metingen en de patiënttevredenheid over zijn of haar postoperatieve esthetiek. We vonden dat er geen significant verschil was in de effecten van MMA op de ademhalingsfunctie en gezichtsesthetiek tussen OSA-patiënten met en zonder een dergelijke deficiëntie. Dit ondersteunt de opvatting dat MMA ook kan worden beschouwd als een geschikte behandeling voor OSA-patiënten zonder maxillomandibulaire deficiëntie.

In **hoofdstuk 3** werden mogelijke voorspellers van chirurgische respons op MMA onderzocht op basis van de meest voorkomende klinisch beschikbare gegevens, d.w.z. patiëntgerelateerde, polysomnografische, cephalometrische en chirurgische

variabelen. In deze retrospectieve studie werden honderd patiënten geïncludeerd. Een chirurgische respons werd bereikt bij 66 patiënten (66%). Multivariate logistische regressie toonde aan dat de aanwezigheid van hart- en vaatziekten, een hogere centrale apneu-index bij aanvang en een grotere ruimte van de achterste luchtwegen onafhankelijk waren geassocieerd met non-respons op MMA. Indien bevestigd in toekomstig onderzoek, kunnen deze voorspellers helpen bij de selectie van patiënten voor MMA.

Drug induced sleep endoscopy (DISE) is een unieke hulpmiddel voor dynamische visualisatie van de ineenstorting van de bovenste luchtwegen. **Hoofdstuk 4** presenteert een retrospectieve studie met als doel te onderzoeken of de bevindingen tijdens DISE voorspellend waren voor de chirurgische respons op MMA. Verder werd de voorspellende waarde van naar ventraal plaatsen van de onderkaak tijdens DISE in termen van MMA-uitkomst onderzocht. In totaal werden 64 patiënten geïncludeerd. Negenendertig patiënten waren responders en 25 waren non-responders. Na correctie voor baseline kenmerken en chirurgische kenmerken, was de aanwezigheid van volledige anteroposterior epiglottische collaps onafhankelijk geassocieerd met non-respons op MMA. Er werd geen significant verband gevonden tussen het effect van het naar ventraal plaatsen van de onderkaak tijdens de DISE op de doorgankelijkheid van de bovenste luchtwegen en de respons op MMA. Er werd geconcludeerd dat DISE een veelbelovend hulpmiddel zou kunnen zijn voor het voorspellen van de uitkomst van MMA-chirurgie, en dat patiënten met een volledige anteroposterior epiglottische collaps mogelijk minder geschikte kandidaten zijn voor MMA.

Hoofdstuk 5 beschrijft een systematische review en meta-analyse waarin de klinische werkzaamheid en veiligheid tussen MMA en multilevel chirurgie (MLS) voor OSA werd vergeleken. In totaal werden twintig onderzoeken naar MMA en negenendertig onderzoeken naar MLS geïncludeerd. We ontdekten dat ongeacht de ernst van de ziekte (d.w.z. baseline apneu hypopneu index [AHI]), MMA een effectievere therapie zou kunnen zijn in vergelijking met MLS bij het verbeteren van OSA, wat een significant hogere AHI-reductie en succespercentage aantoont. Het aantal grote en kleine complicaties van MMA is echter hoger dan die van MLS.

Hoofdstuk 6 presenteert een systematische review met als doel de klinische werkzaamheid en veiligheid van MMA en upper airway stimulation (UAS) bij de

behandeling van OSA te vergelijken. Eenentwintig studies over MMA en negen studies over UAS werden opgenomen. Het huidige bewijs suggereert dat zowel MMA als UAS effectieve en over het algemeen veilige therapieën voor OSA zijn. Vanwege de merkbare verschillen tussen MMA-cohort en UAS-cohort in leeftijd en baseline AHI, kan er echter geen solide conclusie worden getrokken over de vergelijking tussen deze twee therapieën.

Hoofdstuk 7 richt zich op de intra-individuele variatie van de bovenste luchtweg gemeten bij computertomografie (CT) scans in liggende positie van eenzelfde patient op twee verschillende tijdstippen. Dit is relevant vanwege het feit dat driedimensionale metingen van de bovenste luchtwegen vaak worden gebruikt om de rol van de anatomie van de bovenste luchtwegen in de pathogenese van OSA te evalueren en om het behandeleffect of ziekteverloop te beoordelen. Naast een betrouwbare meetmethode is het noodzakelijk om de mate van intra-individuele variatie van de bovenste luchtwegen op verschillende scans te weten voor een nauwkeurige evaluatie en vergelijking van de bovenste luchtwegen. Daarom werden tien proefpersonen met twee CT-datasets (3-6 maanden interval) bestudeerd. Er was aanzienlijke intra-individuele variatie in CT-metingen van de bovenste luchtwegen, met hetzelfde patiëntinstructieprotocol voor beeldacquisitie. De minimale dwarsdoorsnede van de totale luchtweg en al zijn segmenten vertoonde over het algemeen de grootste variatie, terwijl de lengte van de totale luchtweg de laagste variatie vertoonde. Sfericiteit was de enige parameter die stabiel was in de tijd, zowel in de totale luchtweg als in elk segment. Onze resultaten suggereerden dat een dergelijke variatie in overweging moet worden genomen bij het interpreteren van de resultaten van evaluatie en vergelijking van de bovenste luchtwegen met behulp van CT.

Hoofdstuk 8 presenteert een vrouwelijke patiënt van middelbare leeftijd wiens ernstige OSA werd veroorzaakt door een ongewoon syndroom, namelijk acromegalie. De patiënte meldde zich op de afdeling KNO vanwege haar steeds slechter wordende slaap en werd gediagnosticeerd met ernstige OSA (AHI = 74.1 episodes/uur). Ze werd verwezen naar de afdeling Mondzieken, Kaa- en Aangezichtschirurgie om te beoordelen of MMA een chirurgische therapeutische optie zou kunnen zijn. Vanwege haar bijzonder gelaatsuitdrukking werd acromegalie vermoed en vervolgens bevestigd doorhormoon analyse en Magnetic Resonance Imaging (MRI). Na transsfenoïdale resectie van haar hypofyseadenoom was haar OSA zo goed als verdwenen (AHI = 5.5 gebeurtenissen/uur). Deze casus benadrukt het belang van een uitgebreid klinisch onderzoek voor OSA-patiënten.

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APPENDICES

- Author contributions
- About the author
- PhD portfolio
- Acknowledgements

AUTHOR CONTRIBUTIONS

CHAPTER 2 | Effects of maxillomandibular advancement on respiratory function and facial esthetics in obstructive sleep apnea patients with versus without maxillomandibular deficiency
Ning Zhou, Jean-Pierre T.F. Ho, Frank Lobbezoo, Ghizlane Aarab, Nico de Vries, Jan de Lange
Conception and design of study: NZ, JH, JL
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CHAPTER 3 | Maxillomandibular advancement for obstructive sleep apnea: A retrospective prognostic factor study for surgical response
Ning Zhou, Jean-Pierre T.F. Ho, Wouter P. Visscher, Naichuan Su, Frank Lobbezoo, Jan de Lange
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CHAPTER 4 | Evaluation of drug-induced sleep endoscopy as a tool for selecting patients with obstructive sleep apnea for maxillomandibular advancement
Ning Zhou, Jean-Pierre T.F. Ho, Nico de Vries, Pien F.N. Bosschieter, Madeline J.L. Ravesloot, Jan de Lange
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CHAPTER 5 | Maxillomandibular advancement versus multilevel surgery for treatment of obstructive sleep apnea: A systematic review and meta-analysis
Ning Zhou, Jean-Pierre T.F. Ho, Zhengfei Huang, René Spijker, Nico de Vries, Ghizlane Aarab, Frank Lobbezoo, Madeline J.L. Ravesloot, Jan de Lange
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Acquisition of data: NZ, ZH, RS
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CHAPTER 6 | Maxillomandibular advancement and upper airway stimulation for treatment of obstructive sleep apnea: A systematic review
Ning Zhou, Jean-Pierre T.F. Ho, René Spijker, Ghizlane Aarab, Nico de Vries, Madeline J.L. Ravesloot, Jan de Lange
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CHAPTER 7 | Intra-individual variation of upper airway measurements based on computed tomography
Ning Zhou, Jean-Pierre T.F. Ho, Cornelis Klop, Ruud Schreurs, Ludo F. M. Beenen, Ghizlane Aarab, Jan de Lange
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CHAPTER 8 | Obstructive sleep apnea caused by acromegaly: Case report
Ning Zhou, Jean-Pierre T.F. Ho, Nico de Vries, Jan de Lange
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ABOUT THE AUTHOR

Ning Zhou was born in 1992 in Rongcheng, China. In 2010, she graduated from high school at the No. 2 high school, Rongcheng, China. In the same year, she started her dentistry study in Shandong University, where she met her other half. After graduating as a dentist in 2015, she was exempted from admission exam and joined the 3-year master program of orthodontics in Shandong University. In 2018, she graduated as an orthodontist and went to Amsterdam with her partner for their PhD. During her PhD, she conducted research at the department of Oral and Maxillofacial Surgery at the Amsterdam UMC and Academic Centre for Dentistry Amsterdam and the department of Orofacial Pain and Dysfunction at the Academic Centre for Dentistry Amsterdam, under the supervision of Prof. dr. Jan de Lange, Prof. dr. Frank Lobbezoo, Prof. dr. Nico de Vries, and Prof. dr. Ghizlane Aarab.

PHD PORTFOLIO

Peer-reviewed publications

Included in this thesis

- **Zhou N**, Ho JPTF, Lobbezoo F, Aarab G, de Vries N, de Lange J. Effects of maxillomandibular advancement on respiratory function and facial aesthetics in obstructive sleep apnoea patients with versus without maxillomandibular deficiency. *Int J Oral Maxillofac Surg*. 2022;S0901-5027(22)00327-7. doi:10.1016/j.ijom.2022.08.012. Epub ahead of print.
- **Zhou N**, Ho JPTF, Visscher WP, Su N, Lobbezoo F, de Lange J. Maxillomandibular advancement for obstructive sleep apnea: A retrospective prognostic factor study for surgical response. *Sleep Breath*. 2022. doi:10.1007/s11325-022-02731-x. Epub ahead of print.
- **Zhou N**, Ho JPTF, de Vries N, Bosschieter PFN, Ravesloot MJL, de Lange J. Evaluation of drug-induced sleep endoscopy as a tool for selecting patients with obstructive sleep apnea for maxillomandibular advancement. *J Clin Sleep Med*. 2022;18(4):1073-1081. doi:10.5664/jcsm.9802
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Other publications

- Ho JPTF, **Zhou N**, Verbraecken J, de Vries N, de Lange J. Central and mixed sleep apnea related to patients treated with maxillomandibular advancement for obstructive sleep apnea: A retrospective cohort study. *J Craniomaxillofac Surg*. 2022;50(7):537-542. doi:10.1016/j.jcms.2022.06.005

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- Huang Z, **Zhou N**, Lobbezoo F, Almeida FR, Cistulli PA, Dieltjens M, Huynh NT, Kato T, Lavigne GJ, Masse JF, Pliska BT, van de Rijt L, Sutherland K, Thymi M, Vanderveken OM, de Vries R, Aarab G. Dental sleep-related conditions and the role of oral healthcare providers: a scoping review. *Sleep Med Rev*. 2022;67:101721. doi: 10.1016/j.smrv.2022.101721

Congress & oral presentations

- *2020 Virtual American Association of Oral and Maxillofacial Surgeons Annual Meeting*. Presentation: "Maxillomandibular Advancement versus Multilevel Surgery for Treatment of Obstructive Sleep Apnea: A Systematic Review and Meta-Analysis".
- *2021 25th Congress of the European Association for Cranio Maxillo Facial Surgery*. Presentation: "Maxillomandibular Advancement versus Multilevel Surgery for Treatment of Obstructive Sleep Apnea: A Systematic Review and Meta-Analysis".
- *2021 Virtual American Academy of Dental Sleep Medicine Annual Meeting*. Presentation: "Evaluation of drug-induced sleep endoscopy as a patient selection tool of maxillomandibular advancement for OSA".
- *2022 26th Congress of the European Association for Cranio Maxillo Facial Surgery*. Presentation: "Comparison of the effects of maxillomandibular advancement on respiration function and facial esthetics between obstructive sleep apnea patients with and without maxillomandibular deficiency".

List of awards

- 2021 American Academy of Dental Sleep Medicine - Student Research Award
- 2022 American Academy of Dental Sleep Medicine - Student Research Award

Courses

- Statistics and Methodology, Academisch Centrum Tandheelkunde Amsterdam (ACTA), 2020
- Scientific Integrity, ACTA, 2020
- Oral Biology, ACTA, 2021
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