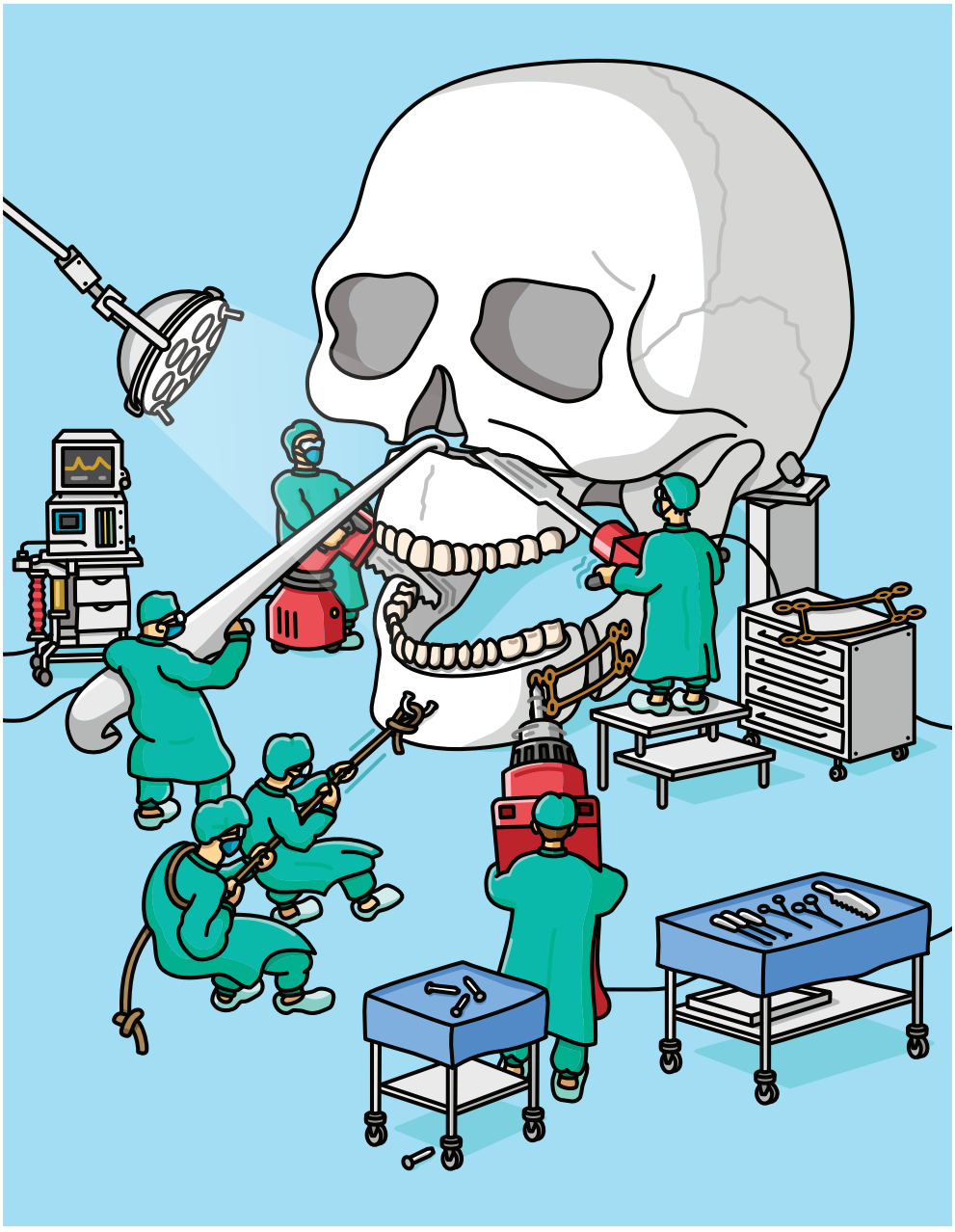
Maxillomandibular advancement

Issues related to indication, surgery, and outcome



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ISBN/EAN: 978-94-6496-032-7

Cover design idea: Jean-Pierre Ho en Teun van Heerenbeek
Cover design: Teun van Heerenbeek
Lay-out: Tiny Wouters
Printed by: Gildeprint

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ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit van Amsterdam op gezag van de Rector Magnificus
prof. dr. ir. P.P.C.C. Verbeek
ten overstaan van een door het College voor Promoties ingestelde commissie, in het openbaar te verdedigen in de Aula der Universiteit
op vrijdag 1 maart 2024, te 11.00 uur

door Jean Pierre Tsie Fung Ho
geboren te Willemstad

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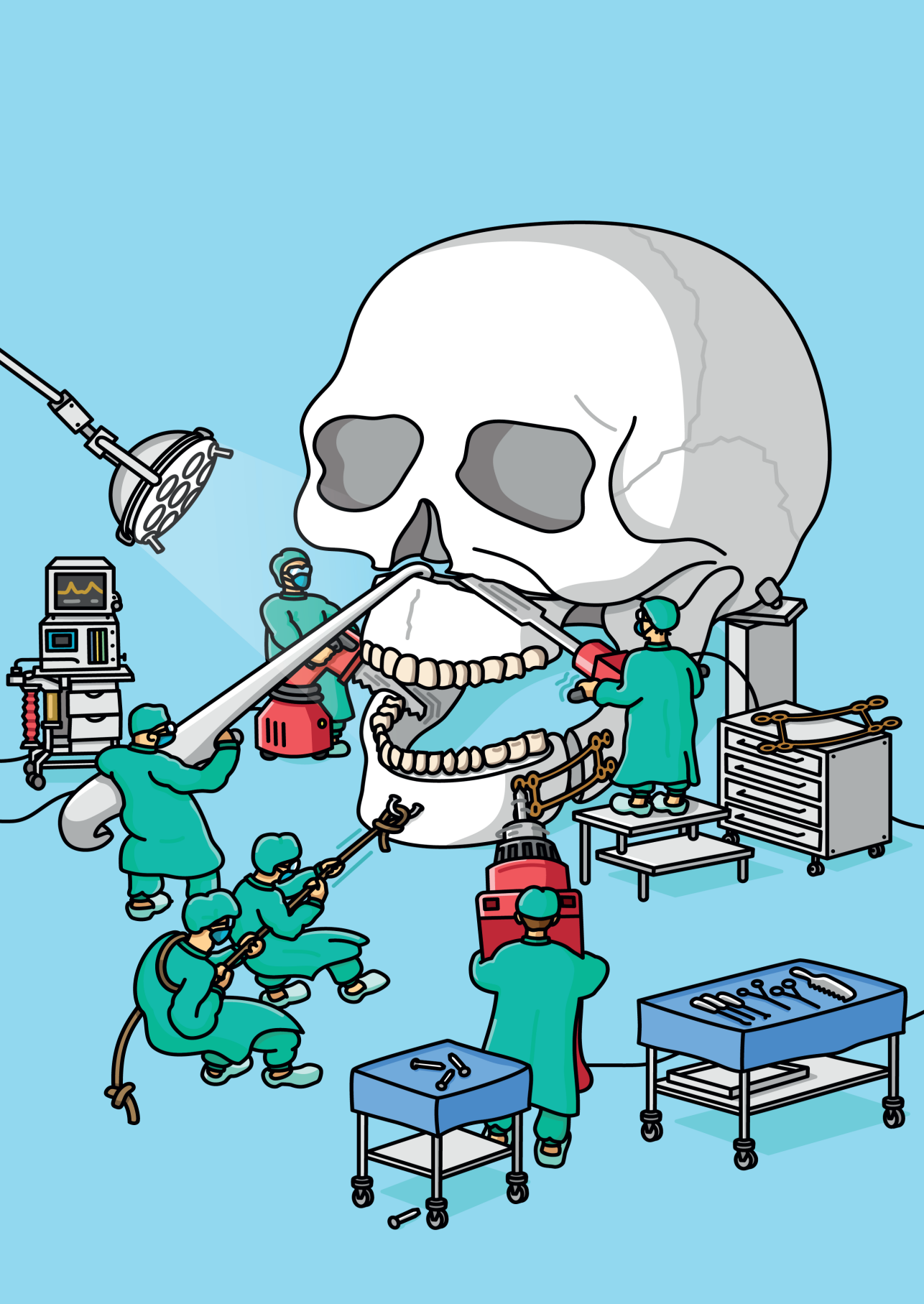
Contents



Chapter 1

A. Introduction of obstructive sleep apnea

B. Background of maxillomandibular advancement

C. Outline of the thesis

A. Introduction of obstructive sleep apnea

* For the sake of clarity, it should be noted that we will only focus on adult OSA in this thesis.

Background of obstructive sleep apnea

Obstructive sleep apnea (OSA) a is sleep-related breathing disorder, where the patient has recurrent episodes of partial or complete upper airway collapse during sleep. This leads to partial and/or complete respiratory cessation, also called hypopneas and apneas[1]. These events result in periodic nocturnal occurrences of hypoxia, hypercapnia, arousals, and eventually fragmentation of sleep[2,3]. Patients can experience subtle changes in their daily life to progressive OSA symptom burden over many years. Therefore, patient can go for extensive periods before their OSA is suspected and recognized. This is one of the reasons why OSA remains largely underdiagnosed and undertreated[4,5]. Patients often complain of a wide variety of symptoms in a various degree of severity, e.g. snoring and excessive daytime sleepiness (Table 1.1)[6].

Table 1.1 Classic symptoms of OSA[6].

Snoring
Excessive daytime sleepiness
Choking or gasping at night
Night sweats
Neurocognitive impairment
Heartburn
Morning headaches
Maintenance insomnia
Erectile dysfunction
Nocturia

Patients can present with OSA at all ages. For that reason, OSA can be divided in pediatric OSA and adult OSA[7]. Pediatric OSA affects approximately 1% to 6% of all children, usually in the ages from 2 to 8 years and is mainly due to enlarged tonsils and/or adenoids, genetics, or craniofacial malformation[8]. Adult OSA affects the majority of patients with a reported presentation of 9% to 38% of the general adult population[9].

With an estimated 1.4 billion of adults between the age of 30 and 69 years globally suffering from OSA, the economic burden of OSA is believed to be immense[10]. In the United States of America alone, it is estimated that cost of diagnosing and treating OSA (in 2015) was approximately $12.4 billion, with the majority (50%) of the cost attributed to positive airway pressure therapy and oral appliance therapy and approximately 43% of the cost attributed to surgical OSA management[11]. Mind you, this is without taking

into account the staggering cost of being undiagnosed, which was estimated to be $149.6 billion (in 2015). This consisted of $86.9 billion attributed to loss of productivity; $26.2 billion due to motor vehicle accidents; $6.5 billion due to workplace related accidents; and $30 billion due to the increased risk of costly medical comorbidities. It was estimates that it would cost the health care system an additional $49.5 billion in order to diagnose and treat every American adult who has OSA[11]. Be it as it may, it was also estimated that the treatment of OSA would provide a projected savings of $100.1 billion, making OSA not only manageable, but also cost effective in the end[11].

Aside from the economic aspects, OSA also has major health-related burden, with OSA being associated with a wide variety of medical conditions e.g., cardiovascular disease, metabolic disease, psychiatric disorders, and neurocognitive impairment[12–14]. And not insignificant, OSA has also been independently associated with a large increased risk for mortality – based on a large community based study[15]. All of these, highlight the fact that prevention, early diagnosis, and adequate treatment are not only important to alleviate the patient health-related burden, but also help reduce the economic burden of OSA.

Etiology of obstructive sleep apnea

Based on the origin of the apneas and hypopneas, sleep apnea is separated into two main categories, namely central sleep apnea (CSA) and obstructive sleep apnea (OSA)[7]. The etiology of CSA is based on the fact that during sleep there are episodes where there is lack of breathing drive as a result of a temporary discontinuation of the respiratory rhythm generator located within the pontomedullary region of the brain[15]. CSA is defined as a lack of respiratory effort during cessations of airflow[16]. A multitude of medical conditions can tend to develop CSA e.g., atrial fibrillation, heart failure, ischemic stroke, spinal cord injury, renal failure, and chronic opioid use[17].

In contrast to CSA, respiratory effort is still maintained during hypopneas and apneas in OSA and respiratory cessation is mainly due to partial and/or complete airway collapse. A wide array of factors can attribute to a decrease airway diameter or integrity leading to OSA – including body weight and fat distribution, patient craniofacial anatomy, genetics, and respiratory control system – making OSA an uttermost complex phenomenon (Figure 1.1) (Table 1.2)[18,19].

Figure 1.1 Current consideration of heterogenicity and complexity of OSA. Illustration from Randerath et al.[18].

Table 1.2 Etiological factors for OSA[19–21].

Non-anatomical patient factors
Obesity
Central fat distribution
Advanced age
Male gender
Supine sleeping position
Pregnancy
Anatomical patient factors
Micrognathia, retrognathia
Increased anterior facial height
Inferiorly and posteriorly positioned hyoid
High arched palate
Dental findings (suggestive of underlying craniofacial deficiency e.g., open bite, overbite, overjet, and proclination of the mandibular incisors)
Inferior displacement of the hyoid
Soft tissue hypertrophy, inflammation, and/or edema (e.g., adenoid, tonsils, soft palate, lateral and pharyngeal walls)
Genetical factors
Physiological respiratory control system
Greater upper airway critical closing pressure (Pcrit) values
Ventilatory instability/(high loop gain)
Loss of neuromuscular control
Low Arousal threshold
Associated medical disorders
Cardiovascular disease (e.g., hypertension, heart failure, and arrythmias)
Metabolic disease (e.g., diabetes mellitus, acromegaly, and hypothyroidism)
Neurological disorders (e.g., stroke, spinal cord injury, and myasthenia gravis)
Obesity hypoventilation syndrome
Congenital disease (e.g., Prader Willi Syndrome, Down Syndrome)
Others factors
Socio-economic status and environmental factors

Although a distinction is made between CSA and OSA, there is a considerable overlap in the pathogenesis and pathophysiology between the both sleep-related breathing disorders, making the distinction somewhat difficult at times and therefore also bring about both entities to occur simultaneously.

Diagnosis of obstructive sleep apnea

As previously mentioned, patient with a suspicion for OSA can present with wide variety of different symptoms[6]. Consequently, it presents a formidable challenge for healthcare professionals to determine if the patient has OSA solely relying on their medical history. For that reason, a frequently applied tool in order to screen patients which are at high-risk for OSA are questionnaires. Questionnaires are easy to administer, are of low-cost, offer a prompt risk analysis on whether or not to further investigate for OSA, and can be used to assess patient-reported outcome especially

when evaluating changes after treatment or over time[22]. There are multiple different validated OSA questionnaires (Table 1.3)[21,22].

Table 1.3 OSA questionnaires[21,22].

Screening questionnaires
Berlin questionnaire
STOP-Bang questionnaire
STOP Questionnaire
NoSAS (Neck, Obesity, Snoring, Age, Sex) score
Perioperative Sleep Apnea Prediction Score
American Society of Anesthesiologists OSA check-list
DES-OSA Score
Functional status measures and health-related quality of life questionnaires
Epworth Sleepiness Scale
Pittsburgh Sleep Quality Index
Functional Outcomes of Sleep Questionnaire
Sleep Apnea Quality of Life Index

In addition to an extensive medical history – with or without the use of questionnaires – a complete physical exam is not only necessary but is of course standard for the evaluation for high-risk patients for OSA. This mainly includes measurement of body mass index (BMI), neck circumference, nasal exam, exam of oral cavity, and oropharynx and hypopharynx exam.

Additional examinations can include radiological examinations. Lateral cephalogram is readily available, of low risk, and an inexpensive imaging technique, which is able to assess craniofacial skeletal and soft tissue anatomy and its relationship to one another. Previous studies have failed to provide robust evidence that a lateral cephalogram is able to distinguish OSA patients form healthy subjects. Nor is there a study that is able to provide a correlation between cephalometric parameters and the AHI on an overnight polysomnography (PSG)[21]. Computer tomography (CT) and cone beam computer tomography (CBCT) are becoming more readily available and can be used for three-dimensional (3D) assessment of the craniofacial structures and upper airway. However, so far high-quality evidence supporting the use of CBCT for airway assessment is still missing. Therefore, CBCT just like lateral cephalogram is mainly indicated for the assessment of craniofacial anatomy and relationship and for treatment planning for skeletal OSA surgery. Magnetic Resonance Imaging (MRI) provides exceptional soft tissue images, and is able to provide additional airway measurements, which are not achievable with cephalometry. Therefore, MRI may be superior to lateral cephalogram. However, studies have shown that MRI just like lateral cephalogram is not able to discriminate between healthy subjects and OSA patients[21].

Traditionally and still to this day sleep testing remains the gold standard for the diagnosis of OSA, with a polysomnography (PSG) – with the use of seven or more channels[23]. A PSG is overnight test, in which sleep stages, limb movements, airflow, respiratory effort, heart rate and rhythm, oxygen saturation, and body position are monitored and recorded. There are 4 different types of sleep studies, namely full overnight in laboratory PSG (level 1 study), portable PSG (level 2 study), four to seven channels home test also known as polygraphy (level 3 study), and one to three channels home test (level 4 study)[21,24]. After recording, the patient sleep is scored based on the American Academy of Sleep Medicine (AASM) scoring manual, which is a required standardized system for all AASM-accredited sleep centers and sleep labs[23]. This manual is updated every few years, with the last update being version 2.4 from 2017[25]. Based on the scoring manual, the AASM defines an apnea in adults as a decline of the peak signal excursion by ≥90% of pre-event baseline for ≥10 s and a hypopnea in adults as a decline of the peak signal excursions by ≥30% of pre-event baseline for ≥10 s in association with either ≥3% arterial oxygen desaturation or an arousal[25,26]. The number of apnea and hypopnea events per hour of sleep is used to indicate the severity of OSA with the use of the Apnea–Hypopnea Index (AHI). The AASM defines – based on the AHI – OSA as mild (AHI 5 events/hour to 15 events/hour), moderate (AHI 16 events/hour to 30 events/hour), and severe (AHI >30 events/hour)[27].

Drug-induced sleep endoscopy (DISE) is an examination of the upper airway – with the use of a flexible fiberoptic endoscope – while the patient is pharmacologically sedated, but is still able to spontaneously respire similar to natural sleep (Figure 1.2)[28,29]. During this examination different sites of obstruction, the type of obstruction, and the severity of the obstruction of the upper airway can be evaluated. In order to report the findings during DISE, multiple different classifying systems have been used, however the VOTE classification system – acronym for Velum Oropharynx base of Tongue Epiglottis – by Kezirian et al. is often propagated due to the fact that it provides the possibility of grading and describing the findings (Table 1.4)[29,30]. It is advocated that DISE is indicated whenever alternatives to positive airway pressure are indicated, such as oral appliance therapy, positional therapy, upper airway surgery, or a combination of different treatment modalities[30].

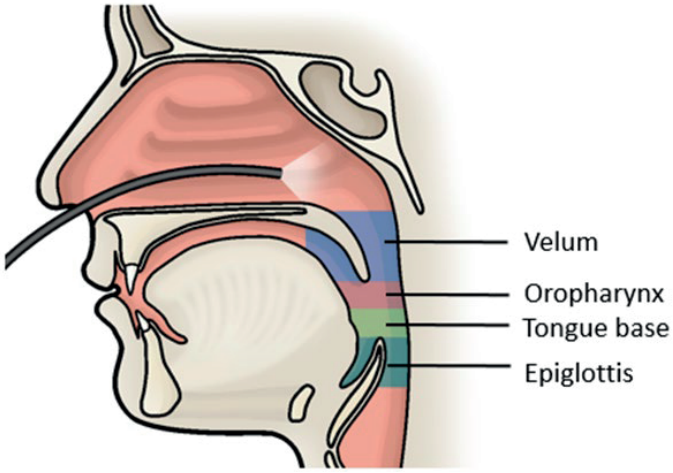


Figure 1.2 Drug induced sleep endoscopy, with four levels of the upper airway, based on the VOTE classification.

Table 1.4 VOTE classification[29].

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.

Non-surgical treatment options for obstructive sleep apnea

Weight reduction

As obesity – and the category of obesity – has been shown to be an important risk factors for acquiring and increasing the severity of OSA, the primary and non-invasive approach to adequately manage OSA should be weight reduction either by applying diet interventions, exercise interventions, or a combination of both[31,32]. It has been proven that a 5% and preferably 10% of weight reduction is able to reduce the severity of patients OSA[33]. The added benefit of weight reduction is not only reduction of OSA severity, but also it also improves cardiac and metabolic comorbidities[34–36]. However, it is a known fact that for weight reduction to be permanent in the long-term additional

lifestyle interventions are mandatory[37]. There have been limited number of studies published, which have investigated whether pharmacological interventions – e.g., topiramate and orlistat – are able to provide weight and OSA severity reduction[38,39]. These interventions show promise however, more long-term data is necessary. Finally, bariatric surgery can also be applied in order to permanently achieve weight reduction. This treatment option will be discussed later in this chapter.

Positive airway pressure

Sullivan first proposed continuous positive airway pressure (CPAP) in 1981[40]. This treatment temporarily resolves the problem of obstruction during its use, through the application of continuous pressurized air through the upper airway, which acts as pneumatic splint. Positive airway pressure (PAP) has proven to be the most effective treatment able to reduce AHI and improve subjective patient outcome[41,42]. Hence, to date CPAP is still considered the gold standard for nonsurgical treatment for OSA (Figure 1.3)[41,43]. Be that as it may, down-side of PAP is that the adherence has been proven to be low, specifically in the long-term[44,45]. Therefore, more than seldomly previous PAP users – although PAP is effective – are in need of an alternative treatment option whenever PAP has become intolerable after some time.

Figure 1.3 A patient illustrated sleeping with a nasal mask for his PAP-device (source and with permission of Vivisol Nederland B.V.).

Mandibular advancement device

Oral appliance therapy – of which the mandibular advancement device (MAD) is the most preferred option – has proven to be a good alternative to CPAP, specifically for mild to moderate OSA (Figure 1.4)[46,47]. The MAD protrudes the mandible, which results in a reduction of the pharyngeal collapsibility. There are many different MADs on the market. MADs are often divided into mono-bloc and dual-bloc or non-custom and custom MADs[48,49]. A recent systematic review concluded that there were no differences found between different types of MAD designs, however custom MADs were found to be superior to non-custom MADs[50]. MADs are however also associated with different adverse effects e.g., transient muscle soreness and temporomandibular joint discomfort, hyposalivation and less often hypersalivation, tongue discomfort, and a sense of suffocation. A more permanent adverse effect is occurrence of dental side effects – mainly increased lower incisor inclination and posterior open-bite[46].

Figure 1.4 A current MAD, the SomnoDent® Avant (source and with permission of Somnomed).

Positional therapy

Positional therapy can provide an alternative treatment for patients with positional OSA (POSA) – which is defined by an AHI in the supine posture double or greater than that in the non-supine postures in addition to an AHI in the non-supine posture of <5 events/hour[51]. Different types of positional therapy have been proposed e.g., tennis balls, pillows, bulky backpacks and more recently position trainers[52–54]. A main disadvantage of many of the positional therapies is adherence. The position trainers

however, are able to slowly and progressively train the patient to turn to a non-supine position with the use of light vibrational stimulus (Figure 1.5)[55].

Figure 1.5 A patient illustrated wearing the sleep position trainer around his chest (source and with permission of Vivisol Nederland B.V.).

Surgical treatment options for obstructive sleep apnea

Surgery is usually mainly indicated as alternative treatment option whenever the patient is unable to tolerate PAP[18,21,43]. There are a multitude of different surgical interventions for OSA (Table 1.5)[18,21]. As endoscopic sinus surgery, nasal surgery, tonsillectomy, soft palate surgery, tongue and hypopharyngeal surgery, bariatric surgery, and tracheostomy are not relevant for this thesis, these options will only be briefly discussed for sack of completeness.

Table 1.5 Possible surgical interventions for OSA [18,21].

Endoscopic sinus surgery
Nasal surgery
Tonsillectomy
Soft palate surgery
Tongue and hypopharyngeal surgery
Bariatric surgery
Tracheostomy
Multilevel surgery
Hypoglossal nerve stimulation
Maxillary and mandibular surgery

Endoscopic sinus surgery

A systematic review and meta-analysis has shown that endoscopic sinus surgery has the ability to decrease AHI in chronic rhinosinusitis patients and OSA[56]. This reduction was however, found to be minor. Moreover, endoscopic sinus surgery was also found to significantly improve patient subjective outcome e.g., Epworth Sleepiness Scale (ESS)[57].

Nasal surgery

Starting at the beginning of the upper airway, the nose is a significant contributor to OSA. Therefore, the main objective in nasal surgery is to improve and optimize the nasal passage in order to alleviate nasal obstruction contributing to the patients OSA and whenever possible to improve PAP tolerance. A meta-analysis has shown that nasal surgery can significantly reduce AHI – albeit a miniscule AHI reduction – and can also improve ESS[58].

Tonsillectomy

There is evidence supporting that enlarge tonsils are associated with increased AHI[59]. Historically tonsillectomy has been combined with uvulopalatopharyngoplasty (UPPP) as an effective therapy – significant reduction of AHI and ESS – for the treatment of OSA[60,61]. Tonsillectomy as a stand-alone therapy for OSA has been extensively investigated, with largely positive results. Camacho et al. concluded in their systematic review and meta-analysis that tonsillectomy can be a successful treatment for adult OSA, especially for those presenting with mild to moderate OSA in conjunction with grade 3 or 4 tonsils[62].

Soft palate surgery

Many different types of procedures can referrer to soft palate surgery. Traditionally UPPP is the most performed type of soft palate surgery – and also still to date the most

commonly performed surgical procedure for the treatment of OSA[21]. The classical UPPP consists of resection of part of the palate and uvula tissue and as previously mentioned also frequently consists of tonsillectomy. In the milestone paper by Sher et al. – in which he first defined surgical success as an AHI reduction of at least 50% and an AHI below 20 events/hour – it was found that UPPP has an success rate of approximately 40%[63]. A systematic review and meta-analysis of Stuck et al. concluded that UPPP ± tonsillectomy is able to reduce respiratory events and daytime sleepiness in adult patients with OSA, depending on BMI, age, OSA severity, and clinical and anatomic staging systems[64]. A major issue is the compelling morbidity associated with UPPP e.g., postoperative pain, edema and bleeding with or without the need for surgical intervention, velopharyngeal insufficiency, and nasal regurgitation. Noteworthy is that recent modifications in UPPP surgical techniques have presented with lower morbidity compared to traditional UPPP[64]. A more modern type of palate surgery is expansion sphincter pharyngoplasty (ESP), first described by Pang and Woodson in 2007[65]. The main goal of this technique is to create more tension in the lateral pharyngeal walls in order to decrease collapsibility of the lateral oropharyngeal wall. There have also been modifications to this technique e.g., adding tonsillectomy and a palatopharyngeus muscle rotation plasty[21]. ESP has shown to have significantly better surgical success rates compared to standard or traditional UPPP, with less need for tissue resection[66,67]. A more modern take on UPPP and ESP with similar outcome, is the palate suture suspension technique. Congruent with UPPP and ESP the goal is to decrease collapsibility of the lateral oropharyngeal wall. However, with this technique little to no tissue is resected by applying anchoring sutures – self-locking bidirectional barbed sutures – in order to readdress the soft palate and lateral oropharyngeal wall with the goal to reduce morbidity and increase efficacy[21,67]. Older techniques of soft palate surgeries consist of transpalatal advancement pharyngoplasty (by Woodson and Toohill in 1993), radiofrequency palatoplasty (by Powell et al. in 1998), lateral pharyngoplasty (by Cahali in 2003), and pillar implants surgery (in 2003)[21,68–70].

Tongue base radiofrequency surgery

Already described by Powell et al in 1999, tongue base radiofrequency surgery aims to create soft tissue fibrosis by applying coagulation and ablation through radiofrequency or coblation[69]. Tongue base radiofrequency surgery is often combined as part of multilevel surgery. However, there are some studies that have shown that tongue base radiofrequency surgery as a stand-alone procedure is effective in specific patients with mild OSA[71].

Tongue suture suspension

Like tongue base radiofrequency surgery, tongue suture suspension is a technique that is often times combined as part of multilevel surgery. Tongue suture suspension is a procedure where the base of tongue is suspended with the use of a suture technique to the lingual cortex of the mandibular symphysis, resulting in an increase of the anterior to posterior space of the hypopharynx. The main advantages of this technique are that it is minimal invasive and reversible if needed. It has been estimated that the surgical success rate – note that whenever surgical success is used throughout this thesis, this will be based on Sher's criteria – for tongue suture suspension as a stand-alone therapy is comparable to UPPP and is approximately 37%[63,72].

Hyoid suspension

Hyoid suspension or hyoidthyroidpexy is a technique designed to address hypopharyngeal and tongue base obstruction, by suspending the hyoid to the inferior border of the mandible. Hyoid suspension is often combined with additional procedures including multilevel surgery, genioglossus advancement or maxillomandibular advancement[21]. Success rates are reported of approximately 52% (BMI below 30) and approximately 17% (BMI of more than 30)[73,74]. Clearly illustrating the importance of proper patient selection.

Lingual tonsillectomy

Lingual tonsillectomy is also a procedure that is often part of multilevel surgery. There are multiple different techniques to perform lingual tonsillectomy e.g., CO_2 laser, electrocautery, harmonic scalpel, coblation, radiofrequency ablation, and a microdebrider under direct or indirect visualization. A more contemporary technique is trans oral robotic surgery with the use of the Da Vinci robot, which has multiple advantages like superior field of view, instrument handling, and the ability to more accurately resect tissue[75]. When performing lingual tonsillectomy in combination with UPPP, it has been found that the success rate can be improved from 40% to approximately 66%[76].

Epiglottis surgery

There are different types of epiglottis surgery, including epiglottoplasty, partial epiglottectomy, and epiglottopexy. No consensus exists on the presence (range 15% to 74%) and clinical significance of epiglottis collapse[77,78]. Therefore, there is still no consensus in the literature when this type pf surgery is indicated. However, epiglottis surgery is often performed in conjunction with other types of surgery for OSA[21].

Genioglossus advancement

Genioglossus advancement was first described by Riley et al. in 1986 as a procedure that was combined with inferior sagittal osteotomy of the mandible with hyoid myotomy. The main objective with genioglossus advancement is to stabilize the hypopharyngeal airway by advancing the genioglossus muscle. To this day it is still performed in combinations with other additional procedures. Although there is limited evidence available on genioglossus advancement as a stand-alone procedure for OSA, it is suggested that genioglossus advancement is able to reduce AHI. However, there is significant heterogeneity in patient selection criteria, use of simultaneous procedures, operative techniques, and length of follow-up[21].

Bariatric surgery

Obesity is a growing entity worldwide. Additionally, obesity has been positively associated with OSA[79]. A systematic review by Wong et al. has shown that bariatric surgery is able to improve OSA in obese patients[80].

Tracheostomy

Tracheostomy – a procedure in which an alternative airway is surgically created in the trachea in order to circumvent the upper airway obstruction – is the first and therefore the oldest treatment for OSA. It was first described by Kuhlo et al. in 1969[81]. A systematic review by Camacho et al. showed that tracheostomy is able to significantly improve apnea index, apnea-hypopnea index, oxygen desaturation index, sleepiness in obese as well as non-obese patients with OSA[82].

Multilevel surgery

As insight grew in the 1990's that OSA was based on obstructions at multiple different levels in the upper airway. More and more centers have been performing surgery on more than one level – e.g., nose, palate, oropharyngeal lateral walls, tongue base, and epiglottis – of obstruction of the upper airway, also called multilevel surgery[21]. It can consist of multiple of the previous discussed surgical procedures in this chapter. Multilevel surgery is mainly indicated whenever PAP therapy is either not tolerated or not able to sufficiently treat the patients OSA. Treatment outcome and occurrence rate of complication after multilevel surgery will be extensively discussed in chapter 2.

Hypoglossal nerve stimulation

Hypoglossal nerve stimulation is a fairly new surgical treatment where an electrical current is relayed to branches of the hypoglossal nerve innervate the tongue protruding

muscles – the genioglossus and geniohyoid muscles – in order to maintain an patent upper airway during sleep[83]. There are multiple devices available for hypoglossal nerve stimulation in different stages of technical readiness level and market availability e.g., the Inspire II (Inspire Medical Systems, MN, USA), the Apnex device (Apnex Medical, MN USA), the ImThera device (LivaNova, London UK), and the GenioTM system (Nyxoah SA, Mont-Saint-Guibert, Belgium)[21]. As the majority of the available literature report on studies which used the Inspire II (Inspire Medical Systems, MN, USA), we will therefore, primarily describe and discuss the Inspire II (Inspire Medical Systems, MN, USA) device for hypoglossal nerve stimulation in this thesis. The inclusion criteria for hypoglossal nerve stimulation are adult patients 18 years and older; moderate to severe OSA (15≤AHI≤65 events/h); <25% of events are central/mixed apneas; PAP failure and/or intolerant; do not present with complete concentric collapse at the level of the velum[21]. Treatment outcome and occurrence rate of complication after hypoglossal nerve stimulation will be extensively discussed in chapter 3.

Maxillary expansion

Maxillary transverse deficiency is considered as a predisposing factor for the development of OSA which is associated with increased nasal resistance and posterior tongue displacement that compromises tongue support and facilitates pharyngeal collapse[18,21,84–86]. In adult OSA patients with dental–maxillary discrepancies, maxillary expansion can be performed with surgically assisted rapid maxillary expansion or distraction osteogenesis maxillary expansion. Both of which use (limited) osteotomies in order to open the closed sutures, after which transverse forces are applied directly in order to create more width in order to expand the nasal cavity which will reduce nasal airflow and increase oral cavity volume to allow for higher tongue posture in rest, which may contribute to the opening of the airway[18,21,87,88]. There is literature available suggesting that maxillary expansion is able to improve OSA in adults[89]. However, more research is necessary to further understand the role of maxillary expansion in the management of adult OSA[18].

Mandibular advancement

Mandibular advancement in pediatric OSA literature can be divided in two surgical techniques, namely mandibular distraction osteogenesis – where the mandible is elongated by slowly and progressively stretching of the osteotomized segments – and mandibular advancement surgery – where the mandible is osteotomized with for example a bilateral sagittal split osteotomy (BSSO) and fixated with osteosyntheses materials[90]. For selected pediatric OSA cases – specifically craniomaxillofacial skeletal abnormalities cases – this procedure has been shown to be a very effective treatment

option and is for that reason not seldomly performed[91]. Although, this procedure was one if not the first skeletal surgeries performed for OSA for the adult population – already reported by Kuo et al. in 1979 – this procedure has been less frequently reported in the literature compared to other skeletal surgical options for OSA, for example maxillomandibular advancement[92]. A systematic review and meta-analysis by Noller et al. found that mandibular advancement is able to drastically improve the AHI from 46 events/hour to 6 events/hour (87% decrease) and the lowest oxygen saturation from 72% to 89%[93]. Regression analyses showed that whenever the mandible was advanced 16mm the success rate was 75%, compared to 35% whenever the mandible was advanced less than 16 mm. Therefore, they concluded that mandibular advancement is indicated in OSA patients with mandibular insufficiency – e.g., micrognathia or retrognathia – due to the fact that by definition by advancing the mandible the dental occlusion will change.

Maxillomandibular advancement

Maxillomandibular advancement will be discussed in chapter 1B.

1B Background of maxillomandibular advancement

On the account that the main focus of this thesis is centered on issue related to maxillomandibular advancement (MMA), in this chapter a more detailed description of the background of MMA will be provided. Other specific issue related to MMA will be discussed separately in outline and specific chapters of this thesis.

Introduction

Maxillomandibular advancement – also known as MMA, bimaxillary surgery for OSA, telegnatic surgery for OSA, orthognathic surgery for OSA, double jaw surgery for OSA, and (lower) facial surgery for OSA – is skeletal surgery where a Le Fort I maxillary osteotomy is performed in combination with a bilateral sagittal split osteotomy (BSSO) of the mandible in order to advance and currently also more and more counter clockwise rotate the maxilla and mandible[18,94]. By maneuvering the maxillomandibular complex anteriorly and counter clockwise the upper airway is not only enlarged and reduced in length, but there is also more tension conceived in the pharyngeal dilator muscles – which has a splinting effect – thus reducing upper airway collapsibility[95,96].

History of maxillomandibular advancement

Riley et al. at Stanford in 1986 were the first to report on MMA. In this case series they reported on nine patients with severe OSA, all of which had multitherapy failure[97]. Already at that time, they performed MMA with perioperative orthodontics in seven out of nine patients. The maxilla and mandible were advanced 4 to 8 mm and 12 to 24 mm, respectively. They found that in all patients the PSG parameters improved after MMA. Since then, many have reported on MMA[98–104]. In The Netherlands, the first case was reported in 1998 by A.G. Becking in his PhD-thesis 'Issue related to orthognathic surgery'[105]. The first case series reported in The Netherlands was by de Lange et al. in 2004. They treated six moderate to severe OSA patients, of which five patients achieved surgical success and one patient was cured after MMA[106].

Indication of maxillomandibular advancement

Although much has been reported about MMA, there is still to date no consensus and gold standard protocol when to perform MMA. The Stanford group published their dynamic upper airway reconstruction for OSA protocol in 1993, in which they propagated that MMA was mainly indicated as phase II surgery, reserved for those cases where UPPP and genioglossus advancement combined with hyoid suspension failed (Figure 1.6)[107]. There have been many advances and changes in insights since the

first presentation of the Stanford protocol. Therefore, a revised version of the Stanford protocol was presented by Liu et al. in 2019 (Figure 1.7)[108]. In this update of the Stanford protocol certain modern techniques were added such as hypoglossal nerve stimulation and maxillary expansion. Additionally, indications are provided for performing MMA earlier instead of as a last resort procedure e.g., dentofacial deformity, severe OSA, and specific airway collapse pattern found during DISE. Others have also advocated that the indication for MMA should be more individualized and based on patient phenotyping[18]. The American Academy of Sleep Medicine 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 (Option)" [109]. In The Netherlands, the latest protocol (Richtlijn Diagnostiek en behandeling van obstructief slaapapneu (OSA) bij volwassenen) states that MMA can be considered in patients with moderate to severe OSA[110].

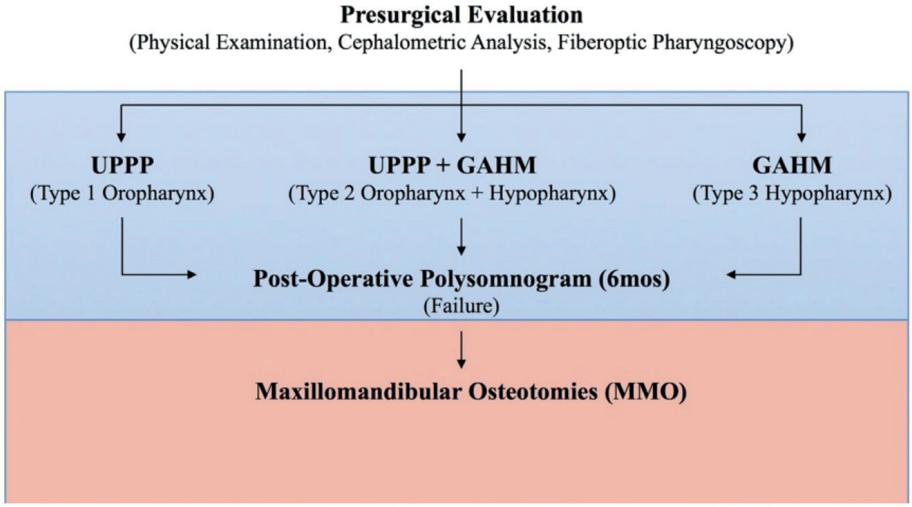


Figure 1.6 Original Stanford protocol. Illustration from Liu et al.[108].

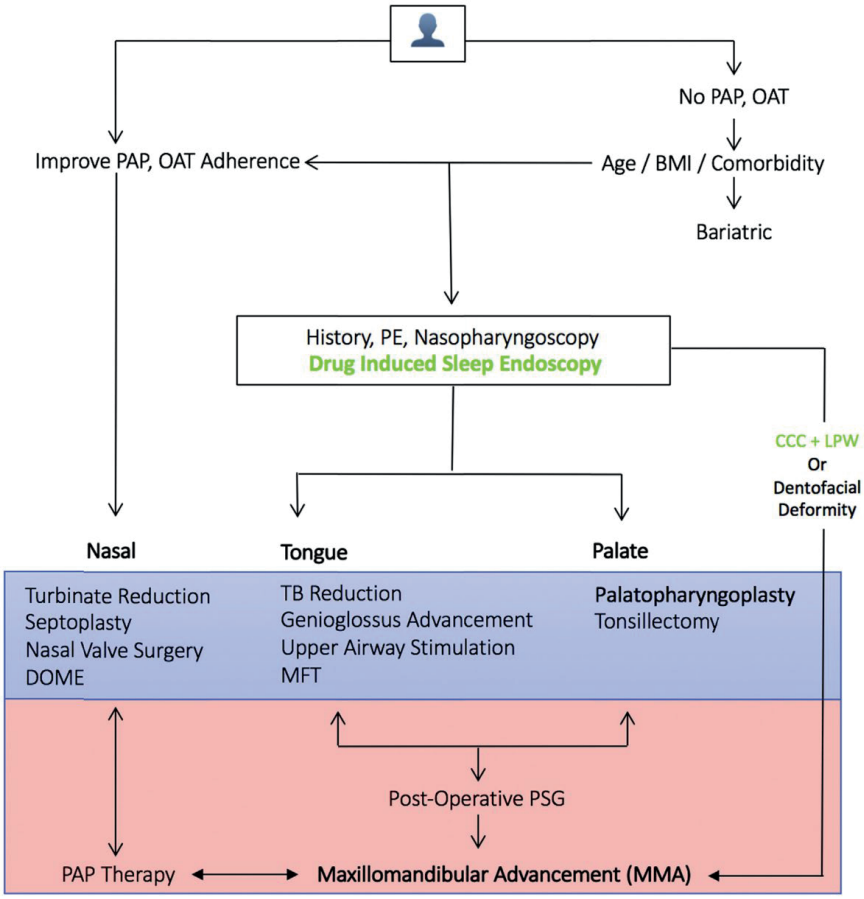


Figure 1.7 Revised Stanford protocol. Illustration from Liu et al.[108].

Current workflow and surgical technique of maxillomandibular advancement at Amsterdam UMC (dated July 5th 2023)

Virtual surgical planning is utilized to preoperatively plan MMA nowadays. In order to do so, the patient receives a CT or CBCT scan a few weeks prior to surgery. With use of proprietary virtual planning software, currently in Amsterdam UMC the 3D CT or CBCT scan and dental model are integrated as a 3D virtual model of the patient in IPS (KLS Martin, Erlangen, Germany), in order to precisely create the virtual surgical plan of the operation (Figure 1.8). Intraoperative surgical splints are then designed for either a maxilla-first or mandible first surgical plan. These 3D printed intraoperative surgical

splints are utilized to translate the virtual surgical plan to the surgical procedure in the operating room (Figure 1.9).

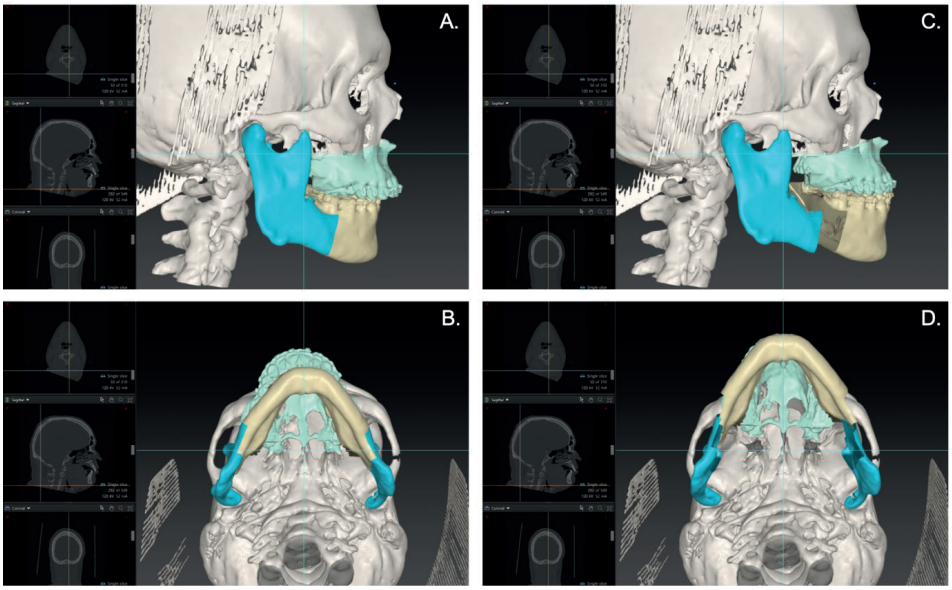


Figure 1.8 Virtual surgical planning for maxillomandibular advancement. A. Sagittal view before MMA. B. Axial view before MMA. C. Sagittal view after MMA. D. Axial view after MMA.

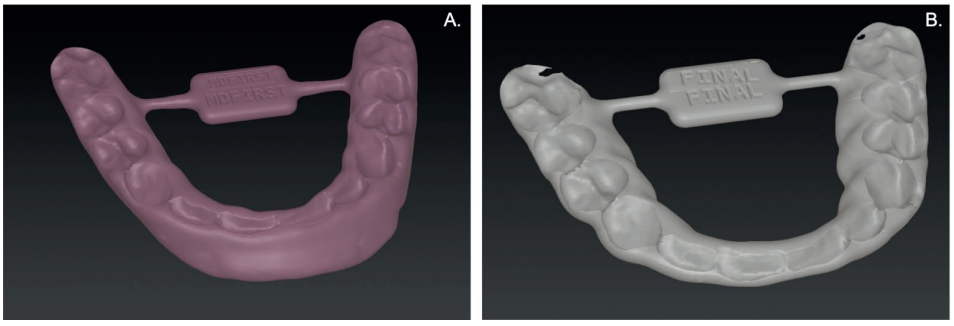


Figure 1.9 3D printed intraoperative surgical splints. A. intermediate intraoperative splint for mandible-first surgical sequence. B. Final intraoperative splint.

Depending on the virtual surgical plan and the 3D printed intraoperative surgical splints, the surgery can either be performed through a maxilla-first or mandible-first surgical sequence [111]. When the mandible-first protocol is used, the bilateral sagittal split osteotomy of mandible is performed first.

Bilateral sagittal split osteotomy of mandible

The patient in under general anesthesia with the use of a nasoendotracheal tube during MMA. Local anesthesia however, is administered to aid with hemostasis of the surgical site. A mucosal incision along the anterior border of the ramus is placed inferiorly, along the external oblique ridge (Figure 1.10).

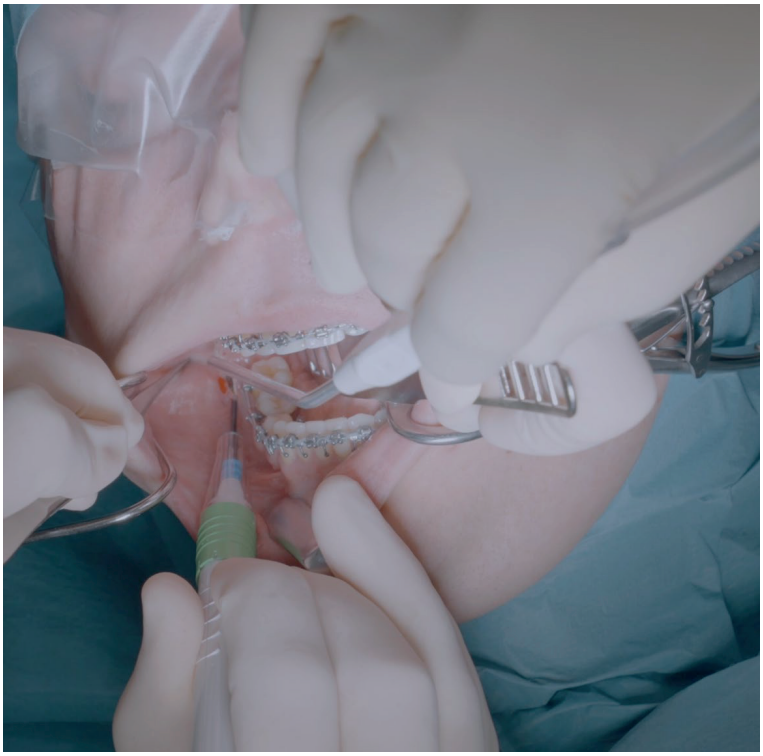


Figure 1.10 Mucosal incision along the anterior border of the ramus for sagittal split.

Subperiosteal dissection is performed to expose the mandible, temporalis muscle, the lingula, and the inferior alveolar nerve. The Hunsuck modification of the Obwegeser and Dal Pont BSSO technique is the standard approach utilized[112]. A horizontal osteotomy is made just above the lingula, approximately 10 mm above and parallel to the occlusal plane. The osteotomy continues inferiorly along the external oblique ridge to the level of the first molar. Then, a vertical osteotomy is made along the buccal surface of the mandibular body, to the inferior border which is extended from the lateral to medial of the inferior border. Care is taken that the osteotomy cuts are only through the cortical bone and not through the cancellous bone, in order not to damage

the inferior alveolar nerve. Osteotomes are sometimes used to separate the bone segments (Figure 1.11).

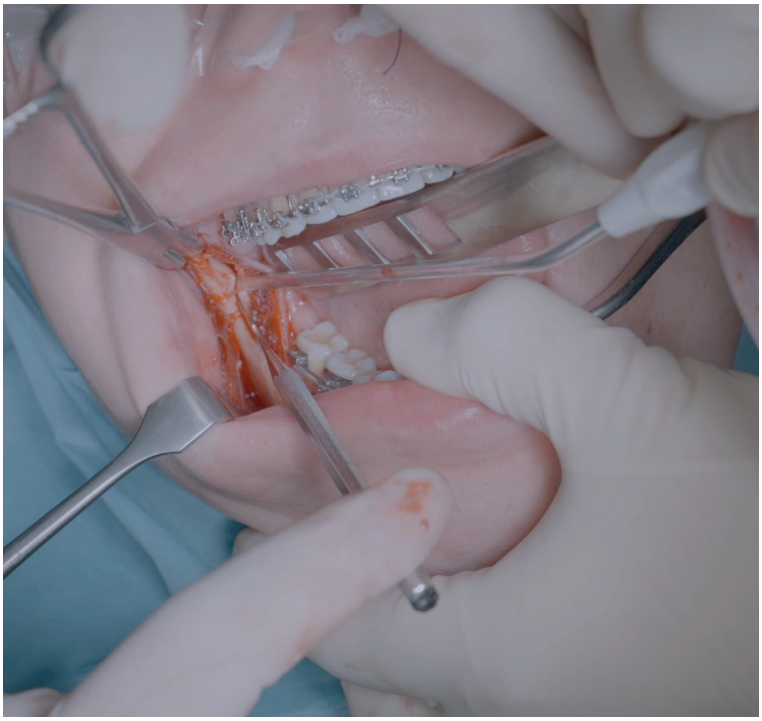


Figure 1.11 Osteotomy cut with the osteotome is made only through the cortical bone.

A Smiths bone spreader and an osteotomy elevator are used to finalize the sagittal split. If necessary, the inferior alveolar nerve is then identified and whenever present in the buccal cortex, it is then completely dissected from the buccal cortex and positioned toward the lingual side (Figure 1.12). The same procedure is then applied to the contralateral side. After which, the tooth bearing segment is repositioned in the virtual planned desired position with the use of the 3D printed intermediate intraoperative surgical splint. Afterwards, intermaxillary fixation is applied, bi-cortical osteosyntheses screws and/or osteosyntheses plates with mono-cortical screws are used to fixate the mandible in the virtual planned desired position (Figure 1.13)[113,114].

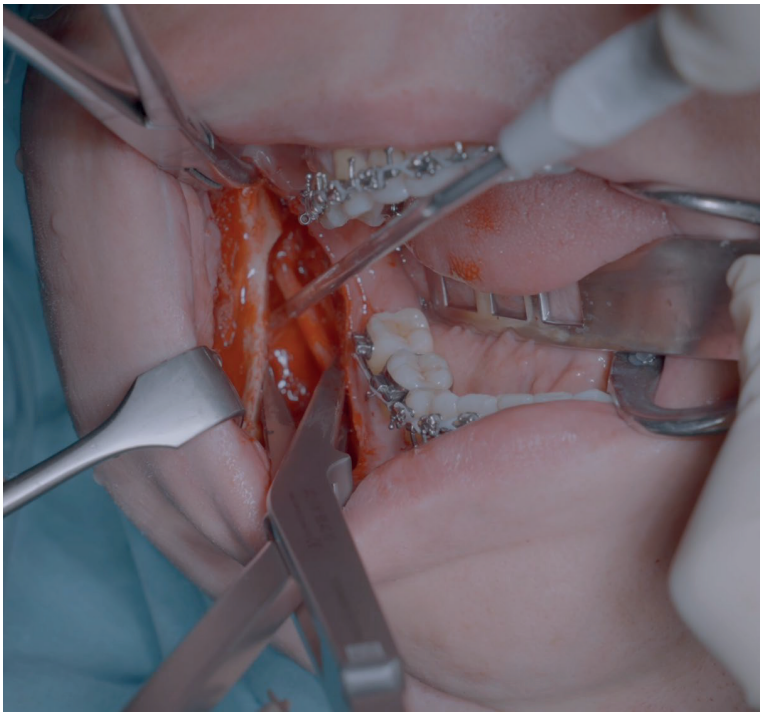


Figure 1.12 Smiths bone spreader is used to finalize the sagittal split. The inferior alveolar nerve is clearly seen and preserved.

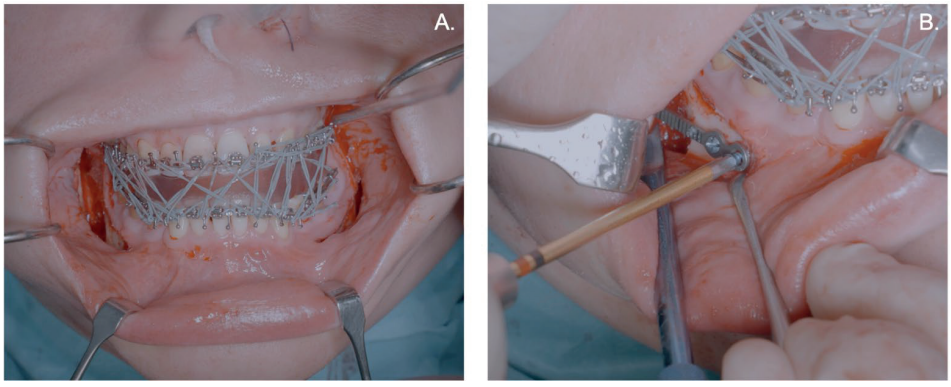


Figure 1.13 A. Intermaxillary fixation with the intermediate splint and power chains. B. Osteosyntheses plate with mono-cortical screws used to fixate the mandible in the planned desired position.

Afterwards, intermaxillary fixation is removed in order to check if the planned occlusion is correctly achieved. Whenever, large osteotomy gaps are created, the choice is made to augment the mandible with the use of autogenous or alloplastic bone or a combination of both.

Le Fort I osteotomy of the maxilla

Before performing a Le Fort I osteotomy, a glabella marker or pin (K-wire or screw) is placed. This will allow for vertical measurements and therefore guarantee correct placement of the maxilla in axial dimension (Figure 1.14).

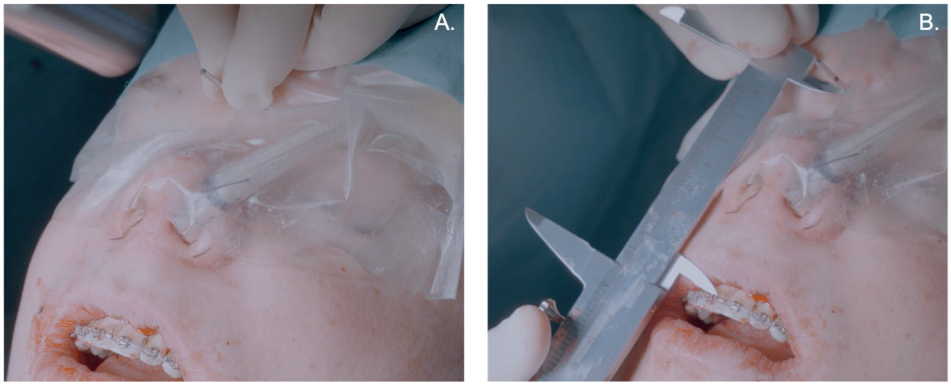


Figure 1.14 A. Placement of a glabella pin. B. Vertical measurement with a caliper.

For the Le Fort I osteotomy a maxillary vestibular incision is placed through the mucosa, which is made from the first molar to the first molar on the contralateral side, in order to expose both the lateral and medial buttresses of the maxilla. Subperiosteal dissection is performed to expose the maxilla (Figure 1.15).

The nasal mucosa is elevated and preferably kept intact. Then, a maxillary osteotomy is made with a bur or saw from the piriform rim to the pterygomaxillary fissures bilaterally. A U-shaped or V-shaped nasal septum osteotome is used to separate the nasal septum from the maxilla (Figure 1.16).

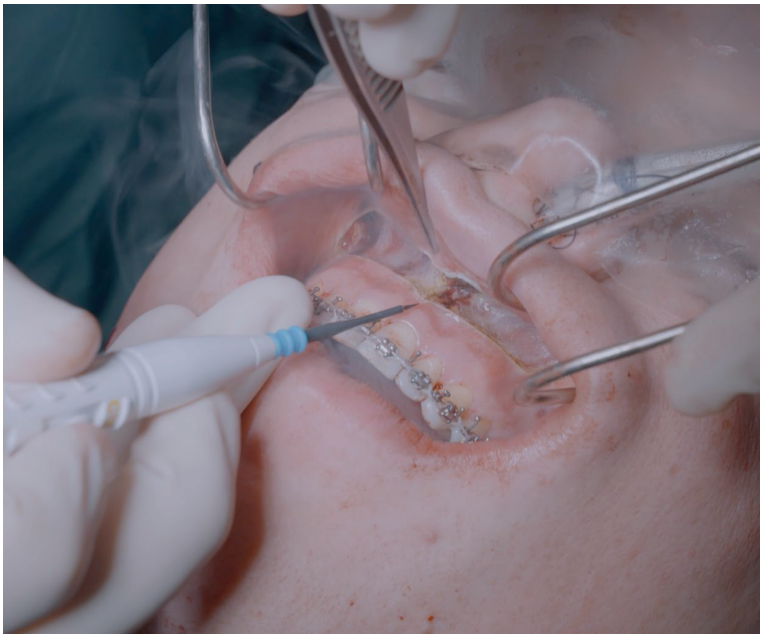


Figure 1.15 Vestibular incision through the mucosa in order to expose the maxilla.

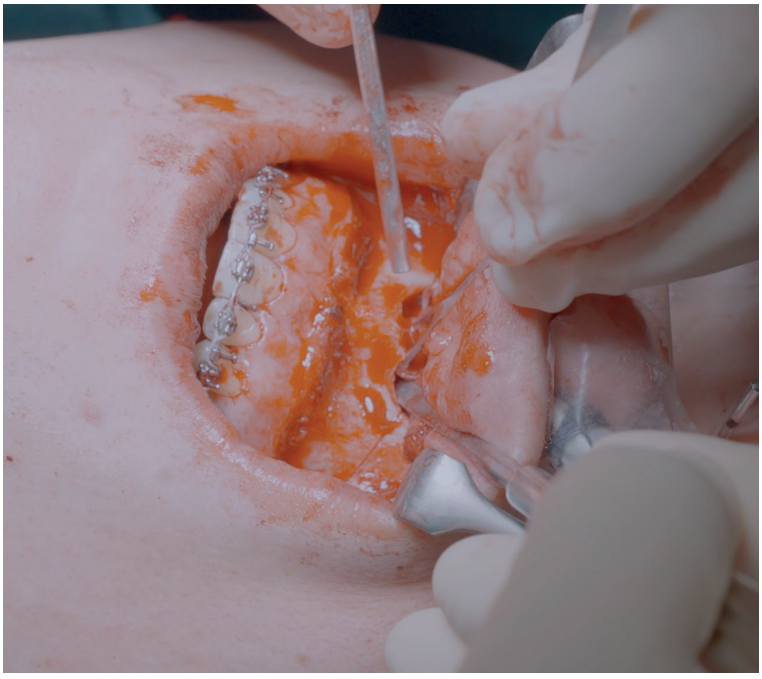


Figure 1.16 V-shaped nasal septum osteotome is used to separate the nasal septum from the maxilla.

The posterior maxillary wall and lateral nasal wall is then fractured with a straight or curved osteotome. A pterygoid osteotome is then used to separate the pterygomaxillary junction. Next is down-fracture of the maxilla, this is performed with a bone-hook and/or a Smiths bone spreader (Figure 1.17).

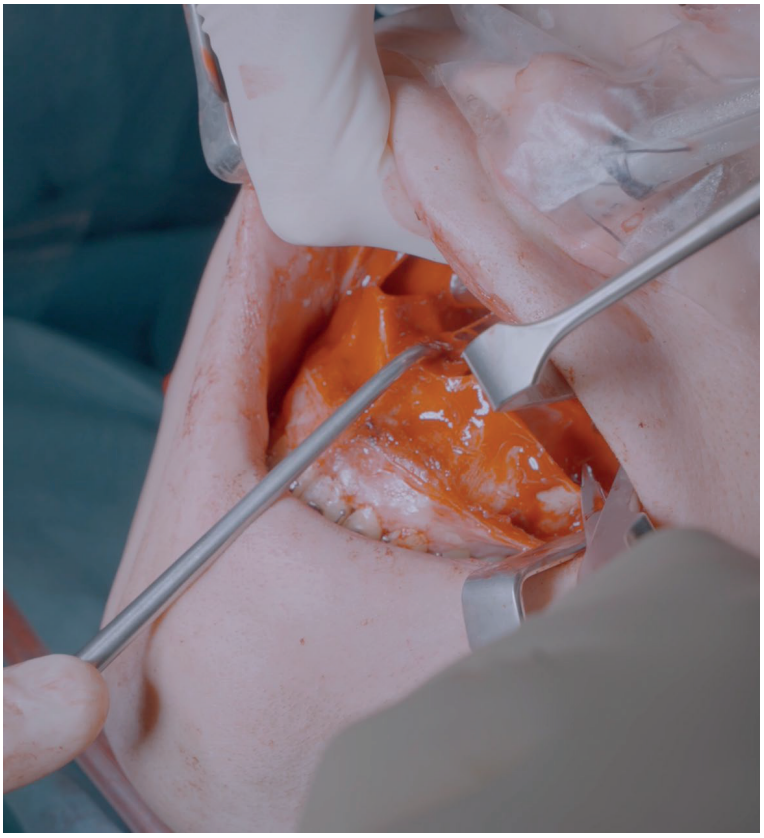


Figure 1.17 Down-fracture of the maxilla with a bone-hook.

Afterwards, the maxilla is adequately mobilized with Rowes forceps, in order to guarantee that the planned advancement and counter clockwise rotation is able to be passively achieved. The final surgical splint – which contains the virtually planned final position of the maxilla – is placed to position the maxilla in the planned position by placing the maxilla and mandible in intermaxillary fixation. Rigid fixation is then accomplished utilizing an array of titanium osteosyntheses plates with mono-cortical screws (Figure 1.18)[94,115]

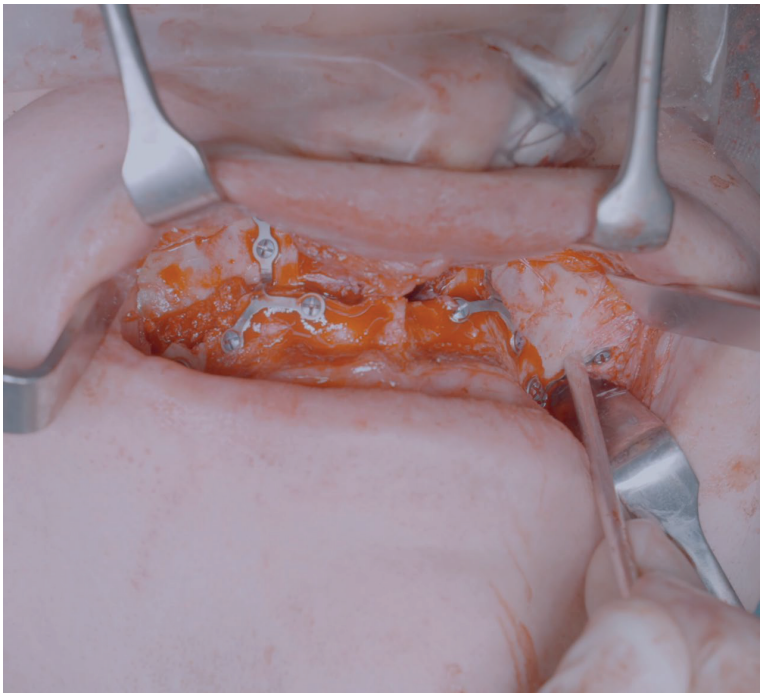


Figure 1.18 Rigid fixation is accomplished utilizing titanium osteosyntheses plates with mono-cortical screws.

After which, intermaxillary fixation is released and the correct occlusion – in other words the correct position of the maxilla – is verified. After confirming proper occlusion, closure of the incisions is performed with the use of absorbable sutures. Whenever, necessary or desired orthodontic elastics can be applied for postoperative guidance of the occlusion[94].

Postoperative care

Due to the fact that patients with OSA have been found to have an increased risk for complications associated with postoperative anesthesia e.g., difficult airway management, upper airway obstruction, and postoperative respiratory failure. This as a result of the anesthesia medication, alteration of the upper airway anatomy, and soft tissue edema postoperatively[21,116–119]. Therefore, patients are monitored on the medium care or intensive care unit in the immediate 24 hours after MMA[120]. After which, they are admitted to the regular oral and maxillofacial surgery ward. The average length of hospitalization is two to four days postoperatively. Patient are provided antibiotics, adequate analgesics – preferably non-opioids but whenever

opioids are necessary and administered patients are placed back on monitoring –, and steroids. Patients are restricted to have a soft diet for approximately four to six weeks postoperatively. The patients can return to their normal activities without physical restriction six weeks postoperatively.
Patients are regularly seen for postoperative follow-up consults at the out-patient clinic at one week, two weeks, six weeks, three months, 6 months, and 12 months postoperatively. However, patients are often checked yearly up until at least two years postoperatively. However, this can vary depending on patients' postoperative recovery. Usually, postoperatively radiographs and/or CT or CBCT are made. An overnight PSG is typically planned for three to six months after MMA, to evaluate therapeutic efficacy.

Outcome of maxillomandibular advancement

The efficacy of MMA has been thoroughly investigated through the years, since the first report of MMA by Riley et al. in 1986[97]. This evident by the many publications on MMA outcome over the past three and a half decade. There have also been a few systematic reviews and meta-analysis published on MMA outcome, including two which are part of this thesis, viz. chapter 2 and 3. Nevertheless, two key systematic reviews and meta-analysis published on MMA outcome are by Holty et al in (2010) and Zaghi et al. in (2016)[121,122]. Holty et al. reported a mean AHI decreased – in 627 adults with OSA – from 63.9 events/hour to 9.5 events/hour after MMA. The surgical success rate and surgical cure was found to be 86% and 43%, respectively. Additionally, they also showed that the mean ESS improved from 13.2 to 5.1 after MMA[121]. Zaghi et al. reported similar highly effective results for MMA, with a mean reduction of AHI and RDI of 47.8 events/hour and 44.4 events/hour, respectively. They reported success of 85.5% and cure rates of 38%. The mean ESS improvement was found to be 10.3 [122]. Thereby, illustrating that to date MMA can be considered the most effective surgical treatment for OSA – not taking tracheostomy in to account of course – with results parallel to that of PAP. A different meta-analysis by Camacho et al. exhibited that MMA is not only effective in the short-term, but it is also still effective in the long-term with a mean AHI reduction of 65.8 events/hour to 7.7 events/hour in the long term (>8 years). Patients that were followed up for >12 years, did however have an increase of AHI to moderate OSA[122]. It has been proposed that possibly extensive weight gain, skeletal relapse, and aging many years after MMA counteract the benefit of MMA, which results in residual AHI increase[123].

Facial esthetics after maxillomandibular advancement

As MMA advances the maxilla and mandible significantly, it is not inconceivable that the patients' face undergoes an alteration. With the lower two thirds of the face

becoming more pronounce. This of course is an issue that is of specific concern to the patient which is contemplating MMA as a therapeutic option of their OSA. Multiple papers have investigated the issue of facial esthetics and MMA. Most papers have looked in to the general appearance of the patients face[124–127]. These have found that healthcare professionals – e.g., surgeons and orthodontist –, patients, and also laypeople are generally neutral to positive about the facial esthetics change after MMA. Patients often are of the opinion that they have gained a more youthful profile after MMA[125]. When it comes to their facial aesthetics, 79% of patients responded affirmatively when asked whether they would recommend the surgical treatment to others128.

1C Outline of the thesis

The main research questions of this thesis:

- Multilevel surgery ranks as the most commonly performed type of surgery for OSA among otolaryngologists. Meanwhile, MMA stands out as the primary choice for skeletal surgery in OSA cases, preferred by oral and maxillofacial surgeons. In addition to these established approaches, the innovative hypoglossal nerve stimulation has gained significant popularity as a promising surgical treatment option. This popularity prompts the question of whether differences exist in clinical outcomes and complication rates among these three surgical choices? – Chapter 2 and 3.
- What patient-related, polysomnographic, cephalometric, and surgical factors can predict the outcomes of MMA? – Chapter 4
- Numerous OSA patients can present with features of both obstructive and central sleep apnea, a condition known as mixed apnea. Of particular interest is the proportion of central and mixed apnea (CMAI%) in relation to the total apnea-hypopnea index, where a value ≥25% serves as an exclusion criterion for hypoglossal nerve stimulation therapy (Inspire II). This raises the question: What is the clinical effectiveness of MMA for OSA patients exhibiting a CMAI% ≥25%? – Chapter 5
- The severity of OSA is expressed by the AHI, computed as the count of apneas and hypopneas per sleep hour. Does the hypopnea-predominant OSA phenotype tend to yield better treatment outcomes following MMA compared to the apnea-predominant OSA phenotype? – Chapter 6
- Within the edentulous population of OSA patients, the standard surgical approach involving intraoperative surgical splints may not be feasible. Can an alternative treatment method, employing 3D-printed osteotomy guides and fixation PSIs to effectively translate the virtual surgical plan into the operating room, be considered clinically viable, accurate, and predictable? – Chapter 7
- Existing literature in both general and orthopedic surgery indicates a correlation between surgeon experience and surgical outcomes. Does the experience of surgeons also play a role in the outcomes of MMA? – Chapter 8
- The literature on orthognathic surgery for dentofacial deformities has indicated a connection between larger surgical translations and rotations and increased surgical inaccuracies. Considering the extensive translations and rotations involved in MMA, how predictable and surgically accurate is this type of procedure? – Chapter 9

This chapter (**chapter 1**) provides a general introduction, including introduction of OSA (**chapter 1A**), background of MMA (**chapter 1B**), and outline of this thesis (**chapter 1C**).

In **chapter 2** we present a systematic review and meta-analysis, in which the clinical efficacy and safety between MMA and multilevel surgery in the treatment of OSA are compared.

Chapter 3 presents a systematic review in which the efficacy and safety of MMA and UAS in the treatment of OSA is comparatively evaluate.

In **Chapter 4**, we look in to different patient-related, polysomnographic, cephalometric, and surgical variables, in order to investigate whether the factors are possible predictors for MMA outcome.

Chapter 5 presents a retrospective cohort study, where we investigate the clinical efficacy of MMA for OSA patients with the presence of CMAI% $\geq$25%.

In **chapter 6**, we perform a retrospective cohort study in order to investigate the influence of apnea-predominant versus hypopnea-predominant obstructive sleep apnea (OSA) on surgical outcome after MMA; and to evaluate whether MMA alters the presence of apnea-predominant to hypopnea-predominant OSA more than vice versa.

Chapter 7 reports on three edentulous OSA patients, which were treated with an alternative splintless treatment protocol that circumvents the use of intraoperative splint, by using computer aided designed and computer aided manufactured osteotomy guides and fixation PSIs. The accuracy and predictability of this splintless treatment protocol is evaluated.

Chapter 8, explores whether there is an association between clinical efficacy outcomes (i.e., polysomnography (PSG) results) of MMA and surgeons' experience; and (2) to assess the association between the occurrence of postoperative complications of MMA and surgeons' experience. The hypothesis is that surgical outcomes after MMA are better when surgeons' MMA-related surgical experience increases.

In **Chapter 9** we performed a retrospective cohort study, where we investigated – with the use of the OrthoGnathicAnalyser – to what extent the preoperative surgical plan is actually achieved during surgery – i.e., the surgical accuracy – when performing MMA

surgery in OSA patients, specifically examining the advancement and counter clockwise rotation of the maxilla and mandible.

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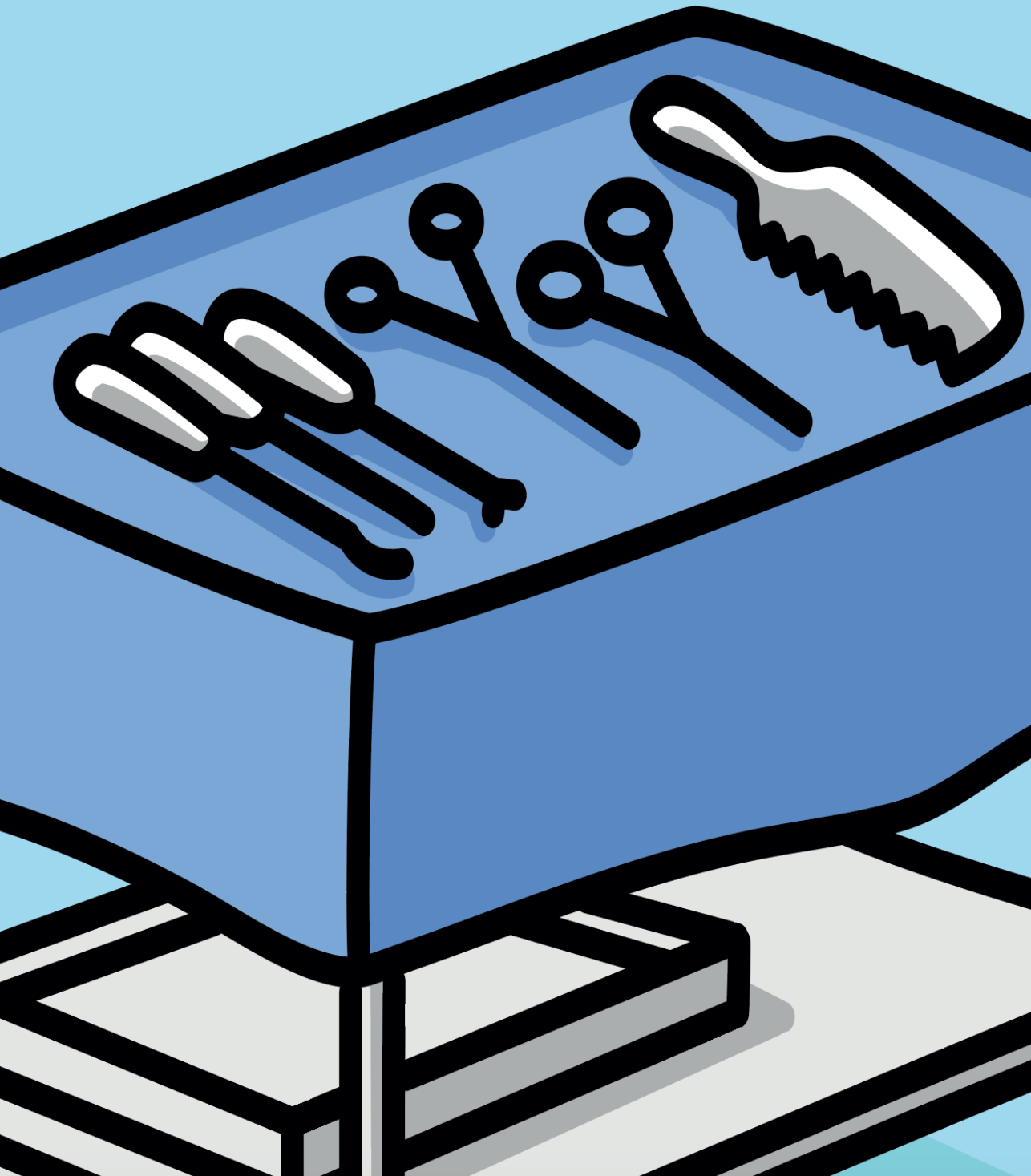
PART I

ISSUES RELATED TO INDICATIONS AND OUTCOME



Chapter 2

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

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Chapter is based on the publication in:

Sleep Medicine Reviews 2021;57:101471

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 AHI, LSAT, ODI, and ESS by -46.2/h, 13.5%, -30.3/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/h, 8.7%, -19.1/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.

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: 1) adult patients (>18 y old) with OSA diagnosed by means of polysomnography (PSG; AHI ≥5/hour); 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 mo; 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 Tables S2.1A and S2.1B).

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).
- 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” [12], and “surgical cure” as “a postoperative AHI <5” [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 ($\overline{x}^*$) and weighted standard deviation ($\overline{SD}^*$) 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 method 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 cut off of $P<0.10$ [20], as well as I^2 statistic with cut off 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/h; 40/h ≤AHI ≤70/h; AHI >70/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 y). 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 Figure S2.1. The search in the electronic database resulted in 3383 publications after deduplication, from which 205 full articles were retrieved for further full-text evaluation.

MMA group

Twenty studies were identified[24-43]. One of these was a 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 2.1. The mean follow-up period from surgery to postoperative PSG was 25.4 mo (range, 6.0 mo - 12.5 y).

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 2.2. The mean follow-up period from surgery to postoperative PSG was 9.9 mo (range, 6.0 mo - 3.3 y).

Table 2.1 Characteristics of studies on maxillomandibular advancement.

Study	Design	N	Age (years) (mean±SD)	% Male	Degree of advancement (mm) (mean±SD)		Follow-up (mean±SD)	BMI (mean±SD)		AHI (mean±SD)		ODI (mean±SD)		ESS (mean±SD)		% Success	% Cure
					Max	Mand		Pre-op	Post- op	Pre-op	Post- op	Pre-op	Post- op	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	59.3±29.0	11.1±8.9					75[c]	
Bianchi et al. 2014	Retro	10	45±14	100	10	10	6m			56.8±5.2	12.3±5.5						
Boyd et al. 2015	Pro	14			7.0±2.3	9.2±3.3	6.6±2.8y			50.0±20.0	8.0±10.7						
Conradt et al. 1997	Retro	15	44±12	93.3			>2y	28.3±3.4		51.4±16.9	8.5±9.4						
Gerbino et al. 2014	Pro	10	44.9		9.2±1.2	10.4±2.2	6m	31.6±5.5	28±1.4	69.8±35.2	17.3±16.7	59.5±5.3	9.1±8			80[d]	
Goh et al. 2003	Pro	11	42.8±8.19	100	10	10	7.7m	29.4±4.6	27.2±3.3	70.7±15.9	11.4±7.4					81.8	
Goodday et al. 2016	Retro	13	37.8±8.57	84.6			9.6m	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
Hsieh et al. 2014	Pro	16	33±7.9	75			12±8m	22±3.3		35.7±18	4.8±4.4					100	
Kastoer et al. 2019	Pro	14	51.1±7.3	57.1			6m	25.7±3.7		40.2±25.6	9.9±7.2	13.5±18.6	4.0±3.5	13±6	9±7		
Li et al. 1999	Retro	175	43.5±11.5	83			6m			72.3±26.7[a]	7.2±7.5[a]					95[e]	
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	71.2±27.0[a]	7.6±5.1[a]					90[e]	
Li et al. 2001	Retro	52	46.6±6.7	82.7	10.5±1.5		6m	32.0±6.0		61.6±23.9[a]	9.2±8[a]					90[f]	
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	75.3±26.4[a]	10.4±10.8[a]					83.3[f]	
Liao et al. 2015	Pro	20	33.4±6.5	85			14±9.3m	22.4±3.4		41.6±19.2	5.3±4			11.9±7.3	7±3	100[c]	

Table 2.1 (continued)

Study	Design	N	Age (years) (mean±SD)	% Male	Degree of advancement (mm) (mean±SD)		Follow-up (mean±SD)	BMI (mean±SD)		AHI (mean±SD)		ODI (mean±SD)		ESS (mean±SD)		% Success	% Cure
					Max	Mand		Pre-op	Post- op	Pre-op	Post- op	Pre-op	Post- op	Pre-op	Post- op		
Lin et al. 2020	Pro	53	35.7±11.7	75.7	4.3±2.9	13.3±3.8	24m	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
Liu et al. 2016	Retro	20	44±12	85	7±1.4		6m	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
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	38.3±10.7	6.45±4.33	34.7±12.5	5.4±4.1	17.4±5.4	0.79±1.41	100	52.9
Veys et al. 2017	Pro	10	44.7±9.5	80	4.8±2.8	8.3±2.3	6m			26.8±12.7	12.3±14.4			14.1±5.9	5.7±3.0	70	40
Vicini et al. 2010	RCT	25	49.1±9.1	92		11	13±2.5m	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
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		56.6±24	25.5±20.6				7.5±4.7	41.4	
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		59.3±14.5	10.9±3.3			12.8±2.8	6.9±2.5	85.7	46.4

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 didn't 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.

Table 2.2 Characteristics of studies on multilevel surgery.

Study	Design	N	Age (years) (mean±SD)	% Male	Follow-up (mean±SD)	BMI (mean±SD)		AHI (mean±SD)		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	Pre-op	Post-op	Pre-op	Post-op			
Subgroup 1. Soft palate level & tongue base level																		
Aynaci	Retro	20	41.7±8.4	85	6m			25.1±6.0	13.40±3.0	80.3±6.0	91.9±1.7			19.8±2.5	11.1±1.5			1.3±0.4
et al. 2018		20	45.0±7.1	80	6m			36.4±4.9	10.0±1.9	78.8±3.5	96.3±1.2			20.1±1.7	6.5±1.3			2.6±0.8
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	84.6±3.4	86.6±2.0					62.5		
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	75.7±8.9	82.3±7.4	44.8±21.4	17.7±15.9			74.4		
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	69.5±9.9	80.0±7.4			12.7±4.3	7.7±4.5	60		5.2±0.9
Cammaroto	Retro	10	58.4±9.9		≥6m	26.8±3.7		34.0±14.0	22.9±13.3					12.3±4.2	8.5±5.4	50		6.7±1.3
et al. 2017		10	52.8±11.4		≥6m	27.0±2.1		35.6±13.9	9.6±9.3					13.0±4.5	4.9±3.9	90		7.1±1.5
		10	48.2±11.4		≥6m	28.8±2.6		37.8±21.6	13.5±7.8					10.4±2.5	3.9±3.6	90		7.1±3.2
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	86.8±8.9	94.6±4.9			10.8±3.2	8.2±2.7	53.8[c]		
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	61.9±12.5	67.8±19.3					63.6[d]		
Chen	Pro	24	42.3±8.3	100	1y	27.5±2.7		46.1±13.3	26.2±18.9									
et al. 2014		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	60.3±7.3	76.9±4.0			13.0±2.6	8.5±2.0	64.4	11.1	
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							61		
Emara et al. 2011	Pro	23			6m	27.5±1.1		40.7±17.4	15.4±10.7	78.9±12.6	87.2±11.1			14.2±2.3	8.3±3.9	86.9		
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]	79.1±5.7[a]	79.4±16.5[a]			11.4±5.0	7.5±4.5	53.6	50	2
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	81.4±10.4	85.9±9.8			15.2±3.1	8.3±3.9			
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	88.9±4.8	90.4±4.3			9.7±3.9	6.9±3.3	47.5		

Table 2.2 (continued)

Study	Design	N	Age (years) (mean±SD)	% Male	Follow-up (mean±SD)	BMI (mean±SD)		AHI (mean±SD)		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	Pre-op	Post-op	Pre-op	Post-op			
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]	72.4±15.2	80.4±12.3							
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	76.4±8.5	82.4±5.4			10.9±4.7	8.7±3.9	73		
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	77.1±10.5	83.3±5.6			9.6±4.9	7.5±4.3	80		5.6±1.3
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	66±16	83±5			12.9±4.9	3.4±2.9	51.1	37.8	7
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	75.5±10.4	82.1±10.9			12.8±5.1	10.0±4.3	60.5		
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	85.6±3.4	88.2±2.4			14.2±3.4	8.2±2.5	55.6		1
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]					13.9±2.2	5.4±4.3	81.8[e]		3.8±1.6
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			15.1±8.2	10.3±7.9	10.6±3.8	7.3±3.2	51.7		3
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					14.8±2.5	7.6±3.2	50[f]		
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	72.9±19.3	84.5±7.1			13.0±2.8	5.6±4.4	55	35	4.1±0.7
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					11.9±4.3	10.2±4.3	66.7		
Turhan et al. 2015	Pro	90	48	91.1	6m	30.7		51.8±18.8	20.5±17.7	75.6±9.3	82.4±6.6	48.0±19.5	18.2±15.5			74.4		
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	76.2±12.4	82.2±11.2			12.2±3.3	8.2±6.1	78[g]		
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					13.75±4	7.6±4.4	33.3		8.3±2.4
		12	54.2±10.8	75	≥6m	27.3±2.0	26.1±2.0	38.5±14.3	9.9±8.6					12±4.9	4.4±4.1	83.3		7.3±1.5
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	70.5±12.4	85.6±10.0			12.2±5.8	5.5±3.6	66.7		
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			30.3±16.9	15.5±13.2	11.9±7.0	5.0±4.4	57.1		

Table 2.2 (continued)

Study	Design	N	Age (years) (mean±SD)	% Male	Follow-up (mean±SD)	BMI (mean±SD)		AHI (mean±SD)		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	Pre-op	Post-op	Pre-op	Post-op			
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					10.5±3.1	7.2±2.3	61.5		
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	73.5±14.8	84±5.3			12.6±5.6	4.1±2.7			
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	66.8±11.3	83.2±2.9			13.8±5.4	5.2±1.6			
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	58.7±8.3	86.0±5.4			12.8±2.2	6.0±1.3	84.4	11.1	
Cillo et al. 2013	Retro	13	43.0±2.4	100	18±3.6m			28.3±13.2	12.1±8.2					15.2±3.0	6.3±3.9			
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]	81.2±2.9	87.2±3.1			15.9±2.7	7.3±2.7	65.2[e]		
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	77±6.2	90.7±3			14.3	5.3	100		16±2
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	72.7±11.9	75.0±12.5			17.1±4.1	8.9±4.9	64.5[h]		
Yi et al. 2011	Pro	26	47	84.6	6m	29.3	28.0	65.6±17.6	30.1±23.1	74±28	82.8			13.5±5.9	6.8±5.2	46.2		

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.

Quality assessment of individual studies

MMA group

The only RCT[41] was considered of good quality (Supplementary Figure S2.2). Of the non-randomized studies, two studies were classified as "high quality", and the other 17 studies as "fair quality" (Supplementary Table S2.2A).

MLS group

The only RCT[53] was considered of fair quality (Supplementary Figure S2.2). 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 S2.2B).

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 y (Table 2.3).

Table 2.3 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/m^2	MMA	359	28.6 ± 6.6	185	29.4 ± 6.2				
	MLS	1420	29.1 ± 4.2	878	28.4 ± 4.1				
AHI,	MMA	393	57.3 ± 26.6	393	10.4 ± 11.2	-46.2	[-52.4, -39.9]	<0.001	<0.001
events/h	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,	MMA	78	35.1 ± 22.8	78	6.3 ± 6.4	-30.3	[-46.3, -14.2]	<0.001	0.322
events/h	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	MMA	340				85.0	[76.4, 91.9]	<0.001	<0.001
rate, %	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, 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.

MLS group

As shown in Table 2.3, 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 y.

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 2.3, nineteen studies, describing 393 patients with weighted preoperative AHI of 57.3 ± 26.6/h, reported a statistically significant improvement in AHI of -46.2/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/h (95% CI, -46.3 to -14.2, *P*<0.001) (Supplementary Figure S2.3). 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 2.3, thirty-seven studies, totaling 1639 patients with weighted preoperative AHI of 42.2 ± 21.0/h, reported a statistically significant improvement in AHI of -24.7/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/h (95% CI, -34.2 to -4.0, *P*=0.010) (Supplementary Figure S2.4). 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 2.4 (Supplementary Figure S2.5).
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 2.3;

Supplementary Figure S2.3). The ESS SMD was -2.15 (95% CI, -3.06 to -1.24) (large effect).

Table 2.4 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.

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 2.3; Supplementary Figure S2.4). 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 2.4 (Supplementary Figure S2.5). 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%-91.9%), and the pooled rate of surgical cure reported in six studies (n=130) was 46.3% (95% CI, 38.0%-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%-69.5%), and the overall pooled rate of surgical cure was 28.1% (95% CI, 13.2%-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 2.4.
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/h, from 40/h to 70/h, and greater than 70/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/h.

Baseline AHI less than 40/h

MMA group

In Table 2.5, three studies, totaling 60 patients with weighted preoperative AHI of 35.7 ± 13.7/h, reported a significant improvement in AHI of -27.1/h (P<0.001), and ESS of -12.7 (P=0.002) (Supplementary Figure S2.3). No study described LSAT. Only one study with 34 patients reported data concerning the preoperative and postoperative ODI (34.7 ± 12.5/h and 5.4 ± 4.1 (P<0.001), respectively). The pooled rates of success and cure were 94.0% (95% CI, 74.3%-99.9%) and 50.0% (95% CI, 35.7%-64.2%), respectively.

Table 2.5 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.

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									
Age, years	MMA	60	39.4 ± 12.4						
	MLS	706	45.2 ± 11.7						
BMI, kg/m^2	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									
Age, years	MMA	215	44.3 ± 10.6						
	MLS	607	45.8 ± 9.7						
BMI, kg/m^2	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	
Baseline AHI greater than 70									
Age, years	MMA	76	44.1 ± 16.4						
BMI, kg/m^2	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.

MLS group

In Table 2.5, fifteen studies, comprising 706 patients with weighted preoperative AHI of 30.7 ± 15.6/h, showed a significant improvement in AHI of -16.7/h (*P*<0.001), LSAT of 4.4% (*P*<0.001), and ESS of -5.4 (*P*<0.001) (Supplementary Figure S2.4). No significant improvement of ODI was found. The pooled rates of success and cure were 57.1% (95% CI, 51.7%-62.5%) and 44.7% (95% CI, 33.2%-56.4%), respectively.
Compared to the MLS, the AHI reduction 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/h to 70/h

MMA group

In Table 2.5, twelve studies, comprising 257 patients with weighted preoperative AHI of 55.7 ± 23.0/h, reported a significant improvement in AHI of -44.1/h (*P*<0.001), LSAT of 11.6% (*P*<0.001), ODI of -30.4/h (*P*=0.030), and ESS of -7.0 (*P*<0.001) (Supplementary Figure S2.3). The pooled rates of success and cure were 82.3% (95% CI, 69.1%-92.5%) and 44.0% (95% CI, 33.1%-55.3%), respectively.

MLS group

In Table 2.5, twenty-two studies, comprising 933 patients with weighted preoperative AHI of 51.0 ± 20.3/h, showed a significant improvement in AHI of -30.7/h (*P*<0.001), LSAT of 9.9% (*P*<0.001), ODI of -28.6 (*P*<0.001), and ESS of -6.1 (*P*<0.001) (Supplementary Figure S2.4). The pooled rates of success and cure were 70.5% (95% CI, 65.4%-75.3%) and 17.4% (95% CI, 7.1%-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/h

MMA group

As shown in Table 2.5, four studies, totaling 76 patients with weighted preoperative AHI of 79.8 ± 28.9/h, reported a significant improvement in AHI of -71.8/h (*P*<0.001), LSAT

of 18.7% (*P*<0.001), and ESS of -7.9 (*P*<0.001) (Supplementary Figure S2.3). No study described ODI. The pooled rate of success was 84.2% (95% CI, 75.5%-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 y) in 98 OSA patients treated by MMA. At a mean follow-up of 8.9 y, a reduction of AHI was shown from 60.8 ± 25.2 to 13.1 ± 15.1/h. The meta-analysis showed a statistically significant improvement of -45.2/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 y) 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 y, AHI and ESS score decreased from 48.8 ± 17.8/h to 14.9 ± 21.5/h, 12.1 ± 4.3 to 7.5 ± 5.9, respectively. The WMD between pre- and post-surgery were -27.4/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/h preoperatively to 15.5 ± 13.2/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 y, AHI and ESS score decreased from 47.9 ± 8.4/h to 18.6 ± 4.1/h, 15.9 ± 2.7 to 7.3 ± 2.7, respectively; the LSAT 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 d (range 2 d-8 d). 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 y).
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 d (range 1.25 ± 0.44 d to 16 ± 2 d) of hospitalization. No death was reported in 1386 patients[22,44-46,48-51,53,56-60,62-71,73-75,77-81]. 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 Figures S2.6 and S2.7). The sensitivity analysis indicated high stability and robustness of the results (Supplementary Figures S2.8 and S2.9).

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, and for the cure rate in patients with baseline AHI from 40 to 70. 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 non-responders 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 mo to 12.5 y, and that of the included MLS studies ranges from 6 mo to 3.3 y. Most of the retrieved studies reported short-term surgical outcomes at 6 mo after surgery. In our study, a significant decrease in AHI of 45.23/h was shown, at a mean follow-up of 8.9 y 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 y to <8 y). However, the mean AHI increased to moderate OSA (mean AHI =23.1/h) in the very long term (≥8 y). The longest follow-up result in MMA was

reported by Pottel et al.[87], the long-term (range 14-20 y) success rate of nine patients performed MMA was 44.44%, and the short-term (within 2 y) success rate was 66.67%. Vigneron et al.[42] reported that the long-term (mean 12.5 y) success rate of MMA was 100% in young patients (age <45) with BMI <25 kg/m^2, AHI <45/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 mo) and long-term (5 y) outcome. At 6 mo, the surgical success and cure rate were 79.41% and 17.65%, respectively; at 5 y, 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 y and 8.4 y 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/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 y 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/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. Regardless of disease severity, MMA may offer greater improvements in AHI compared to MLS. However, the complication rate of MMA is higher than that of MLS. This conclusion is based on separate analysis of MMA and MLS studies.

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Supplementary information

Table S2.1A 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 S2.1B 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 S2.2A 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 S2.2B 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.

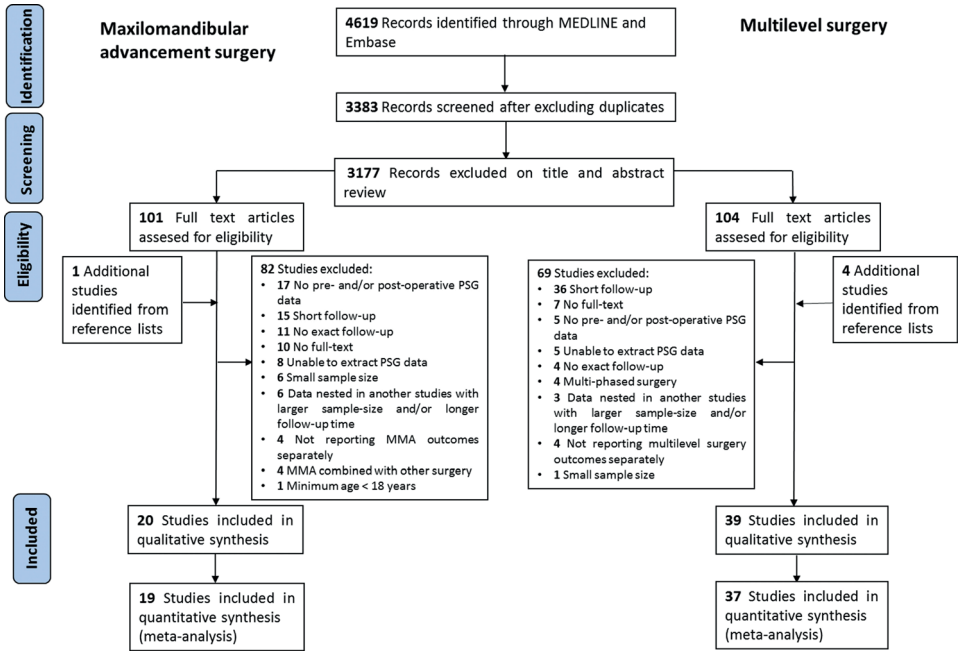


Figure S2.1 PRISMA flow diagram of the study selection process.

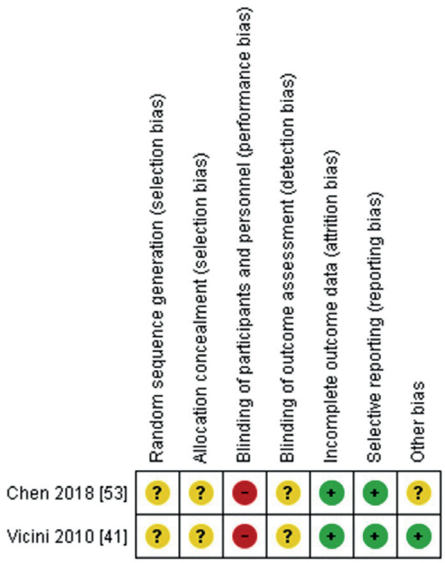
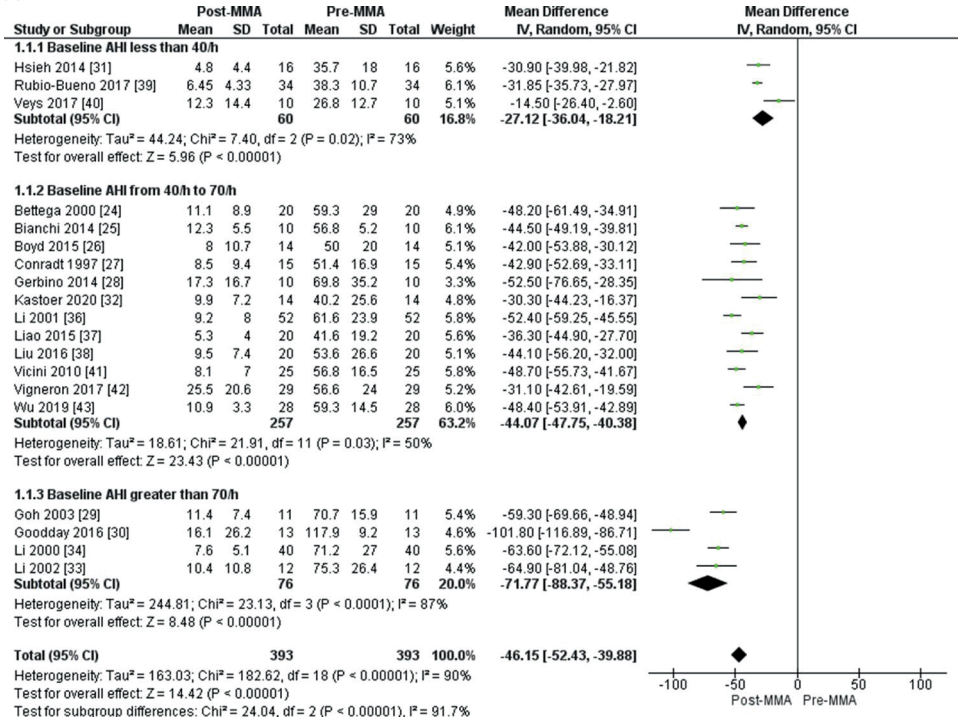
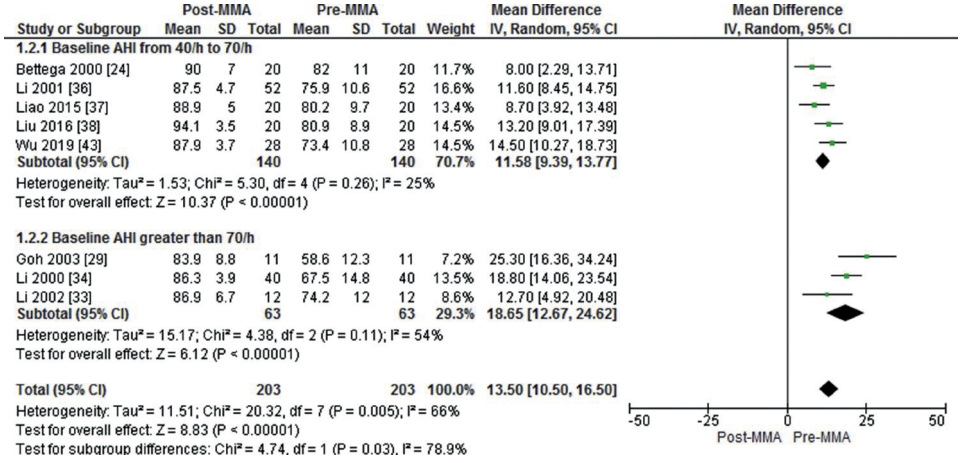


Figure S2.2 Risk of bias assessment of randomized controlled trials using the Cochrane Collaboration "Risk of bias" tool.

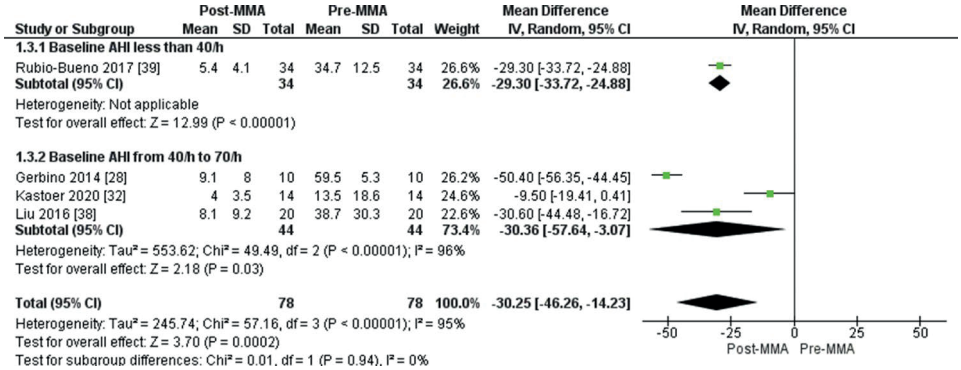
A


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 2020 [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

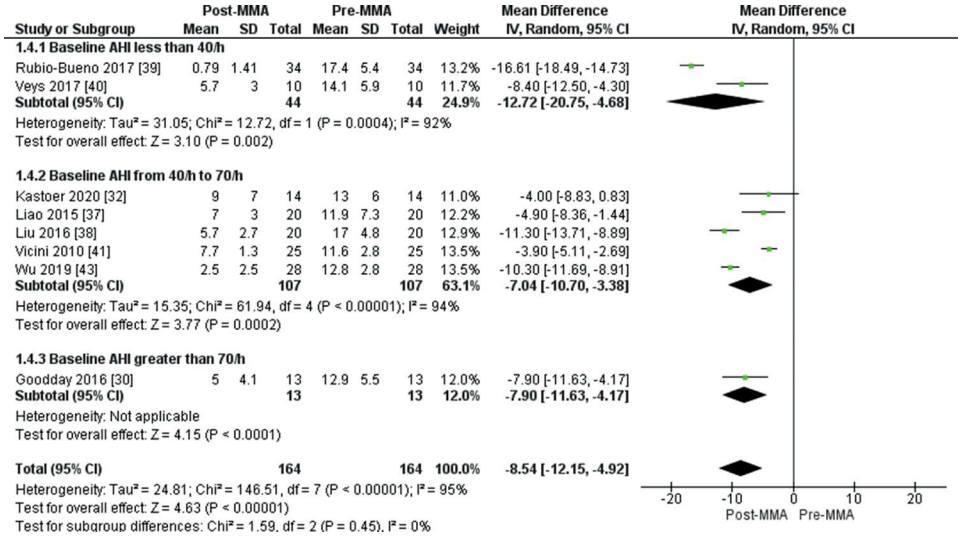
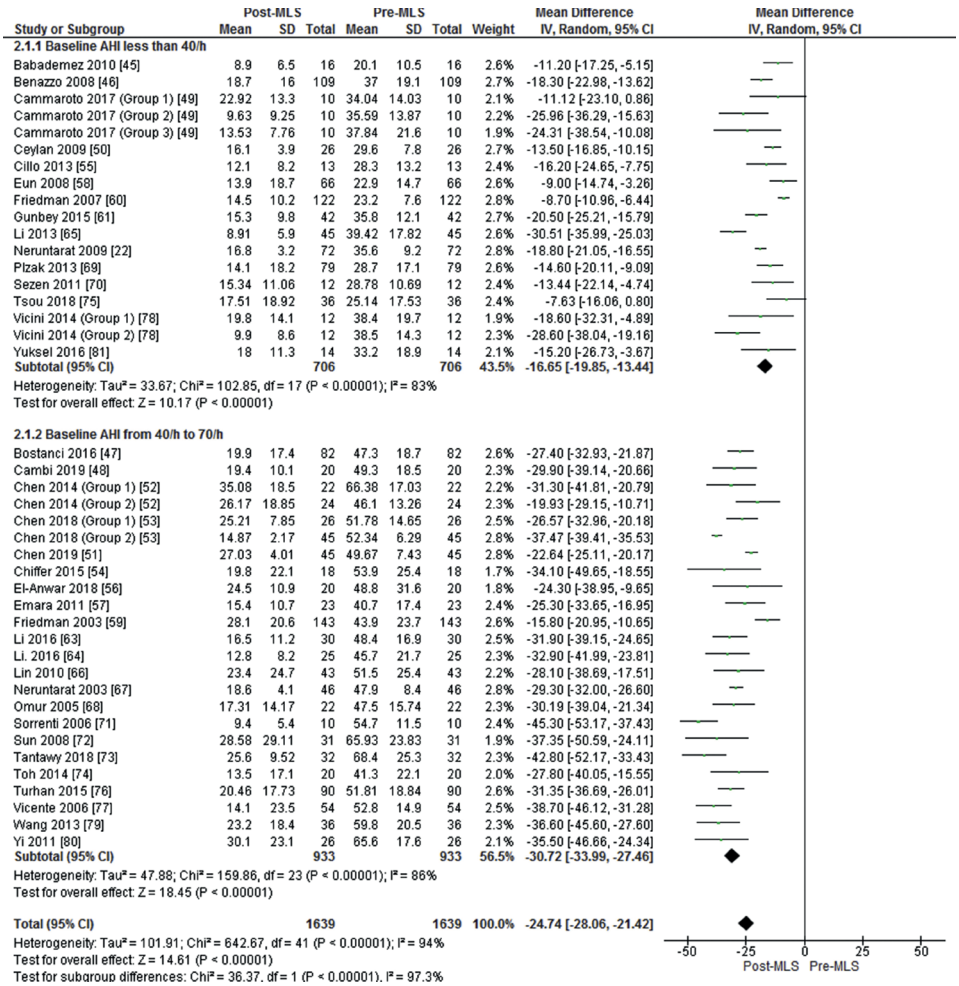
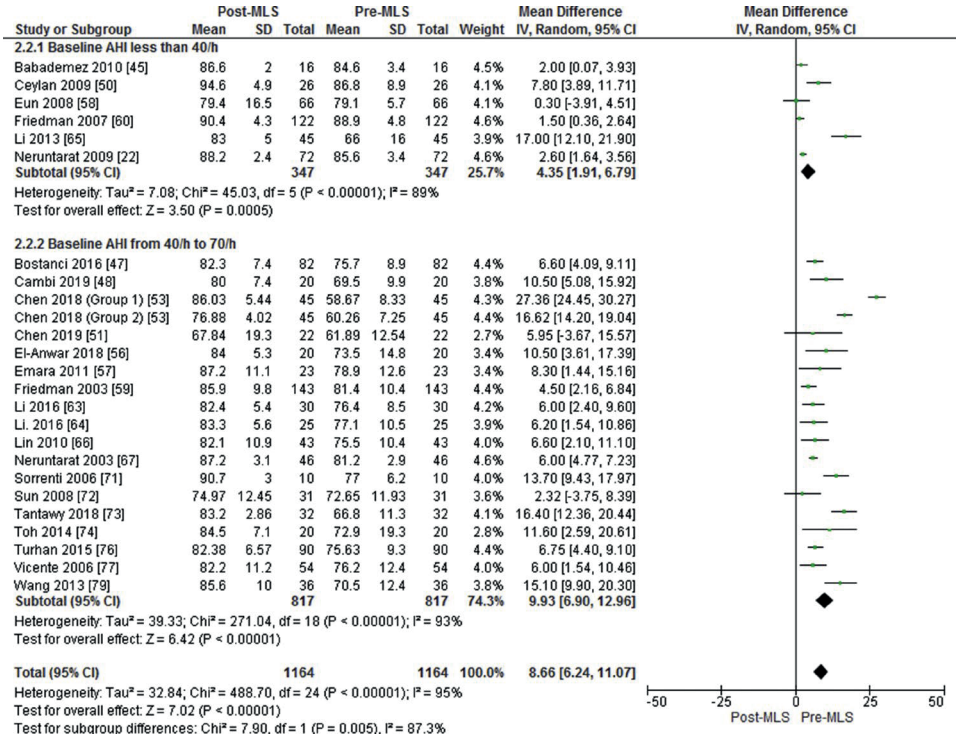


Figure S2.3 Pre- and post-MMA mean difference for apnea-hypopnea index (A), lowest oxygen saturation (B), oxygen desaturation index (C), and Epworth sleepiness scale (D).
CI, confidence interval; MMA, maxillomandibular advancement; SD, standard deviation.

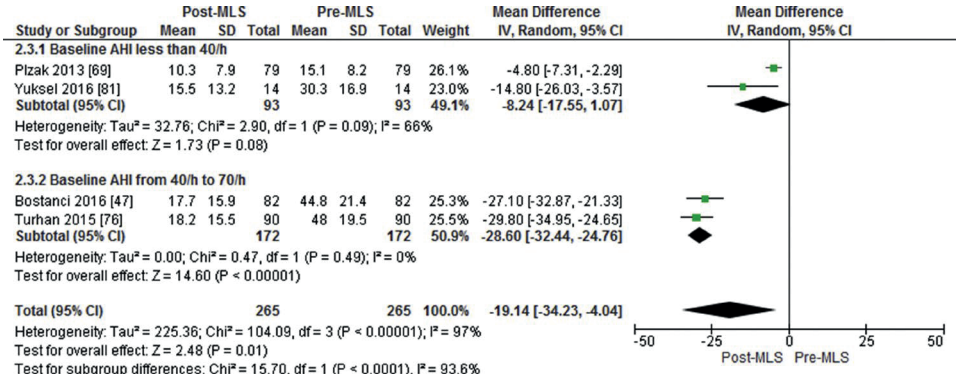
A


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]
Cammaroto 2017 (Group 1) [49] 22.92 13.3 10 34.04 14.03 10 2.1% -11.12 [-23.10, 0.86]
Cammaroto 2017 (Group 2) [49] 9.63 9.25 10 35.59 13.87 10 2.2% -25.96 [-36.29, -15.63]
Cammaroto 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
Plzak 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

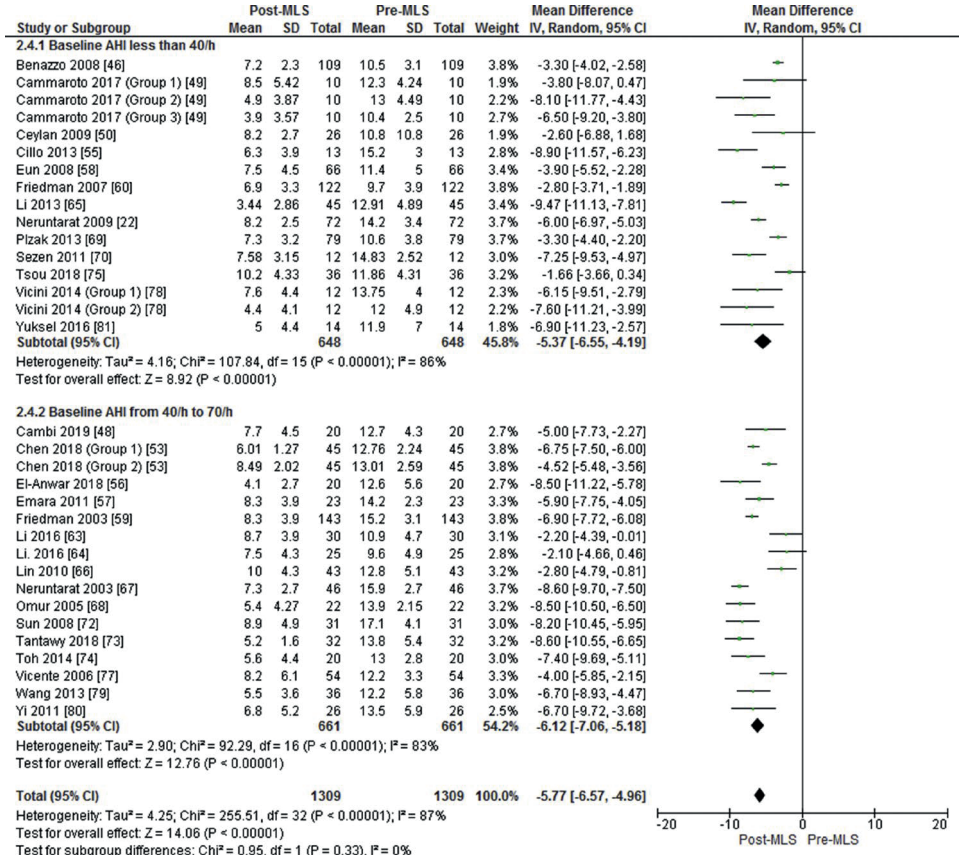
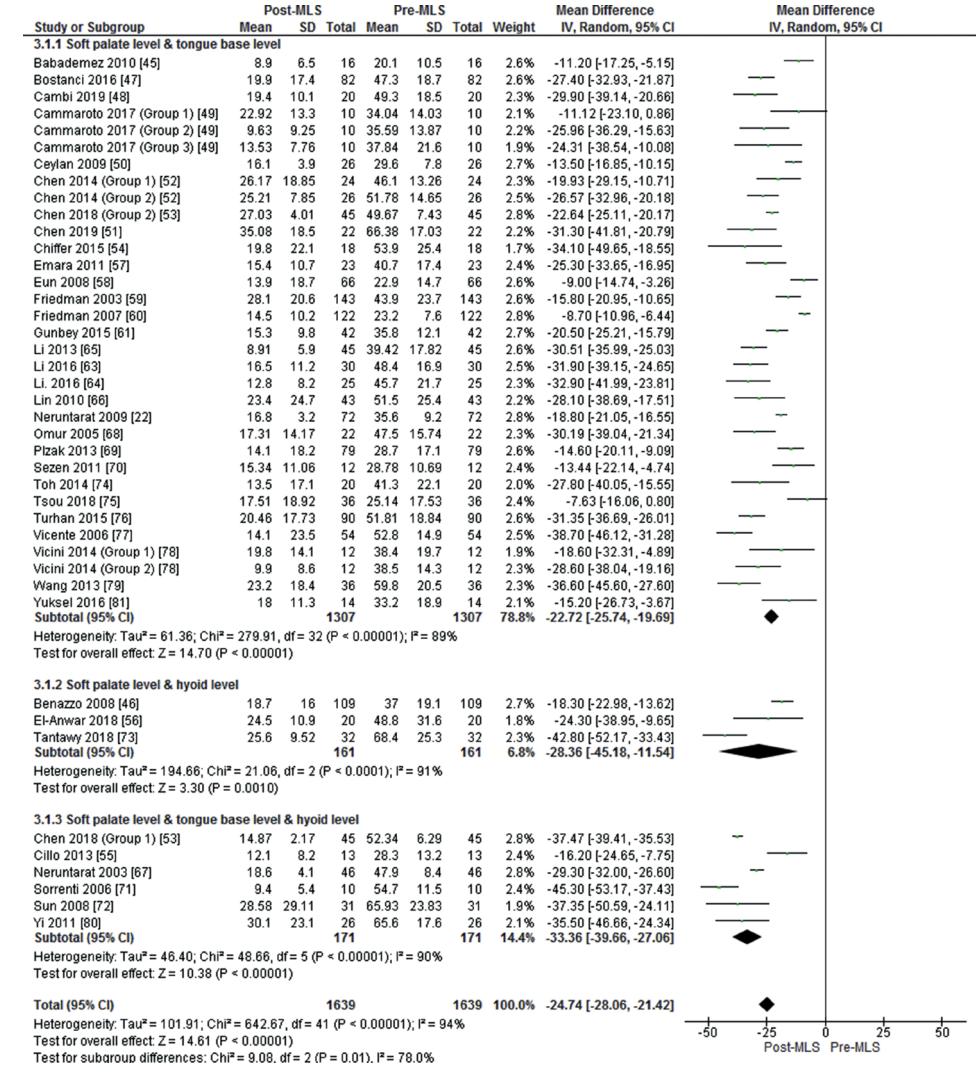
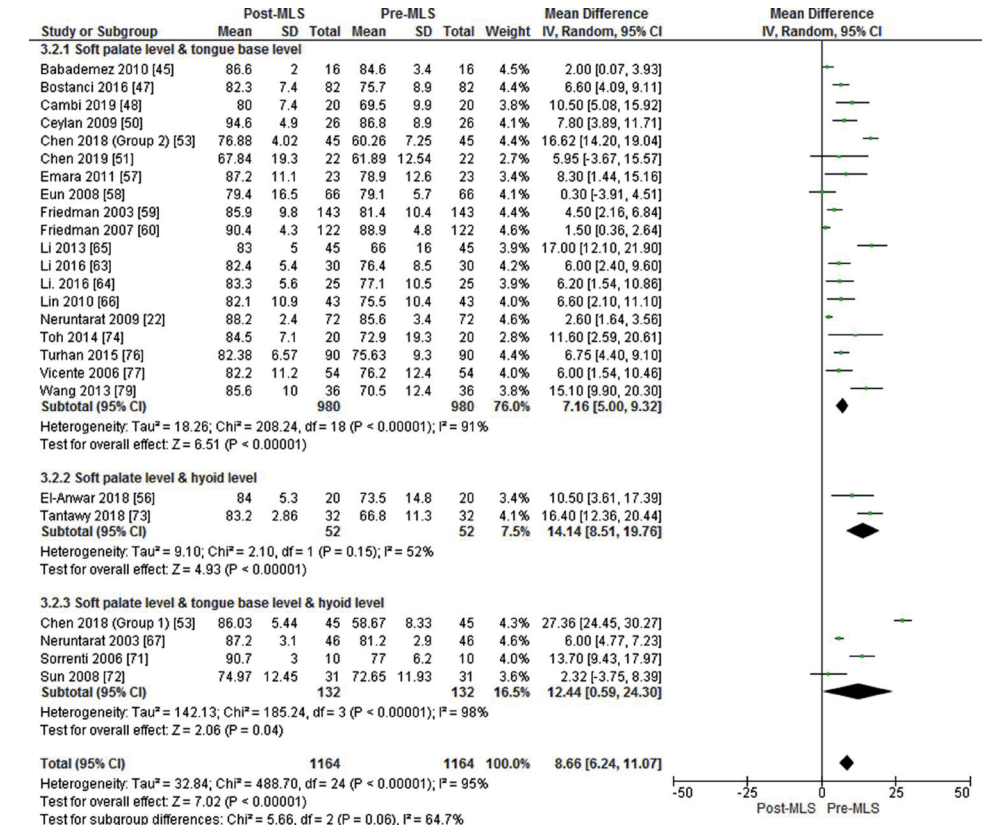


Figure S2.4 Pre- and post-MLS mean difference for apnea-hypopnea index (A), lowest oxygen saturation (B), oxygen desaturation index (C), and Epworth sleepiness scale (D).
CI, confidence interval; MLS, multilevel surgery; SD, standard deviation.

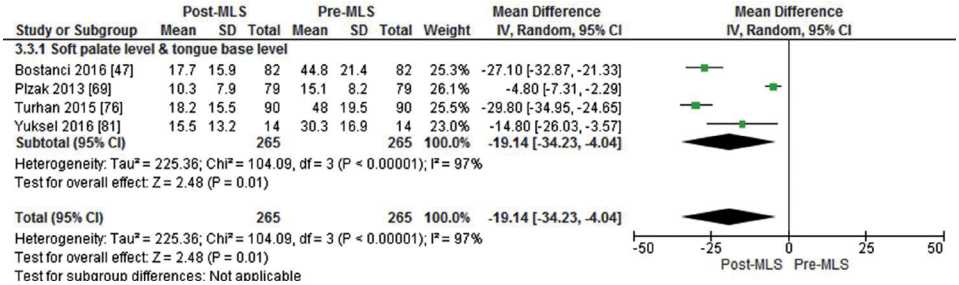
A


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]
Cammaroto 2017 (Group 1) [49] 22.92 13.3 10 34.04 14.03 10 2.1% -11.12 [-23.10, 0.86]
Cammaroto 2017 (Group 2) [49] 9.63 9.25 10 35.59 13.87 10 2.2% -25.96 [-36.29, -15.63]
Cammaroto 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]
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]
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 [-38.95, -9.65]
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] 14.87 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
Bababemez 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]
Plzak 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

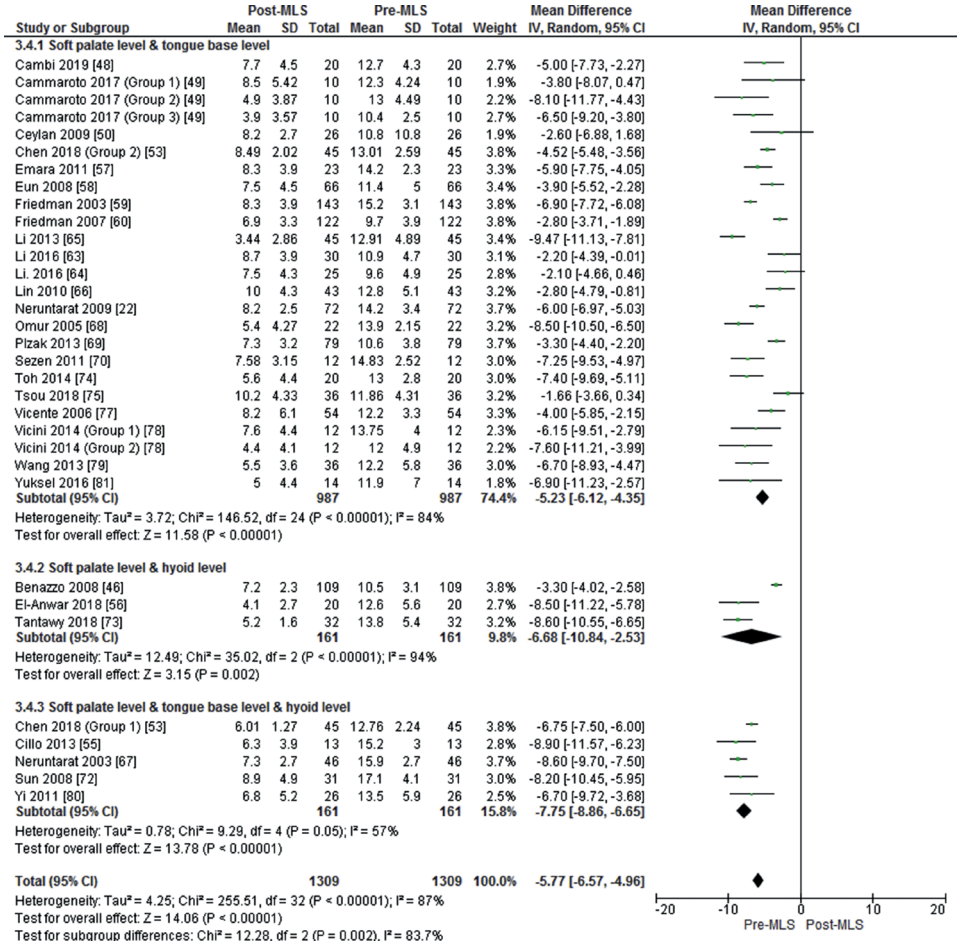
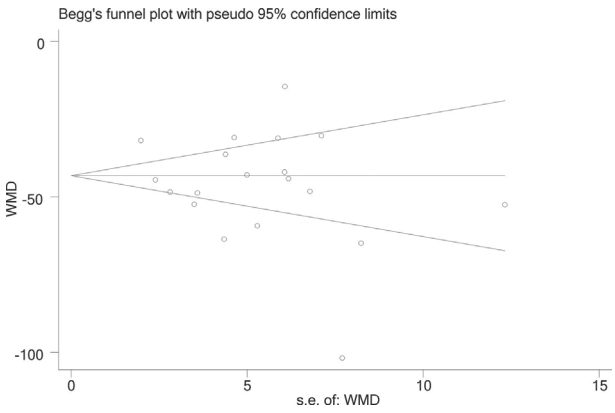


Figure S2.5 Pre- and post-MLS mean difference for apnea-hypopnea index (A), lowest oxygen saturation (B), oxygen desaturation index (C), and Epworth sleepiness scale (D) - three subgroups according to the different target levels of obstructive sites addressed by surgery.
CI, confidence interval; MLS, multilevel surgery; SD, standard deviation.

A



B

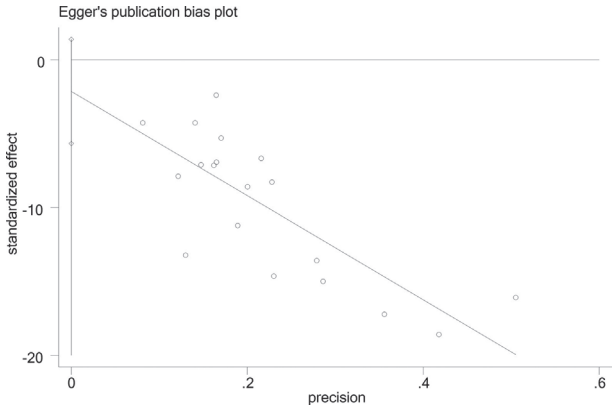
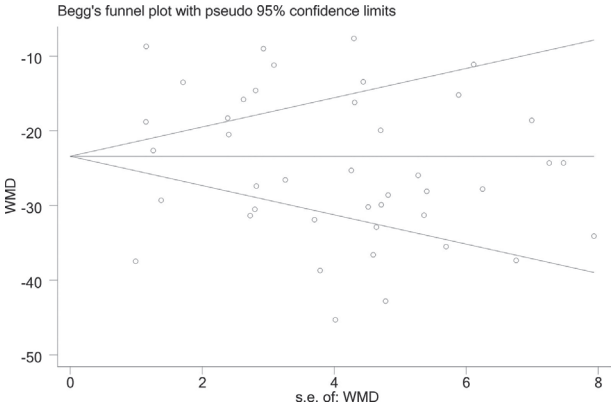


Figure S2.6 Begg's funnel plot (A) and Egger's publication bias plot (B) for all maxillomandibular advancement surgery studies in meta-analysis.
s.e., standard error; WMD, weighted mean difference.

A



B

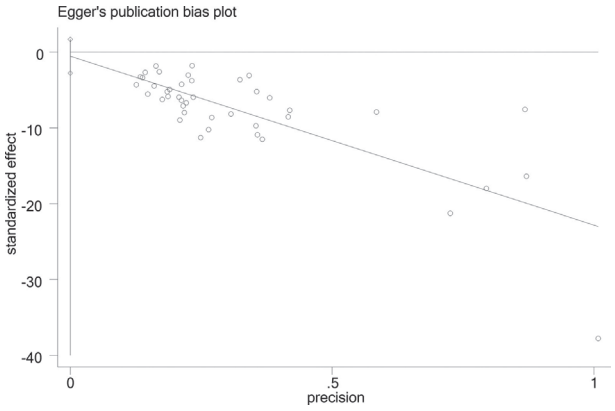


Figure S2.7 Begg's funnel plot (A) and Egger's publication bias plot (B) for all multilevel surgery studies in meta-analysis.
s.e., standard error; WMD, weighted mean difference.

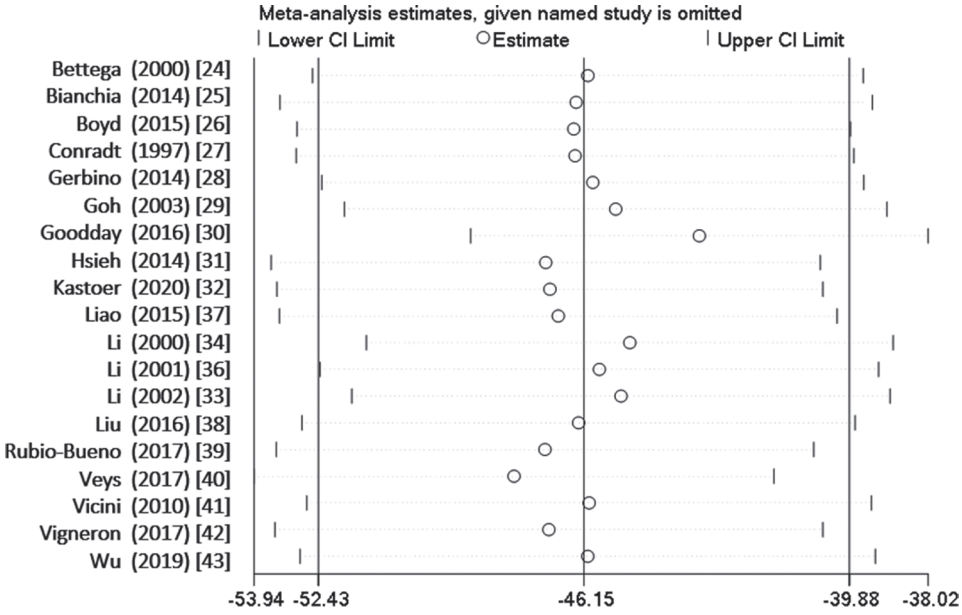


Figure S2.8 Sensitivity analysis of AHI in meta-analysis for maxillomandibular advancement surgery studies. CI, confidence interval.

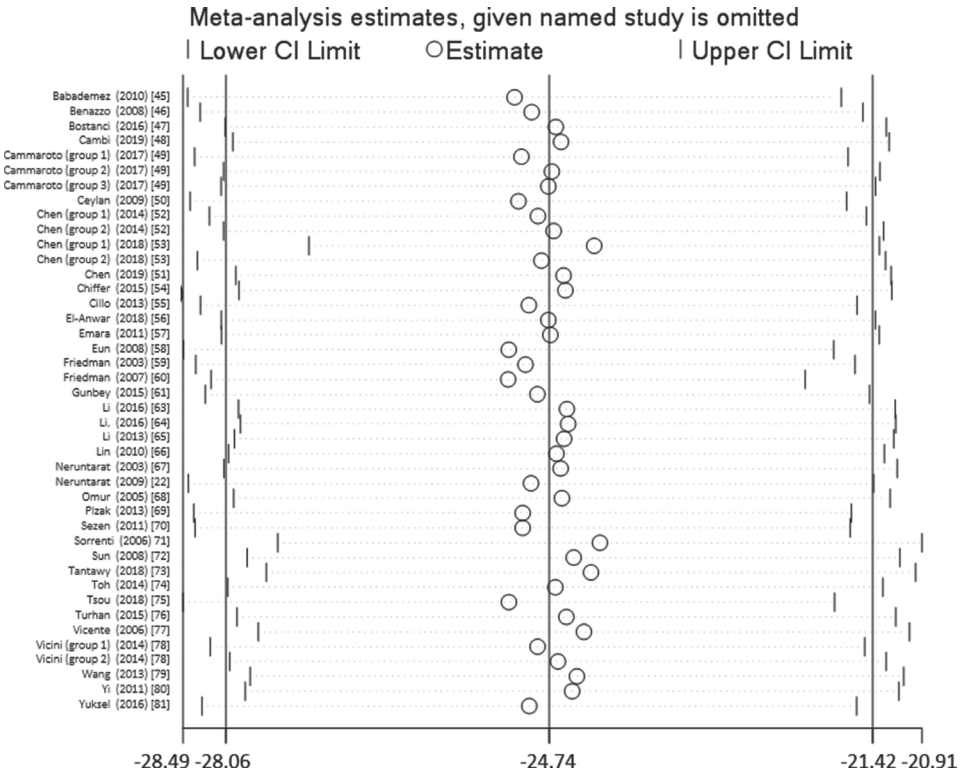
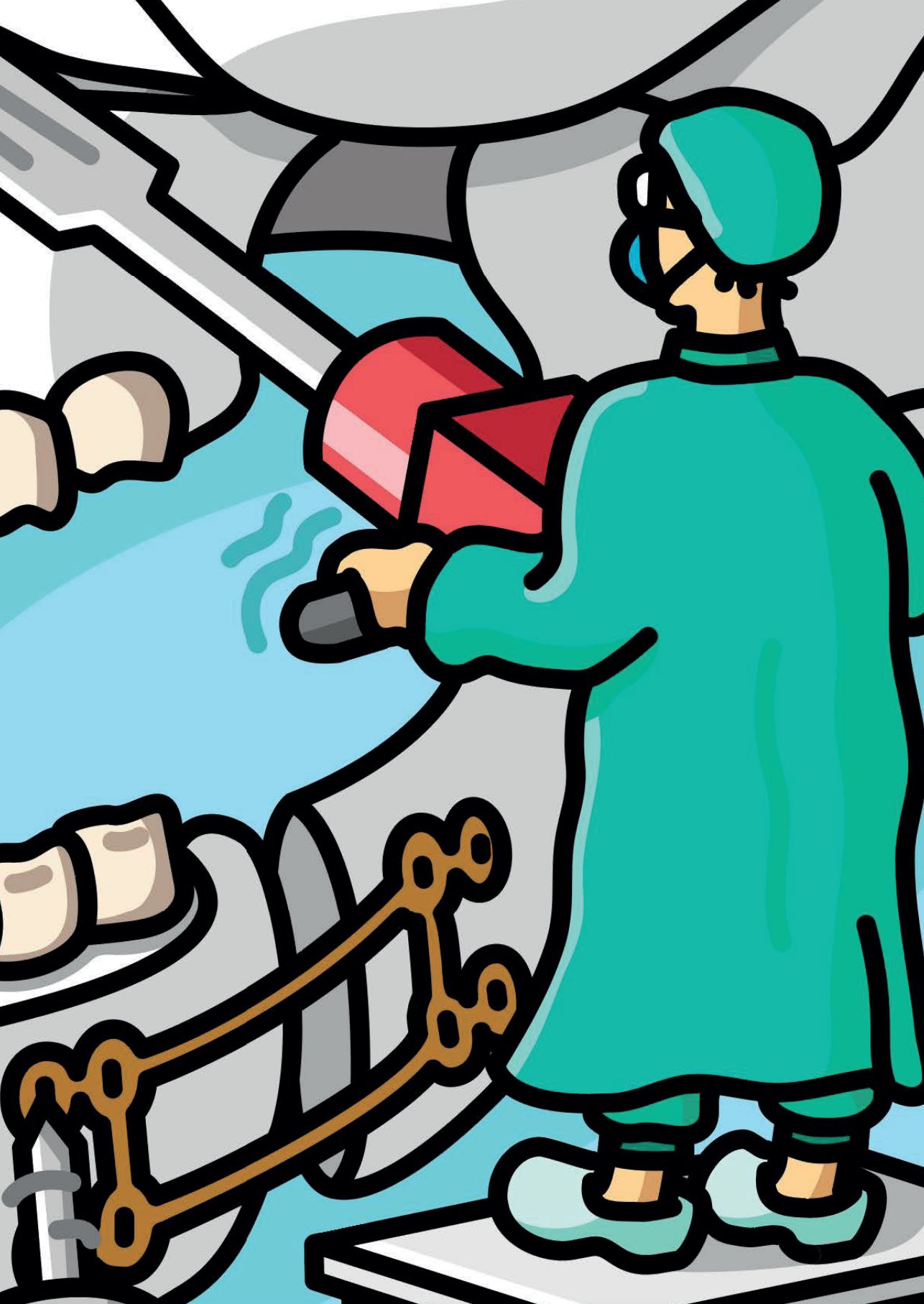


Figure S2.9 Sensitivity analysis of AHI in meta-analysis for multilevel surgery studies. CI, confidence interval.



Chapter 3

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

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Chapter is based on the publication in:

Journal of Clinical Medicine 2022;11:6782

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 database 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 study 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 complications after MMA and UAS were facial paresthesia in the 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.

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 nerves 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 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 is 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.

Materials and 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 systematic review was registered at PROSPERO (PROSPERO ID: CRD42021261394; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=261394 (accessed on 14 November 2022)).

Selection criteria

The inclusion criteria were: (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: (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 14 December 2021. Search terms and search strategies used for each database are available in Supplementary Materials (Table S3.1 (a)).

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 or minor depending on the needs for endoscopic or interventional radiologic procedures or reoperation 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 was 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 and at least 50% reduction in AHI after surgery" [22], and surgical cure was defined as "a postoperative AHI <5" [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 using the I^2 statistic with a 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 3.1. A total of 2952 studies were screened after deduplication, and 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 a weighted age of 42.2 ± 11.5 years and a 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 a longer follow-up period were nested in another included study[38]. The characteristics of these studies are shown in Table 3.1.

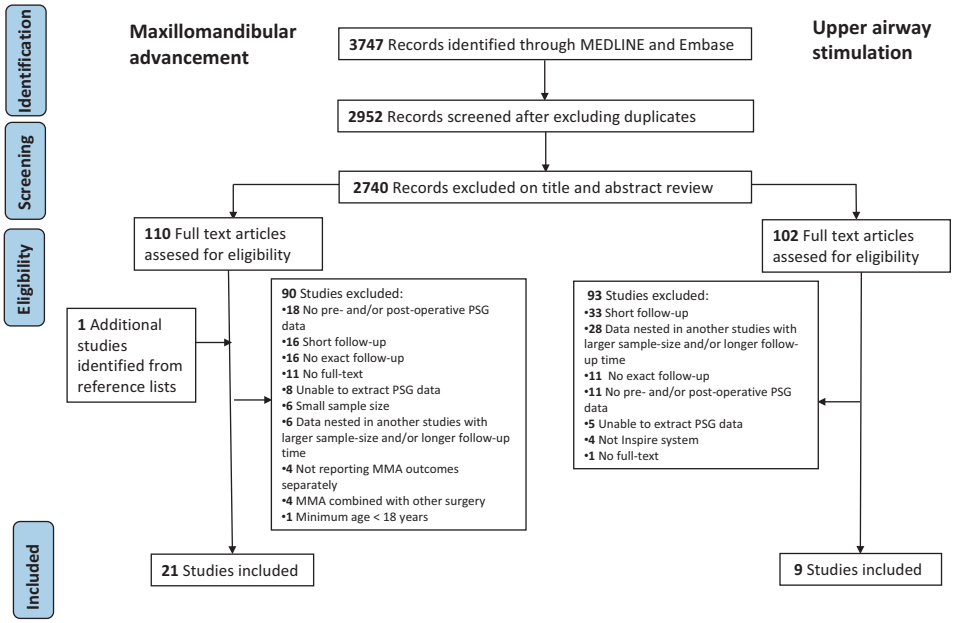

Figure 3.1 PRISMA flow diagram of the study selection process.

UAS group

In total, nine studies[15,48-55] were identified, yielding 1029 patients (male 96.2%) with a weighted age of 55.1 ± 10.1 years and a 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 3.2.

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.

Table 3.1 Characteristics of studies on maxillomandibular advancement.

Study	Design	N	Age (years) (mean±SD)	% Male	Degree of advancement (mm) (mean±SD)		Follow-up (mean±SD)	BMI (mean±SD)		AHI (mean±SD)		ODI (mean±SD)		ESS (mean±SD)		% Success	% Cure
					Max	Mand		Pre-op	Post- op	Pre-op	Post- op	Pre-op	Post- op	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	59.3±29.0	11.1±8.9					75[c]	
Bianchi et al. 2014	Retro	10	45±14	100	10	10	6m			56.8±5.2	12.3±5.5						
Boyd et al. 2015	Pro	14			7.0±2.3	9.2±3.3	6.6±2.8y			50.0±20.0	8.0±10.7						
Conradt et al. 1997	Retro	15	44±12	93.3			>2y	28.3±3.4		51.4±16.9	8.5±9.4						
Gerbino et al. 2014	Pro	10	44.9		9.2±1.2	10.4±2.2	6m	31.6±5.5	28±1.4	69.8±35.2	17.3±16.7	59.5±5.3	9.1±8			80[d]	
Goh et al. 2003	Pro	11	42.8±8.19	100	10	10	7.7m	29.4±4.6	27.2±3.3	70.7±15.9	11.4±7.4					81.8	
Goodday et al. 2016	Retro	13	37.8±8.57	84.6			9.6m	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
Hsieh et al. 2014	Pro	16	33±7.9	75			12±8m	22±3.3		35.7±18	4.8±4.4					100	
Kastoer et al. 2019	Pro	14	51.1±7.3	57.1			6m	25.7±3.7		40.2±25.6	9.9±7.2	13.5±18.6	4.0±3.5	13±6	9±7		
Li et al. 1999	Retro	175	43.5±11.5	83			6m			72.3±26.7[a]	7.2±7.5[a]					95[e]	
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	71.2±27.0[a]	7.6±5.1[a]					90[e]	
Li et al. 2001	Retro	52	46.6±6.7	82.7	10.5±1.5		6m	32.0±6.0		61.6±23.9[a]	9.2±8[a]					90[f]	
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	75.3±26.4[a]	10.4±10.8[a]					83.3[f]	
Liao et al. 2015	Pro	20	33.4±6.5	85			14±9.3m	22.4±3.4		41.6±19.2	5.3±4			11.9±7.3	7±3	100[c]	

Table 3.1 (continued)

Study	Design	N	Age (years) (mean±SD)	% Male	Degree of advancement (mm) (mean±SD)		Follow-up (mean±SD)	BMI (mean±SD)		AHI (mean±SD)		ODI (mean±SD)		ESS (mean±SD)		% Success	% Cure
					Max	Mand		Pre-op	Post- op	Pre-op	Post- op	Pre-op	Post- op	Pre-op	Post- op		
Lin et al. 2020	Pro	53	35.7±11.7	75.7	4.3±2.9	13.3±3.8	24m	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
Liu et al. 2016	Retro	20	44±12	85	7±1.4		6m	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
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	38.3±10.7	6.45±4.33	34.7±12.5	5.4±4.1	17.4±5.4	0.79±1.41	100	52.9
Veys et al. 2017	Pro	10	44.7±9.5	80	4.8±2.8	8.3±2.3	6m			26.8±12.7	12.3±14.4			14.1±5.9	5.7±3.0	70	40
Vicini et al. 2010	RCT	25	49.1±9.1	92		11	13±2.5m	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
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		56.6±24	25.5±20.6				7.5±4.7	41.4	
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		59.3±14.5	10.9±3.3			12.8±2.8	6.9±2.5	85.7	46.4

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 didn't 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.

Table 3.2 Characteristics of studies on upper airway stimulation.

Study	Study Design	N	Age (years) (mean±SD)	% Male	Follow-up (month)	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		
Bachour et al. 2021	Retro	15	52.9±6.6	86.7	18±9.6	29.1±3.3	30.1±4.5	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
Heiser et al. 2017	Pro	20	57±12	100	12	28.1±13.1		28.9±7.6	6.6±5.1						
Philip et al. 2018	Pro	10	52.0±9.4	100	6	28.8±3.3		46.7±12.2	14.5±8.9	38.1±21.1	10.5±9.9	15.9±3.5	10.0±6.1		
Steffen et al. 2019	Retro	18	51.5		24	27.9±4.5	28.0±4.7	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
Steffen et al. 2020	Pro	38	58.0±10.0	97.4	36	29.1±3.9	28.6± 3.3	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
Suurna et al. 2021	Pro	782			14.3±7.0	29.2±4		35.8±15.0	14.5±14.9			11.4±5.5	7.1±4.6	69.7	
Van de Heyning et al. 2012	Pro	28	55.1±9.2	96.4	6	29.5±2.5		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	
Vanderveken et al. 2013	Retro	21	55±11	95.2	6	28±2		38.5±11.8	20.3±20.6			8.2 ± 5.0[a]	6.4 ± 4.3[a]	62	
Woodson et al. 2018	Pro	97	54.4±10.3		60	28.6±2.5		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

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.

Quality assessment

MMA group

One of the included studies was an RCT of MMA and auto titrating positive airway pressure (APAP), one was a retrospective quasi-experimental study, ten were prospective cohort studies, and nine were retrospective cohort studies. As only the 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 the 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 S3.2 (a)).

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 S3.2 (b)).

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/h and a weighted postoperative AHI of 10.1 ± 10.8/h.
Of 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 an ODI reduction but without a p value. The weighted pre- and postoperative ODIs were 35.1 ± 22.8/h and 6.3 ± 6.4/h, respectively.

UAS group

Of the selected studies, the study by 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 an AHI reduction but did not report a P value. The weighted pre- and postoperative AHIs in 1003 patients were 35.2 ± 14.7/h and 15.0 ± 16.1/h, respectively.

Of six studies[15,49-52,55] reporting pre- and postoperative ODI, the study by Bachour et al.[55] did not find 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 ODIs were 26.5 ± 16.0/h and 14.6 ± 18.5/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 values were 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 the Functional Outcomes of Sleep Questionnaire (FOSQ) ($P<0.05$)[30]. Veys et al. assessed the subjective outcome of MMA using the 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 values were 11.4 ± 5.4 (n=1006) and 7.0 ± 4.6 (n=1001), respectively.

Two studies reported pre- and post-UAS FOSQ scores. The STAR trial cohort demonstrated an increase in 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] and ranged from 41.1% to 100%. Surgical cure rate of MMA was reported in seven studies[11,34,42-45,47] and 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] and 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/h. At a mean follow-up of 5.0 years, the weighted postoperative AHI was 11.1 ± 13.0/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/h. At a mean follow-up of 4.2 years, the weighted postoperative AHI was 12.3 ± 14.8/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, 10 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. Additionally, 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 subjectively perceived a decrease in sensation. Facial paresthesia in the 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 ranges 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 serious intraoperative 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 to analyze the minor complication rate. In that study[56], the rates of minor surgery-related and device-related complications 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 the 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 complications were 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 9 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. In this review, the trials for MMA tended to be published earlier than those for UAS. Therefore, for some patients in the UAS group, MMA could have been considered at first as an alternative therapy to CPAP and not been chosen. It should be noted that UAS therapy has stricter and clearer inclusion criteria (e.g., 15/h ± AHI ± 65 /h, absence of CCCp during DISE)[14,17] for patients, especially in comparison to MMA. There is therefore discrepancy of patients' baseline characteristics between the MMA cohort and UAS cohort. In this review, the MMA cohort has younger age and higher baseline AHI compared to the UAS cohort. Moreover, it is impossible for us to compare other patients' characteristics associated with OSA, such as the size of tongue, retrolingual space, and jaw position. 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. Another point to be noted is that the variations in MMA surgeries are

probably greater than in UAS as the training and the lineage of potential variations are much higher in MMA than in UAS.

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 retrolingual opening to stimulation[57]. Therefore, we are of the 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 procedures and the role of pathogenesis of OSA on the outcome of both surgeries require clarification 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 outcome 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) using the Functional Outcomes of Sleep Questionnaire (FOSQ). 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 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 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 levels of patient satisfaction. However, the comparison of improvement in patient-perceived measures between the two therapies must 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 (median 19 years; range 14-20 years) success rate of MMA was 44.44% (4/9). Of the nine patients who attended long-term re-evaluation, the median ages at the time of MMA surgery and re-evaluation were 43 years (range 34-63 years) and 62 years (range 49-82 years), respectively. At the long-term follow up, two of the six patients who were initially successfully treated by MMA had relapse of OSA with AHI comparable to preoperative values. Both patients had significant weight gain (+4.1 and +7.9 kg/m^2). 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. Additionally, they concluded that the good candidates for long-term success of MMA were the young patients (<45 years old) with BMI <25 kg/m^2, AHI < 45/h, SNB angle <75°, narrow retrolingual space (<8 mm), 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 from the last decade, the longest follow-up period of the UAS studies was 5 years, from the STAR trial[15]. The success rates of UAS in the STAR trial cohort were 66% (83/126), 74% (73/98), and 75% (53/71) at 1, 3, and 5 years, respectively.

In UAS therapy for OSA treatment, patients' adherence is necessary to guarantee clinical efficacy[65]. The STAR trial revealed a high adherence to UAS therapy in the long-term, with a 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 treatments for patients with moderate-to-severe OSA. In order to maintain 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 procedures for OSA, with relatively low rates 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 had a history of smoking had higher risk of complications, which included removal of hardware[67]. The most common minor complication of MMA detailed in the literature 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 a large degree of advancement further increases 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. Notably, 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]. Current evidence suggests that both MMA and UAS appear to be safe approaches in OSA treatment, and compared to MMA, treating OSA with UAS may lead to fewer 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. 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. Overnight admission to the 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 patients undergoing MMA for OSA view the change in facial appearance as neutral or 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, the 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]. 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.

Since the primary target patient population differs between MMA and UAS, these two procedures are usually not put on par in the current practice guidelines. In the current Stanford protocol, UAS and MMA are considered phase I and phase II surgical procedures, respectively[74]. It has been proposed that these two procedures might be considered as complementary therapies[17]. For example, UAS may be considered when a patient fails to respond to MMA or for a patient with relapse of OSA after previously successful MMA[75]. It is interesting to note that in a recent study[76], Sarber et al. evaluated the efficacy of UAS therapy in 18 OSA patients who did not meet all FDA criteria for UAS and found promising treatment outcomes. They suggested that future studies must consider the expansion of current FDA criteria for UAS, particularly in BMI and AHI criteria. Thus, to optimize surgical outcomes, reduce rates 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.

In addition to MMA and UAS, there are other evidence-based therapeutic options for OSA, which include behavioral strategies (e.g., weight loss), medical therapy (e.g., CPAP), other surgical options, and adjuvant therapy (e.g., pharyngeal muscle training)[77,78]. Of the non-CPAP therapies for OSA, more invasive procedures, such as MMA, are not well accepted. Oral appliances offer a non-invasive option for managing OSA, the most common of which are mandibular advancement devices (MADs). MADs modify the position of the jaw, the tongue, and other supporting structures of the upper airway, thereby increasing upper airway volume and preventing collapse of the upper airway[79]. MADs are recommended as a first-line therapy for mild-to-moderate OSA and for severe OSA after CPAP failure, intolerance, or refusal[80]. Growing evidence suggests that MADs could achieve favorable outcomes regardless of the severity of OSA[81,82].

In the era of precision medicine, the interconnected risk factors for OSA must be considered in order to achieve precision medicine in OSA[78]. The combined modern therapies for OSA must be adjusted continuously in respect to recent scientific research

in order to deliver the best results for patients, emphasizing their quality of life in addition to medical care. Therefore, any of the therapies may either have an important role as monotherapy in the treatment of OSA or could be used in combination with the other therapies. The greater the complexity of a clinical case, the greater the need for multidisciplinary collaboration.

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[83], except for one RCT and one quasi-experimental trial, 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. Additionally, 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 trials and comparative cohort studies 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 the current literature. Lastly, our review is exclusively based on studies published in English, which can introduce a language bias[84].

Conclusions

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.

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Supplementary tables

Table S3.1a 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 S3.1b 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 S3.2a Methodological appraisal of the individual studies according to MINORS assessment tool – maxillomandibular advancement surgery.

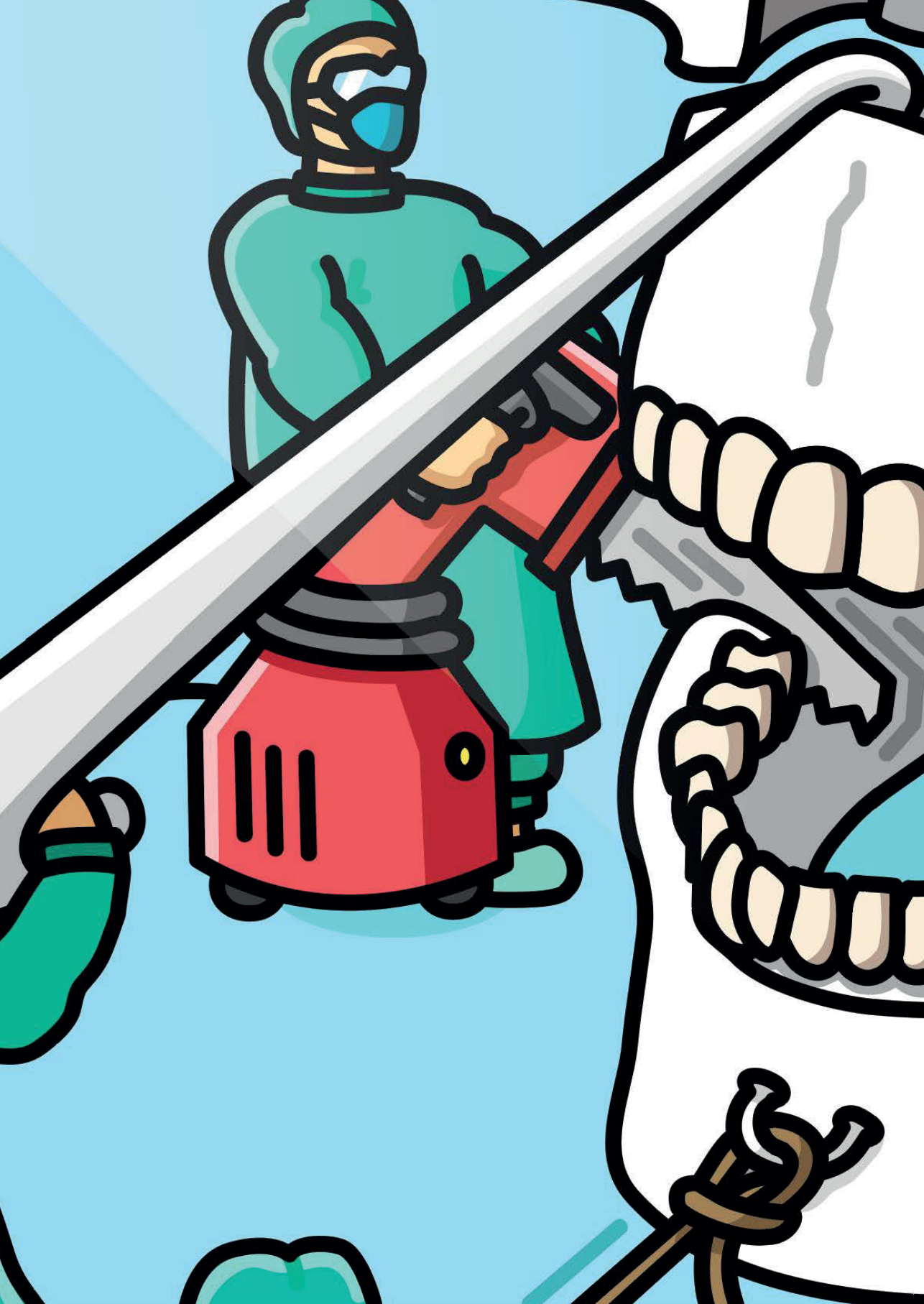
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Total score	Quality
Bettega et al. 2000	2	2	0	2	1	2	2	0					11	Fair
Bianchi et al. 2014	2	2	0	2	1	2	0	0					9	Fair
Boyd et al. 2015	2	2	2	2	1	2	0	2					13	High
Conradt et al. 1997	2	2	0	2	1	2	2	0					11	Fair
Gerbino et al. 2013	2	2	2	2	1	2	2	0					13	High
Goh et 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 S3.2b 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.



Chapter 4

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

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Chapter is based on the publication in:

Sleep and Breathing 2023;27:1567-1576

Abstract

Purpose

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 comprised 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

In 100 patients (82% male; mean age 50.5 years), the mean apnea hypopnea index [AHI] was 53.1 events/h. The rate of favorable surgical response was 67%. Based on multivariate analysis, patients with cardiovascular disease (CVD) had 0.140 times lower odds of a favorable response 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 respond favorably to MMA (OR: 0.828 [0.687, 0.997], *P*=0.047; and 0.724 [0.576, 0.910], *P*=0.006), respectively.

Conclusion

The findings of this study suggest that the surgical outcome of MMA may be less favorable when patients with OSA 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.

Introduction

Maxillomandibular advancement (MMA) is a skeletal surgery for treatment of obstructive sleep apnea (OSA). MMA 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 non-responders to MMA, it is essential and clinically meaningful to identify the potential responders and non-responders 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 remains incomplete. Consequently, the clinicians' ability to predict MMA outcome and pre-select suitable candidates for MMA is limited and is based mainly 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 patients with OSA, from the most common clinically available data (patient-related, polysomnographic, cephalometric, and surgical variables).

Methods and materials

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) the 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 Le Fort 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" [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 4.1; Supplementary Figure S4.1 and Figure S4.2).
To quantify the reliability of the measurements, the same observer repeated the tracings in 20 randomly selected radiographs one month later.

Table 4.1 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.

Maxillomandibular advancement

The MMA procedures were completed by two dedicated OSA surgeons and consisted of a Le Fort 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 non-responders, 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 non-responders. 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) cut-off 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 4.2. 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 non-responders are presented in Supplementary Table S4.1.

Table 4.2 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

Data presented as median (Q1–Q3). AHI, apnea hypopnea index; LSAT, lowest oxygen saturation; n, number of patients; ODI 3%, 3% oxygen desaturation index.
* Statistically significant difference preoperative versus postoperative values (*P* value <0.05)

Baseline and surgical characteristics and surgical response

Compared to responders, the occurrences of hypertension and CVD were significantly higher in non-responders (*P*=0.003 and 0.001, respectively). Preoperative CAI was significantly higher in non-responders (*P*=0.011) (Table 4.3). ICC of the cephalometric analysis ranged from 0.859–0.998, which indicated an excellent intra-observer reliability[15]. Of the cephalometric variables, non-responders had a significantly larger superior-posterior airway space (SPAS; *P*=0.002) than responders (Table 4.4). There

were no significant differences between responders and non-responders in the other baseline characteristics. In terms of surgical characteristics, no significant difference was found between responders and non-responders (Table 4.4).

Table 4.3 Patient-related variables and polysomnographic variables in responders and non-responders.

Variable	Responder (n=67)	Non-responder (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			
I	17 (25.4%)	6 (18.2%)	
II	38 (56.7%)	18 (54.5%)	0.487
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)	
5-8 lost teeth	28 (41.8)	13 (39.4)	0.527
9-31 lost teeth	16 (23.9)	10 (30.3)	
32 lost teeth	8 (11.9)	6 (18.2)	
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

Continuous data presented as mean ± standard deviation or median (Q1–Q3), categorical data presented as number with percentage. 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.

* Statistically significant difference responders versus non-responders (*P* value <0.05)

[a] Number of patients =55

[b] Number of patients =29.

Table 4.4 Cephalometric variables and surgical variables in responders and non-responders.

Variable	Responder	Non-responder	*P*-value
Cephalometric variables (responder: n=64; non-responder: 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			
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; non-responder: 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)	

Continuous data presented as mean ± standard deviation or median (Q1–Q3), categorical data presented as number with percentage. 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.
* Statistically significant difference responders versus non-responders (*P* value <0.05)

Prediction of surgical response

The univariate analyses revealed six independent variables with a *P* value <0.1 (Supplementary Table S4.2). After collinearity diagnostics test, all the six variables were

included in the multivariate model, including age, hypertension, CVD, CAI, ANB, and SPAS (Table 4.5).

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).

Table 4.5 Logistic regression model for predicting surgical response to maxillomandibular advancement.

Univariate analysis					**Multivariate analysis (adjusted for the covariables: gender, BMI, AHI, advancement of A-point, and advancement of B-point)**			
Independent variable	**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.			
Presence	-1.465	0.454	0.231 (0.095-0.563)	0.001	-1.964	0.662	0.140 (0.038-0.513)	0.003
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.

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% —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 patients with OSA 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 non-responders (6% (4/67) vs. 9% (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 group and predominant OSA group have equally elevated upper airway collapsibility (i.e., critical closing pressure [Pcrit]); however, the patients with predominant OSA differed from the patients with pure OSA in showing less breathing control stability[23]. The finding that patients with OSA and 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 or not treatment for central respiratory instability in patients with predominant OSA 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 patients with OSA. 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 ± 1.7 mm, *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 patients with OSA and 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 patients with OSA and 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 cases of OSA 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 allow 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, the findings suggest 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.

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Supplementary information

Table S4.1 Preoperative and postoperative polysomnographic values and upper airway measurements in responders and non-responders.

Variables	Responder (n=67)	Non-responder (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 non-responders; $P<0.05$ was considered statistically significant.

Table S4.2 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
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

Table S4.2 (continued)

Variable	Coefficient B	SE	OR (95%CI)	*P*-value
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	0.071	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
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.

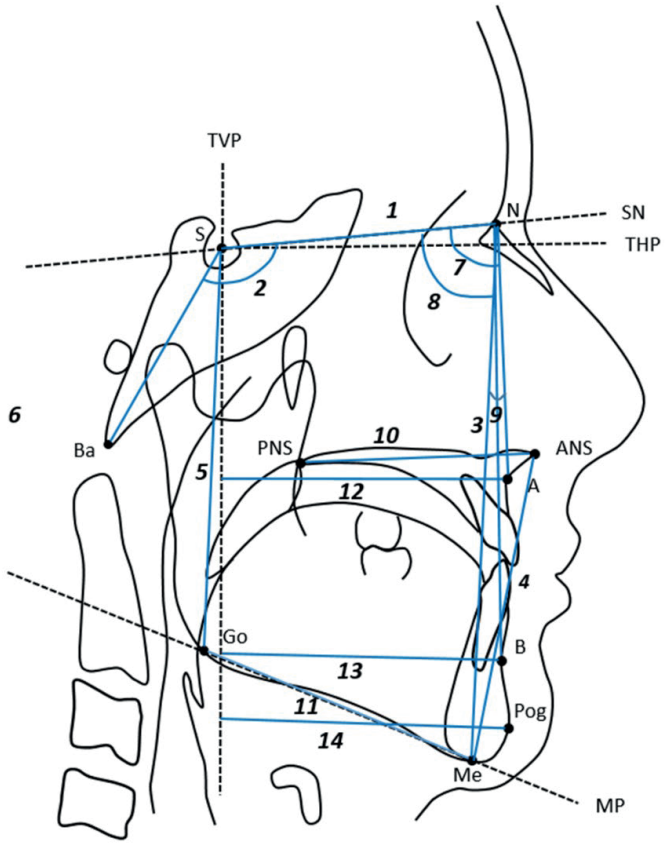


Figure S4.1 **Landmarks, reference lines, and the corresponding hard tissue variables used in the study.** Landmarks: A, A-point (subspinale); ANS, anterior nasal spine; B, B-point (supramentale); Ba, basion; Go, gonion; Me, menton; N, nasion; PNS, posterior nasal spine; Pog, pogonion; S, sella. Reference 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

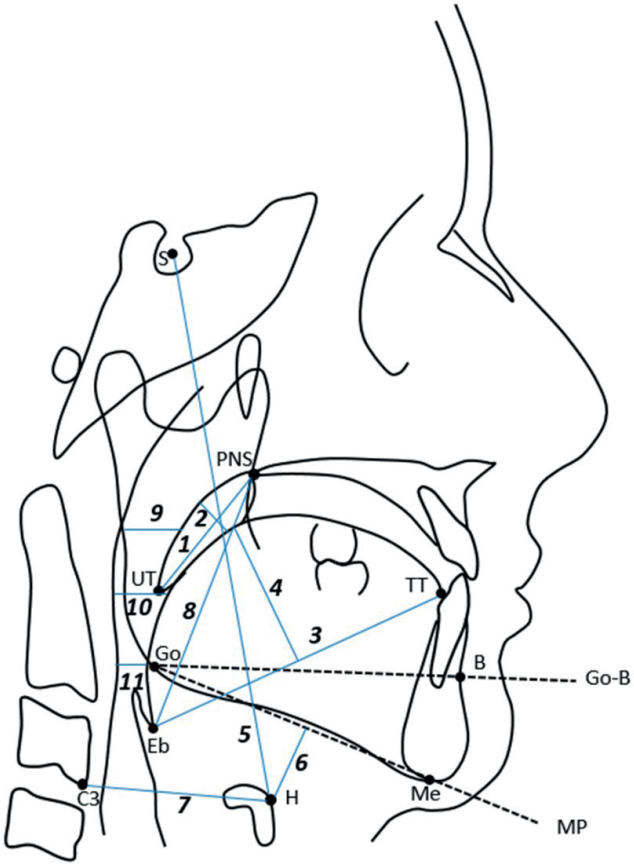
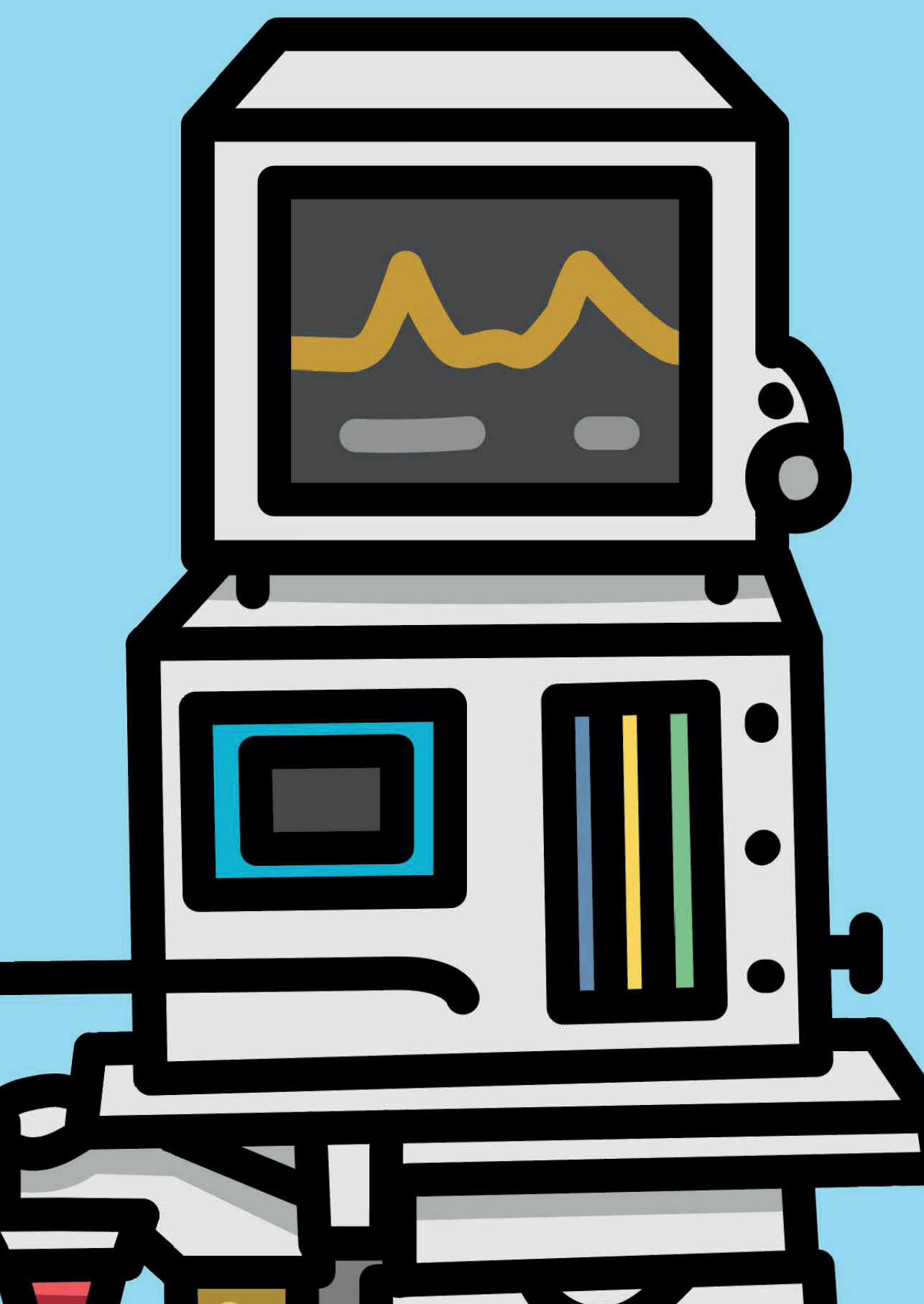


Figure S4.2 **Landmarks, reference lines, and the corresponding soft tissue variables used in the study.** Landmarks: B, B-point (supramentale); C3, the most anterior-inferior point of the third cervical vertebra; Eb, epiglottis base; Go, gonion; H, hyoid point; Me, menton; UT, uvula tip; PNS, posterior 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)



Chapter 5

Central and mixed sleep apnea related to patients treated with maxillomandibular advancement for obstructive sleep apnea: A retrospective cohort study

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Chapter is based on the publication in:

Journal of Cranio-Maxillo-Facial Surgery 2022;50(7):537-542

Abstract

The aim of this study was to evaluate the clinical efficacy of maxillomandibular advancement (MMA) for obstructive sleep apnea (OSA) patients with a percentage of central and mixed apnea index in the total apnea-hypopnea index (CMAI%) ≧25%.

Patients treated with MMA for OSA were retrospectively evaluated for baseline and postoperative patient data and polysomnographic results. The pre- and postoperative obstructive, central and mixed apnea parameters were compared.

Of the included 78 patients, 21 patients (27%) presented with CMAI% ≧25% (median CMAI%, 49.1%; 35.9-63.8) prior to MMA. In 67% of these cases, MMA resulted in CMAI% <25 (median CMAI%, 6.1%; 2.1 -8.9) and significantly improved the apnea-hypopnea index (AHI) (P<0.001), the lowest oxyhemoglobin saturation (P<0.001), central and mixed apnea index (P<0.001), percentage of central and mixed apneas of total AHI (P=0.004), central apnea index (P<0.001), and mixed apnea index (P<0.001). CMAI % ≧25% emerged in 25% of patients after MMA (median CMAI%, 49.1%; 35.9-63.8).

Within the undeniable limitations of the study, it seems that the presence of CMAI% ≧25% should not be regarded as a contraindication for MMA in OSA patients.

Introduction

Obstructive sleep apnea (OSA) is a disorder in which the patient has recurrent events of upper airway collapse and obstruction. This leads to periods of absent and/or reduced respirations during sleep, also called apneas or hypopneas[1].
Ever since its inception in 1981, continuous positive airway pressure (CPAP) has been considered the gold standard for nonsurgical management of OSA[2-4]. Despite the efficacy and the advantages of CPAP, adherence to CPAP is not optimal, specifically in the long term[5,6].
As an alternative for patients who are not willing and/or able to adhere to CPAP, maxillomandibular advancement (MMA), in which the maxilla and mandible are advanced and rotated counter-clockwise by performing a combination of a Le Fort I osteotomy and a bilateral sagittal split osteotomy, might offer a surgical solution[3,7-9]. MMA has provided considerable success rates comparable to those of CPAP, ranging from 83% to 100%[10-13].
In addition to obstructive sleep apnea, some individuals may exhibit characteristics of both obstructive and central sleep apnea, called mixed apnea. Considering the different pathophysiological mechanisms between the central and obstructive components of sleep apnea, most sleep surgeons are reluctant to perform surgery on the upper airway in OSA patients who also present with a large extent of central and mixed apneas. The percentage of central and mixed apnea index of the total apnea-hypopnea index (CMAI%) ≧25% is also considered to be a negative predictor for certain OSA treatments, namely upper airway stimulation, and is therefore generally considered to be an exclusion criterion for upper airway stimulation[14,15]. However, the effect of the presence of CMAI ≧25% on MMA outcome remains unknown.
The aim of this study was to evaluate the clinical efficacy of MMA for OSA patients with the presence of CMAI% ≧25%.

Materials and methods

This study was deemed not to be subject to the Medical Research Human Subjects Act by the Medical Ethics Committee of the Amsterdam University Medical Centers (UMC), location Academic Medical Center (AMC) (reference number W21_012 # 21.014). Therefore, a formal approval was waived. Patients were sent a letter to inform them that their medical records, polysomnography results and radiological images were going to be used for study purposes. They were given the option to object and to opt out of inclusion in the study. No additional medical information was requested from these patients. This study was performed in accordance with the Declaration of Helsinki

guidelines for human research, 1964, and amended in 2013 (64th WMA General Assembly, Fortaleza, Brazil). It was conducted at the Department of Oral and Maxillofacial Surgery of the Amsterdam UMC, location AMC, The Netherlands.

Study population

Consecutive patients who were treated for OSA with MMA between 2011 and 2020 at the Department of Oral and Maxillofacial Surgery at the Amsterdam UMC, location AMC, and who met the inclusion criteria for this study were eligible for our study. The inclusion criteria were as follows: 1) patients 18 years of age or older; 2) presence of mild to severe OSA with an apnea-hypopnea index (AHI) ≧5 events/h as determined by a preoperative polysomnography; 3) refusal to start and/or unable to tolerate or continue CPAP therapy; 4) completion of MMA for treatment of OSA; and 5) presence of a polysomnography at least 3 months postoperatively. Exclusion criteria were as follows: 1) patients who declined to agree to the use of their patient record data for research purposes; 2) patients who underwent other adjunctive procedures at the time of MMA (e.g., multi-piece Le Fort osteotomy, temporomandibular joint reconstruction); and 3) previous history of Le Fort I osteotomy or bilateral sagittal split osteotomy, cleft palate and syndromic patients. The included patients' medical records were reviewed and data were collated. Preoperative (baseline) patient data included sex, age, body mass index (BMI), and neck circumference in centimeters (cm).

Maxillomandibular advancement surgery

MMA surgery consisted of a Le Fort I osteotomy for the maxilla and Hunsuck-Dal Pont modification of the Obwegeser bilateral sagittal split osteotomy for the mandible. The bimaxillary complex was advanced and, in certain cases, counter-clockwise rotation was applied[8]. Earlier patients were treated with a conventional two-dimensionally planned operation with manually manufactured occlusal splints. Treatment of more recent patients was virtually planned, and computer-aided design/computer-aided manufacturing intraoperative occlusal splints were used[16]. Due to the increased risk of complications after significant surgical upper airway alteration, all patients received extensive postoperative monitoring in either the intensive or the medium care unit[17-19]. After being discharged from the intensive or medium care unit, the patients were transferred to a general post-surgery ward in order to recover further[20].

Polysomnography

The included level 1 and 2 sleep studies were performed at least 3 months postoperatively, interpreted and scored by a clinical neurophysiologist specialized in

scoring sleep studies, based on the latest version of the AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications, at the time that the sleep study was conducted[21,22]. The preoperative and postoperative polysomnography variables collected included apnea-hypopnea index (AHI), lowest oxyhemoglobin saturation (LSAT), central apnea index (CAI), mixed apnea index (MAI), central and mixed apnea index (CMAI), and percentage of central and mixed apneas of the total AHI (CMAI%). Surgical success was defined according to the Sher criteria, with an AHI reduction of at least 50% and an AHI below 20[23].

Radiographic cephalometric measurements

A standard lateral cephalogram was taken before and at least 1 week after surgery. Steiner radiographic cephalometric analyses were performed with Viewbox (version 4; dHAL Software, Kifissia, Greece). The cephalometric variables included the skeletal landmarks of sella (S), nasion (N), A-point (A), B-point (B), and pogonion (Pog)[24] (Supplementary data Figure S5.1). The preoperative and postoperative lateral cephalometric data consisted of SNA, SNB, ANB, PAS (distance between the base of the tongue and the posterior pharyngeal wall, derived from a line connecting B-point to gonion in millimeters [mm]), advancement of A-point, advancement of B-point, and advancement of pogonion.

Statistical analysis

Statistical analysis was performed using SPSS (version 26.0; IBM Corp., Armonk, NY, USA). Descriptive statistical analysis was performed for all demographic and outcome variables. Demographic variables were reported as the mean in conjunction with the standard deviation and the range. The outcome variables were reported as the median and interquartile range (IQR) for continuous variables, and frequency and percentage for categorical variables. Cephalometric measurement outcomes were reported as the mean with the standard deviation and the range. Normality was tested using the Shapiro-Wilk test. To compare the paired continuous data, the paired-sample t-test was used when the data were normally distributed, whereas the Wilcoxon signed rank test was used when the data were not normally distributed. For all analyses, a *P* value of less than 0.01 was considered statistically significant.

Results

Baseline demographic characteristics are shown in Table 5.1. In total, 78 patients were included in our study. There were 63 male (81%) and 15 female (19%) patients. The

mean age was 51.7 ± 9.0 (31-75) years. The mean BMI was 29.1 ± 3.9 (18.0-37.9) kg/m^2 and the mean neck circumference was 42.3 ± 4.0 (30.0-49.0) cm. Preoperatively, 21 of the 78 patients (27%) had CMAI% ≧25%, including 19 male (91%) and 2 female (9%) patients. For this group, the mean age was 50.0 ± 9.3 (36-70) years, the mean BMI was 28.4 ± 3.8 (18.7-34.7) kg/m^2, and the mean neck circumference was 42.8 ± 3.8 (33.0-48.0) cm. There was no significant difference in baseline characteristics between the included study population versus the excluded population (Supplementary data Table S5.1).

Table 5.1 Demographic variables of the study population.

Demographic variable	Total study population	Pre-op CMAI% <25%	Pre-op CMAI% ≧25%
Number of patients(*n*)	78	57	21
Age (years)			
Mean ± SD	51.7 ± 9.0	52.5 ± 8.9	50.0 ± 9.3
Range	31.0–75.0	31.0–75.0	36.0–70.0
Gender			
Male (*n*)	63	44	19
Female (*n*)	15	13	2
BMI (kg/m^2)			
Mean ± SD	29.1 ± 3.9	29.3 ± 4.0	28.4 ± 3.8
Range	18.0–37.9	18.0–37.9	18.7–34.7
Neck circumference (cm)			
Mean ± SD	42.3 ± 4.0	42.1 ± 4.2	42.8 ± 3.8
Range	30.0–49.0	30.0–49.0	33.0–48.0

Number of patients and sex are presented as number of persons. Age, BMI and neck circumference are presented as mean with SD and range in years, kg/m^2 and cm respectively. BMI, body mass index; cm, centimeters; CMAI%, percentage of central and mixed apneas of total apnea-hypopnea index; kg/m^2, kilograms per square meter; SD, standard deviation.

The preoperative and postoperative polysomnography results for the study population are presented in Tables 5.2 and 5.3. The postoperative polysomnography studies were performed at 5.0 ± 2.7 months after MMA. For the total study population, both the median preoperative AHI and the LSAT improved significantly after MMA (P<0.01). This was in line with the median central and mixed apnea parameters, namely CAI, MAI and CMAI, which all improved significantly postoperatively, except for CMAI%, which increased from 7.1% (IQR, 1.9-31.2%) before MMA to 7.4% (IQR, 1.5-26.7%) after MMA (P<0.01).

Table 5.2 Preoperative and postoperative polysomnography results for the total population, and subpopulation with CMAI% <25 and ≧25 prior to MMA.

	Pre-op	Post-op	*P*
Total study population			
AHI (events/h)	51.2 (36.5–69.0)	13.1 (6.7–23.9)	<0.001
LSAT (%)	79.0 (73.0–84.0)	86.0 (82.0–89.0)	<0.001
CMAI (events/h)	4.0 (0.7–13.0)	0.8 (0.2–2.8)	<0.001
CMAI% (%)	7.1 (1.9–31.2)	7.4 (1.5–26.7)	0.918
CAI (events/h)	0.6 (0.2–2.0)	0.3 (0.0–0.9)	0.002
MAI (events/h)	2.3 (0.1–10.3)	0.3 (0.0–1.7)	<0.001
Patients with pre-op CMAI% ≧25			
AHI (events/h)	59.0 (38.0–76.7)	17.2 (7.2–33.5)	<0.001
LSAT (%)	80.0 (73.5–85.5)	86.0 (83.5–89.5)	<0.001
CMAI (events/h)	25.8 (16.6–37.7)	1.3 (0.6–6.8)	<0.001
CMAI% (%)	49.1 (35.9–63.8)	8.3 (5.5–34.8)	0.004
CAI (events/h)	3.4 (1.4–7.6)	0.3 (0.1–1.0)	<0.001
MAI (events/h)	19.2 (13.1–34.6)	0.6 (0.3–5.0)	<0.001
Patients with pre-op CMAI% <25			
AHI (events/h)	47.1 (34.0–64.4)	12.5 (6.4–20.6)	<0.001
LSAT (%)	79.0 (73.0–84.5)	86.0 (81.0–89.0)	<0.001
CMAI (events/h)	1.8 (0.4–37.7)	0.7 (0.1–2.5)	0.153
CMAI% (%)	4.2 (1.0–7.5)	7.1 (0.7–23.0)	0.001
CAI (events/h)	0.4 (0.1–1.0)	0.2 (0.0–1.0)	0.532
MAI (events/h)	0.7 (0.0–3.6)	0.1 (0.0–1.5)	0.240

Polysomnography results are presented as median events per hour or percentage with IQR (Q1-Q3). A value of *P*<0.05 was considered statistically significant. AHI, apnea-hypopnea index; CAI, central apnea index; CMAI, central and mixed apnea index; CMAI%, percentage of central and mixed apneas of total AHI; events/h, events per hour; IQR, interquartile range; Postop, postoperative (after MMA); Preop, preoperative (before MMA); LSAT, lowest oxygen saturation; MAI, mixed apnea index; MMA, maxillomandibular advancement; Q1-Q3, quartile 1 to quartile 3.

For the 21 patients with a preoperative CMAI% ≧25%, the median AHI and median LSAT improved significantly after MMA (*P*<0.01). The median preoperative CAI, MAI, CMAI and CMAI% were all significantly reduced after MMA (*P*<0.01). Surgical success was achieved in 10 of these 21 patients (48%) (Table 5.3). Postoperatively, only 7 patients (33%) still had CMAI% ≧25%. In 2 of these 7 (29%) patients with persistent CMAI% ≧25% after MMA, surgical success was still achieved (Table 5.3).

On the other hand, 57 of the 78 patients (73%) had a preoperative CMAI% <25%. In this group MMA significantly improved both AHI and LSAT (*P*<0.01) (Table 5.3). In 14 patients (25%), an emergence of CMAI% ≧25% was present after MMA. These 14 patients had a preoperative median AHI of 40.9 (IQR, 29.3-65.8) events/h, with a median LSAT of 80.5% (IQR, 74.8-85.3%). Although there was an increase in CMAI% ≧25% after MMA, in all of these 14 patients both median AHI and median LSAT improved to 19.5 (IQR, 8.9-33.9) events/h and 84.0% (IQR, 80.8-88.0%), respectively. In 7 of these 14 (50%) patients with new-onset CMAI% ≧25% after MMA, surgical success was achieved (Table 5.3).

Table 5.3 Polysomnography results before and after MMA for total population, and subpopulation with a CMAI% <25 and ≧ 25 before and after MMA.

	Total population			Pre-op CMAI%<25			Pre-op CMAI%≧25		
	Complete group	Post-op CMAI%<25	Post-op CMAI%≧25	Complete group	Post-op CMAI%<25	Post-op CMAI%≧25	Complete group	Post-op CMAI%<25	Post-op CMAI%≧25
Number of patients	78 (100)	57 (73)	21 (27)	57 (100)	43 (75)	14 (25)	21 (100)	14 (67)	7 (33)
Pre-op AHI (events/h)	51.2 (36.5–69.0)	51.7 (36.5–68.3)	47.7 (34.8–73.5)	47.1 (34.0–64.4)	47.8 (36.2–68.1)	40.9 (29.3–65.8)	59 (37.6–74.6)	59 (36.8–68.4)	64.8 (37.6–85.3)
Post-op AHI (events/h)	13.1 (6.7–23.9)	11.7 (6.4–17.8)	24.1 (10.5–37.6)	12.5 (6.4–20.6)	11.1 (5.6–16.7)	19.5 (8.9–33.9)	17.2 (7.2–33.5)	13.8 (7.2–30.7)	34.6 (18.7–47.2)
Pre-op LSAT (%)	79.0 (73.0–84.0)	78.0 (73.0–84.0)	80.5 (74.3–85.8)	79.0 (73.0–84.0)	78 (71.5–83.0)	80.5 (74.8–85.3)	80.0 (73.5–85.5)	80 (75.3–84.5)	79.5 (58.0–87.0)
Post-op LSAT (%)	86.0 (82.0–89.0)	87.0 (83.0–89.0)	84.0 (80.3–88.0)	86.0 (81.0–89.0)	86.0 (82.5–89.0)	84.0 (80.8–88.0)	86 (82.0–89.0)	87 (85.0–88.5)	84 (67.8 0 90.3)
Pre-op CMAI (events/h)	4.0 (0.7–13.0)	2.6 (0.8–9.5)	7.7 (0.4–20.4)	1.8 (0.4–5.0)	1.8 (0.4–4.0)	3.5 (0.1–7.8)	25.8 (16.6–37.7)	25.5 (15.3–40.1)	26.8 (16.7–42.5)
Post-op CMAI (events/h)	0.8 (0.2–2.8)	0.4 (0.1–1.2)	10 (3.5–16.7)	0.7 0.1–2.5)	0.3 (0.0–1.0)	8.0 (3.9–16.5)	1.3 (0.6–6.8)	0.8 (0.4–1.4)	11.9 (7.8–23.8)
Pre-op CMAI% (%)	7.1 (1.9–31.2)	6.8 (1.9–24.8)	15.5 (2.5–40.6)	4.2 (1.0–7.5)	3.9 (1.1–7.1)	8.4 (0.8–16.2)	49.1 (35.9–63.8)	51.3 (35.7–66.3)	48.2 (43.4–62.3)
Post-op CMAI% (%)	7.4 (1.5–26.7)	5.5 (0.2–8.2)	42.9 (29.3–69.0)	7.1 (0.7–23.0)	3.7 (0.0 -8.1)	42.6 (29.3–68.2)	8.3 (5.5–34.8)	6.1 (2.1–8.9)	42.4 (28.2–57.3)
Pre-op CAI (events/h)	0.6 (0.2–2.0)	0.5 (0.2–1.5)	1.0 (0.2–6.3)	0.4 (0.1–1.0)	0.3 (0.2–0.7)	0.4 (0.1–1.6)	3.4 (1.4–7.6)	2.7 (1.3–7.7)	6.7 (5.4–11.2)
Post-op CAI (events/h)	0.3 (0.0–0.9)	0.1 (0.0–0.4)	1.3 (0.5–2.8)	0.2 (0.0–1.0)	0.1 (0.0–0.7)	1.5 (0.5–2.7)	0.3 (0.1–1.0)	0.1 (0.0–0.3)	1.9 (0.4–3.0)
Pre-op MAI (events/h)	2.3 (0.1–10.3)	1.9 (0.2–8.2)	6.7 (0.1–13.2)	0.7 (0.0–3.6)	0.7 (0.0–3.4)	1.3 (0.0–6.7)	19.2 (13.1–34.6)	21.9 (13.6–36.5)	15.2 (11.0–32.0)
Post-op MAI (events/h)	0.3 (0.0–1.7)	0.1 (0.0–0.6)	6.6 (1.8–14.9)	0.1 (0.0–1.5)	0.0 (0.0–0.3)	5.4 (2.0–14.7)	0.6 (0.3–5.0)	0.5 (0.3–1.2)	10.3 (5.0–22.9)
Surgical success (%)	47 (61)	38 (67)	9 (43)	37 (65)	30 (70)	7 (50)	10 (48)	8 (57)	2 (29)

The number of patients and surgical successes are reported as number with percentage (%). Polysomnography results are presented as median events/h or percentage with IQR (Q1-Q3). AHI, apnea-hypopnea index; events/h, events per hour; CAI, central apnea index; CMAI, central and mixed apnea index; CMAI%, percentage of central and mixed apneas of total AHI; IQR, interquartile range; Postop, postoperative (after MMA); Preop, preoperative (before MMA); LSAT, lowest oxygen saturation; MAI, mixed apnea index; MMA, maxillomandibular advancement; Q1-Q3, quartile 1 to quartile 3.

The median preoperative CAI for the total population was 0.6 (IQR, 0.2-2.0) events/h and was statistically significantly reduced to 0.3 (IQR, 0-0.9) events/h after MMA (*P*<0.01). Of the 78 patients, only 1 patient (1%) was found to have the appearance of a CAI ≧5 events/h after MMA (Table 5.4).

Table 5.4 Preoperative and postoperative polysomnography results for the one patient with the emergence of CAI of ≧5 events/h after MMA.

Sex	**M**
Age (years)	54
BMI (kg/m^2)	19.7
Neck circumference (cm)	37
Pre-op AHI (events/h)	12.9
Post-op AHI (events/h)	32.9
Pre-op LSAT (%)	86
Post-op LSAT (%)	80
Pre-op CMAI (events/h)	0.4
Post-op CMAI (events/h)	13.5
Pre-op CMAI% (%)	3.1
Post-op CMAI% (%)	40.9
Pre-op CAI (events/h)	0.0
Post-op CAI (events/h)	5.6
Pre-op MAI (events/h)	0.4
Post-op MAI (events/h)	7.9

Polysomnography results are presented as events/h or percentage. AHI, apnea-hypopnea index; BMI, body mass index; cm, centimeters; CAI, central apnea index; CMAI, central and mixed apnea index; CMAI%, percentage of central and mixed apneas of total AHI; events/h, events/h; kg/m^2, kilograms per square meter; LSAT, lowest oxygen saturation; M, male; MAI, mixed apnea index; Postop, postoperative (after MMA); Preop, preoperative (before MMA).

Discussion

Little is known about the association between central and/or mixed apnea – specifically, the percentage of the central and mixed apnea index of the total apnea-hypopnea index (CMAI%) ≧25% – and maxillomandibular advancement (MMA) in obstructive sleep apnea (OSA) patients.

In the present study, there was no statistically significant difference between the efficacy of MMA between patients with and without CMAI% ≧25% (*P*=0.166). This supports the notion that the presence of CMAI% ≧25% is not an absolute contraindication for the surgical success of MMA. However, compared to the high surgical success rates (85%) reported for MMA in a recent meta-analysis, patients presenting with CMAI% ≧25% with a surgical success rate of 48% in our study might be considered as less ideal candidates for MMA[13].

MMA was able to resolve the presence of CMAI% ≧25% in 67% of these cases. This finding could highlight and broaden the indication scope for MMA. Because the presence of CMAI% ≧25% is an exclusion criterion for upper airway stimulation, the case could be made that potential candidates for upper airway stimulation, who are currently excluded based on the presence of the CMAI% ≧25% criterion, might suitably undergo MMA as a phase 1 treatment[14,15]. Although MMA could result in surgical success, it might also alleviate the presence of the CMAI% ≧25% component in a substantial number of patients. In those cases in which clinically relevant OSA still persists, patients might then be eligible for upper airway stimulation, comparable to the treatment protocol by Yu et al. in which a combination of MMA and upper airway stimulation was suggested as complementary therapies in those cases in which contraindicative drug-induced sleep endoscopy findings and/or more severe OSA are present[15].

Also, one should be aware of the fact that in the present study, a patient category was found (25%) that exhibited an emergence of CMAI% ≧25% after MMA. The phenomenon of MMA altering the type of sleep apnea is not new. Vonk et al. reported that 66% of non-positional patients with OSA became positional patients with OSA after MMA[25]. However, to the best of the authors' knowledge, no previous studies have described this type of "treatment-emergent central and mixed sleep apnea" (TECMSA) phenomenon. Therefore, it is unclear to what extent other treatment modalities also exhibit this phenomenon. An occurrence that has also previously been described is "treatment-emergent central sleep apnea" (TECSA), also called "complex sleep-disordered breathing" or "complex sleep apnea." It has been reported that this treatment-emergent sleep apnea condition has a prevalence of 0.6%-20%[26]. In TECSA, there is an emergence of central sleep apnea after the onset of treatment in OSA patients[27,28]. This has primarily been reported after treatment with continuous positive airway pressure (CPAP), mandibular advancement devices, upper airway surgery, upper airway stimulation, and even after surgical relief of nasal obstruction[29-33]. Goodday and Fay examined the occurrence of TECSA after MMA, and found an occurrence of 2%[34]. In the present study, TECSA was found to be 0%. An explanation could be the inconsistent definition of TECSA. Goodday and Fay used the criterion of a central apnea index (CAI) of ≧5 events/h after MMA to define TECSA. In contrast, the definition of TECSA in the present study was based on the criteria of the International Classification of Sleep Disorders version 3 (ICSD-3)[35]. If the present study was to apply the same criteria used by Goodday and Fay, the results would be in line with their findings, with a TECSA of 1% (n=1). Additionally, in line with the findings of Goodday and Fay, it was found in the present study that MMA reduced CAI for the total population as well as for the patients with preoperative CMAI% ≧25%.

The authors acknowledge that, because of the retrospective nature of the present study, certain limitations might be present. First, the fact that there were a limited number of participants in the study is a point that should be addressed. However, to justify our inclusion of a sufficient sample size, we performed a *post hoc* power analysis for all six primary outcomes (AHI, LSAT, CAI, MAI, CMAI, CMAI%) based on the Wilcoxon signed rank test after the statistical analyses had been performed in the study. The power of the outcomes was 1, 1, 0.85, 0.97, 0.98, and 0.06 respectively. This indicated that all the outcomes had sufficient power in the statistical analyses except for the CMAI%. Therefore, the sample size included in the study could be regarded as sufficient. A possible explanation for the lower power of the CMAI% could be that the changes pre- and postoperatively were very tiny, because this study group consisted of mainly obstructive apneas, in addition to a small component of central and mixed apneas.

Secondly, the argument could be raised that with median advancements of the maxilla and mandible of approximately 7 and 9 mm, respectively – based on the preoperative and postoperative lateral cephalogram (mean, 1.3 ± 3.8 months; range, 0.1-24.0 months) (Supplementary data Table S5.2) – a limitation of this study could be that the advancement of the maxilla and mandible was too limited compared to what has been previously advocated in the literature, that is, more than 10 mm for the maxilla and mandible, to achieve success[7,36]. However, because of the limited interest in, and the limited published data on, central sleep apnea-related issues surrounding MMA, the results of our study offer some valuable insight into this topic. Additionally, it would be advantageous to gain more insight into these issues in other skeletal surgeries for OSA, which have been described with good success rates[37-42]. As this is the first study that has focused specifically on issues related to central sleep apnea and mixed apnea surrounding MMA in adult OSA patients, it would also be interesting to see whether these issues are present in children with OSA, as well and to evaluate what effect surgery has on the obstructive, central and mixed apnea components in these children[43,44]. Finally, a longer follow-up of these patients, including polysomnography after 12 months, is necessary, and a longer follow-up of TECMSA patients is warranted in order to gain more insight into this new phenomenon.

Conclusion

Within the undeniable limitations of the study, it seems that the presence of CMAI% ≧25% should not be regarded as a contraindication for MMA in OSA patients.

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Supplementary data

Table S5.1 Included study population versus excluded population.

Demographic variable	Total study population	Excluded population	*P*
Number of patients (*n*)	78	23	
Age (years)			
Mean ± SD	51.7 ± 9.0	49.9 ± 11.1	0.425
Range	31.0–75.0	29.0–63.0	
Gender			
Male (*n*)	63	17	0.560
Female (*n*)	15	6	
BMI (kg/m^2)			
Mean ± SD	29.1 ± 3.9	31.0 ± 3.9	0.145
Range	18.0–37.9	22.8–45.8	
Neck circumference (cm)			
Mean ± SD	42.3 ± 4.0	40.9 ± 4.5	0.523
Range	30.0–49.0	34.5–45.0	
AHI			
Median ± IQR	51.2 (36.5–69.0)	41.2 (34.0–65.1)	0.449
Range	5.5–105.1	6.4–103.3	
LSAT			
Median ± IQR	79.0 (73.0–84.0)	81.0 (63.8–87.8)	0.601
Range	30.0–90.0	51.0–92.0	

Number of patients and gender are presented as number of persons. Age, BMI and neck circumference are presented as mean with SD and range in years, kg/m^2, and cm respectively. PSG results are presented as events/hour or percentage. p <0.05 was considered statistically significant. AHI, apnea-hypopnea index; BMI, body mass index; cm, centimeters; IQR, interquartile range; kg/m^2, kilograms per square meter; LSAT, lowest oxygen saturation; SD, standard deviation; Q1–Q3, quartile 1 – quartile 3.

Table S5.2 Radiographic cephalometric measurements before surgery (T0), mean 1.3 months follow-up after surgery (T1), and mean 27.7 months follow-up after surgery (T2) for total population.

	T0 (n=78)	T1 (n=78)	T2 (n=51)	Δ_{T2-T1}	$P_{T0\ vs\ T1}$	$P_{T1\ vs\ T2}$
SNA (°)	80.3 ±4.1	87.3 ± 5.3	87.5 ± 4.5	-0.5 ± 1.3	<0.001	0.006
SNB (°)	75.8 ± 5.2	81.2 ± 5.6	82.4 ± 4.7	0.2 ± 2.1	<0.001	0.543
ANB (°)	4.6 ± 3.4	6.0 ± 3.1	5.2 ± 2.8	-0.6 ± 2.2	<0.001	0.029
PAS (mm)	9.0 ± 3.1	13.8 ± 4.1	11.7 ± 4.0	-2.1 ± 3.5	<0.001	<0.001
Advancement A (mm)		7.1 ± 2.3	7.2 ± 2.8	-0.2 ± 1.7		0.814
Advancement B (mm)		9.4 ± 3.8	10.3 ± 3.2	0.4 ± 3.1		0.186
Advancement Pog (mm)		9.3 ± 4.5	10.2 ± 4.0	0.3 ± 3.5		0.320

Data is presented as mean ± standard deviation. *P*<0.05 was considered statistically significant. A, A-point; ANB, angle from A-point to N to B-point; B, B-point; n, number of patients; $P_{T0\ vs\ T1}$, *P* values compare T0 and T1 values; $P_{T1\ vs\ T2}$, *P* values compare T1 and T2 values; PAS, pharyngeal airway space; mm, millimeters; Pog, pogonion; SNA, angle from S to N to A-point; SNB, angle from S to N to B-point; T0, before surgery; T1, 1.3 months after surgery; T2, 27.7 months after surgery; Δ_{T2-T1}, difference between T1 and T2 values.

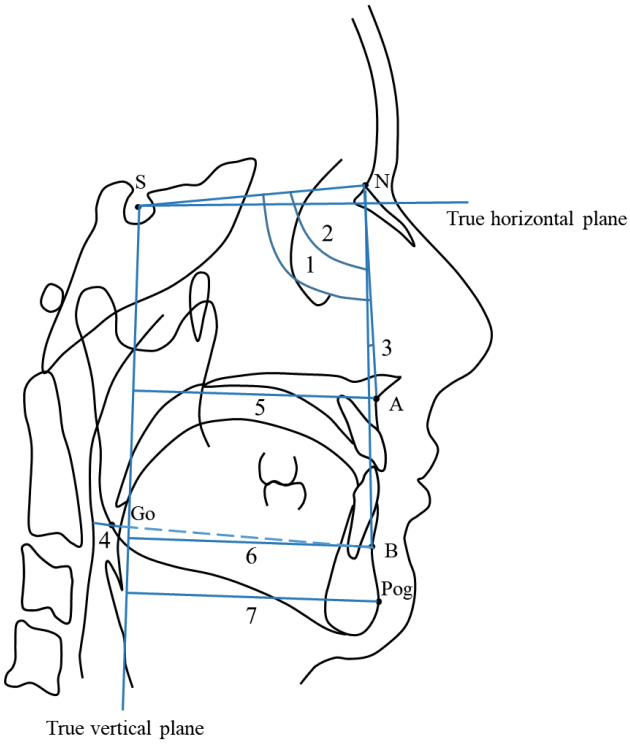
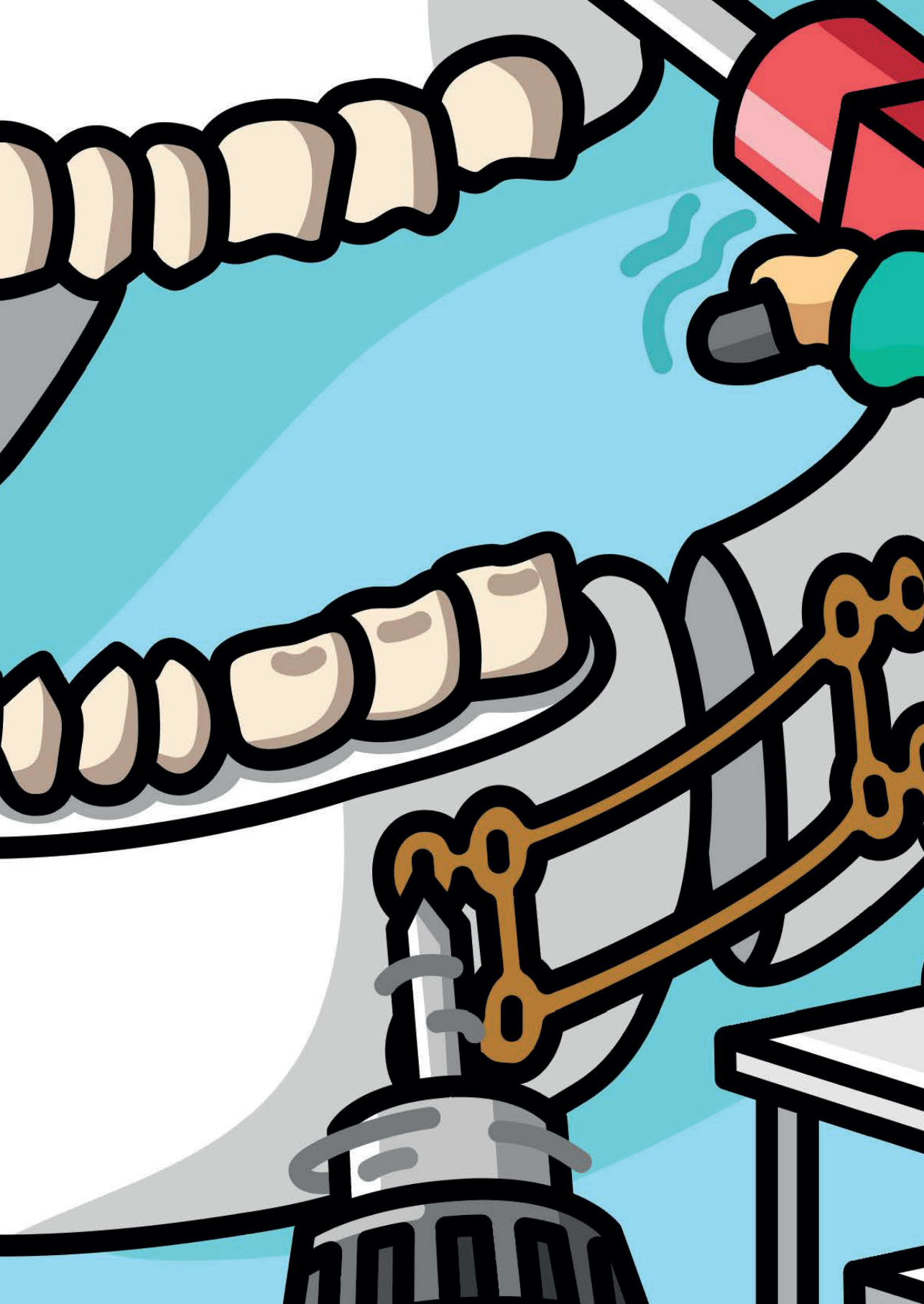


Figure S5.1 Cephalometric measurements.
1, SNA, angle from S to N to A-point (degree); 2, SNB, angle from S to N to B-point (degree); 3, ANB, angle from A-point to N to B-point (degree); 4, PAS, pharyngeal airway space (mm); 5, A-point to true vertical plane (mm); 6, B-point to true vertical plane (mm); 7, pogonion to true vertical plane (mm).



Chapter 6

Obstructive sleep apnea resolution in hypopnea-predominant versus apnea-predominant patients after maxillomandibular advancement

Jean-Pierre T.F. Ho, Ning Zhou, Jan de Lange

Chapter is based on the publication in:

Journal of Clinical Medicine 2022;12(1):311

Abstract

This retrospective cohort study aimed: (1) to analyze the influence of apnea-predominant versus hypopnea-predominant obstructive sleep apnea (OSA) on surgical outcome after maxillomandibular advancement (MMA); and (2) to evaluate whether MMA alters the presence of apnea-predominant to hypopnea-predominant OSA more than vice versa. In total 96 consecutive moderate to severe OSA patients, who underwent MMA between 2010 and 2021, were included. The baseline apnea–hypopnea index, apnea index, and oxygen desaturation index were significantly higher in apnea-predominant group, while the hypopnea index was significantly higher in hypopnea-predominant group (P<0.001). No significant difference was found between apnea-predominant group and hypopnea-predominant group in the degree of advancement of A-point, B-point, and pogonion. Surgical success and cure were significantly higher in the hypopnea-predominant group compared to the apnea-predominant group, 57.4% versus 82.1% (P=0.021) and 13.2% versus 55.5% (P=0.012), respectively. Of the 68 (70.8%) apnea-predominant patients, 37 (54.4%) shifted to hypopnea-predominant after MMA. Of the 28 (29.2%) hypopnea-predominant patients, 7 (25%) shifted to apnea-predominant postoperatively. These findings suggest that preoperative hypopnea-predominant OSA patients might be more suitable candidates for MMA compared to preoperative apnea-predominant OSA patients. Additionally, MMA proved to alter the presence of apnea-predominant to hypopnea-predominant OSA to a larger extend than vice versa.

Introduction

Obstructive sleep apnea (OSA) is a sleep breathing disorder, where patients have recurrent episodes of partial or complete upper airway collapse and obstruction. This leads to periods of absent and/or reduced respirations during sleep, called apneas and hypopneas, respectively[1]. Both of these two events result in brief periods of arousal, which in turn leads to marked sleep fragmentation[2]. The apnea–hypopnea index (AHI) —calculated by the number of apneas and hypopneas per hour of sleep— has been criticized for decades, however to this day it is still used to diagnose, objectively measure and express the severity of OSA, and to evaluate desired treatment effect[3]. The American Academy of Sleep Medicine defines an apnea in adults as a decline of the peak signal excursion by ≥90% of pre-event baseline for ≥10 s and a hypopnea in adults as a decline of the peak signal excursions by ≥30% of pre-event baseline for ≥10 s in association with either ≥3% arterial oxygen desaturation or an arousal[4,5].

The economic burden of OSA is believed to be immense, with an estimated 1.4 billion adults between the age of 30 and 69 years suffering from OSA globally[6]. The estimated cost in the United States of OSA related motor vehicle collisions in the year 2000 was estimated to be 15.9 billion dollars[7]. Additionally, sleep disorders are believed to cost approximately 130 billion dollars annually in the United States[8]. In addition to these economic aspects, the health-related burden of OSA is also quite compelling, with OSA being associated with cardiovascular disease, metabolic disease, psychiatric disorders, and neurocognitive impairment[9-11]. For these reasons it is crucial that physicians are not only able to recognize OSA, but also are able to suggest and/or provide adequate treatment to these patients.

Continuous positive airway pressure (CPAP) is considered the first-line treatment for moderate to severe OSA, due to its high efficacy and noninvasive character[12-14]. A major disadvantage, however, is the fact that the adherence to CPAP has proven to be poor specifically in the long term[15,16]. For these patients —who cannot tolerate and/or are unable to adhere to CPAP— maxillomandibular advancement (MMA) might provide an alternative treatment option with success rates similar to that of CPAP[13,17,18]. However, no matter how efficient MMA has proven to be, there is still up to approximately 15% of MMA patients that are considered non-responders[18].

The identification of specific risk factors and/or predictors for treatment success are essential for physicians in order to adequately treat patients and to optimally utilized resources. Previous research has established that certain factors are associated with a higher MMA success rate, i.e., lower body mass index, younger age, smaller neck circumference, and greater maxillary advancement[19,20]. Additionally, cardiovascular disease, complete anteroposterior epiglottic collapse found during drug induced sleep endoscopy, and larger superior posterior airway space seen on lateral cephalograms all

were found to be associated with lower success rates[21,22]. Specific findings on preoperative polysomnography —e.g., AHI, positional dependency, central and mixed apnea index— have been investigated in order to see whether they were predictive for MMA outcome[19,22-24]. However, what is not yet clear is the impact of hypopnea-predominance versus apnea-predominance in the AHI on outcome after MMA.
Therefore, the aim of this study was (1) to analyze whether hypopnea-predominant OSA was more likely to have better resolution of OSA when compared to apnea-predominant OSA after MMA; and (2) to evaluate whether MMA alters the presence of apnea-predominant OSA to hypopnea-predominant OSA after MMA and vice versa.

Materials and methods

Ethical considerations

This study was deemed not to be subject to the Medical Research Human Subjects Act by the Medical Ethics Committee of the Amsterdam University Medical Centers (UMC), location Academic Medical Center (AMC) (reference number W22_269 # 22.328). Therefore, a formal approval was waived. Patients were sent a letter to inform them that their medical records, polysomnography results and radiological images were going to be used for study purposes. They were given the option to object and opt out of inclusion in the study. This study was performed in accordance with the Declaration of Helsinki guidelines for human research, 1964, and amended in 2013 (64th WMA General Assembly, Fortaleza, Brazil). It was conducted at the Department of Oral and Maxillofacial Surgery of the Amsterdam UMC, location AMC, The Netherlands.

Study participants

We performed a single-center retrospective study including a consecutive series of patients with OSA undergoing MMA surgery between 2010 and 2021 at the Department of Oral and Maxillofacial Surgery at the Amsterdam UMC, location AMC. Patients who met the inclusion criteria were eligible for this study. The inclusion criteria were: adults aged $\geqslant$18 years; (2) diagnosis of moderate to severe OSA (apnea-hypopnea index [AHI] $\geq$15 events/hour) as determined by a preoperative overnight polysomnography (PSG); (3) continuous positive airway pressure (CPAP) therapy failure or intolerance; (4) presence of a follow-up PSG at least 3 months postoperatively. The exclusion criteria were: (1) No consent to the use of the patient record data for research purposes; (2) absence of apnea index (AI) and/or hypopnea index (HI) in preoperative and/or postoperative PSG report; (3) patients who underwent other adjunctive procedures at the time of MMA (e.g., multi-piece Le Fort osteotomy,

temporomandibular joint reconstruction); (4) previous history of Le Fort I osteotomy or bilateral sagittal split osteotomy (BSSO); and (5) cleft palate and/or craniofacial syndromic patients. The included medical records were reviewed, and data were collected. Preoperative (baseline) patient data included gender, age, and body mass index (BMI).

Maxillomandibular advancement surgery

All MMA procedures were completed using standardized surgical techniques by two dedicated surgeons, which included a Le Fort I osteotomy for the maxilla in combination with a Hunsuck–Dal Pont modification of the Obwegeser BSSO for the mandible. Both maxilla and mandible were advanced anteriorly and whenever possible counterclockwise rotated[25].

Prior to the availability of three-dimensional (3D) planning, patients were treated with a traditional two-dimensionally planned surgical procedure with manually manufactured intraoperative occlusal splints. After the availability of 3D planning, patients were virtually planned and computer-aided design/computer-aided manufacturing intraoperative occlusal splints were used[25,26].

Immediately postoperatively, all patients received extensive postoperative monitoring in either the intensive or medium care unit[25,27-29]. After being discharged from the intensive or medium care unit, the patients were transferred to a general post-surgery ward for further recovery[30].

Polysomnography

All patients underwent level 1 or level 2 PSG preoperatively and at least 3 months postoperatively. PSG recordings were manually checked and scored according to the standards of the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events[4]. The collected preoperative and postoperative PSG variables included AHI, AI, HI, oxygen desaturation index (ODI), and lowest oxyhemoglobin saturation (LSAT).

Patients were designated into the apnea-predominant OSA group (AP-group) whenever the AHI ≥5 events/hour and more than 50% of the AHI consisted of apneas (AI/AHI >50%). Patients presenting with an AHI of ≥5 events/hour and with apneas less than 50% of the AHI (AI/AHI <50%), were allocated to the hypopnea-predominant OSA group (HP-group)[31-33]. Patients with the ratio of AHI during rapid eye movement (REM) sleep (REM-AHI) to AHI during non-REM sleep (NREM-AHI) >2 and NREM-AHI <15 events/hour were classified as REM-related OSA[34]. Positional OSA was defined as an AHI at least twice as high in supine position as in non-supine position[35].

Surgical success was defined according to Sher's criteria, with an AHI reduction of at least 50% and an AHI below 20 events/hour postoperatively[36]. Patients meeting the criteria for surgical success were referred to as responders. Surgical cure was defined as a postoperative AHI below 5 events/hour[37].

Cephalography

A standard lateral cephalogram was obtained on all patients before and at least one week after MMA. All cephalograms were traced by one examiner using the Viewbox (version 4; dHAL Software, Kifissia, Greece). The following baseline cephalometric measurements were obtained: SNA (angle from sella to nasion to A-point), SNB (angle from sella to nasion to B-point), ANB (angle form A-point to nasion to B-point), and posterior airway space (PAS; distance between the base of the tongue and the posterior pharyngeal wall, derived from a line connecting B-point to gonion). Degree of maxillary advancement was traced from A-point displacement with respect to the vertical reference line (VRL). Degree of mandibular advancement was traced from B-point and pogonion (pog) with respect to VRL, respectively (Figure 6.1).

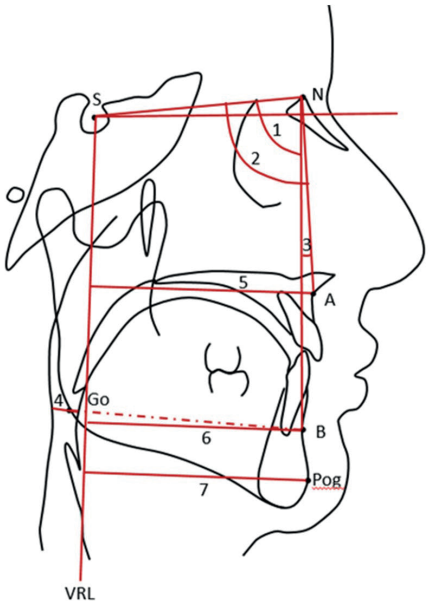


Figure 6.1 Cephalometric measurements. Landmark and reference line: A, A-point; B, B-point; Go, gonion; N, nasion; Pog, pogonion; S, sella; VRL, vertical reference line. Variables: 1, SNA, angle from sella to nasion to A-point (degree); 2, SNB, angle from sella to nasion to B-point (degree); 3, ANB, angle from A-point to nasion to B-point (degree); 4, PAS, posterior airway space (mm); 5, A-point to vertical reference line (mm); 6, B-point to vertical reference line (mm); 7, pogonion to vertical reference line (mm).

Excessive daytime sleepiness

Excessive daytime sleepiness as one of the main symptoms and burden of OSA, was scored preoperatively with the use of the Epworth Sleepiness Scale questionnaire (ESS)[38]. This self-administered questionnaire contains 8 questions, to which respondents were asked to rate on a 4-point Likert-scale (0-3).

Statistical analysis

Statistical analysis was performed using SPSS (version 26.0; IBM Corp., Armonk, NY, USA). Continuous variables were reported as the mean and standard deviation (SD) when data were normally distributed or median and interquartile range (IQR) when data were not normally distributed. Categorical variables were reported as frequency and percentage. Normality was tested using the Shapiro-Wilk test. To compare baseline characteristics between AP-group and HP-group, the independent t-test was used in case of normally distributed data and the Mann-Whitney U test was used in case of non-normally distributed data. To compare the paired continuous data, the paired-sample t-test was used when data were normally distributed, while the Wilcoxon signed rank test was used when data were not normally distributed. The chi-squared test was used to compare the rates of surgical success and cure between groups. To correct for possible confounders in surgical outcome, a multivariate logistic regression analysis was performed. Linear regression analysis was performed to investigate the association between pre-op ESS and apnea and/or hypopnea-predominant OSA group. For all analyses, a P value <0.05 was considered statistically significant.

Results

At the department of Oral and Maxillofacial Surgery at the Amsterdam UMC, location AMC, a total of 114 patients underwent MMA for OSA, between 2010 and 2021. Of those patients eighteen were excluded due to the following reasons: No consent from the patient for the use of their data for research purposes (n=3), incomplete pre- and/or postoperative PSG data (n=9), mild OSA (n=4), and other adjunctive procedures performed at the time of MMA (n=2). Therefore, 96 patients were included in this study, 77 males (80.2%) and 19 females (19.8%). The mean age was 50.9 ± 9.9 years. The median body mass index (BMI) was 29.7 (27.4-32.2) kg/m^2. A detailed overview of baseline characteristics of the total population is presented in Table 6.1.

Table 6.1 Baseline characteristics of the total population, AP-group and HP-group.

	Total Population (*n*=96)	**Preoperative AP-Group (*n*=68)**	**Preoperative HP-Group (*n*=28)**	***P*-Value**
Age (years)	50.9 ± 9.9	50 [44, 58]	53.5 [46.3, 59.8]	0.631
Gender (*n*, %)				
Female	19 (19.8%)	11 (16.2%)	8 (28.6%)	0.166
Male	77 (80.2%)	57 (83.8%)	20 (71.4%)	
BMI (kg/m^2)	29.7 [27.4, 32.2]	29.6 [27.2, 31.6]	30.3 [27.9, 33.3]	0.124
Previous upper airway surgery (*n*, %)				
Yes	40 (41.7%)	33 (48.5%)	7 (25%)	0.034
No	56 (58.3%)	35 (51.5%)	21 (75%)	
SNA (degree)	80.0 ± 3.9	79.9 ± 4.2	80.4 ± 3.0	0.575
SNB (degree)	75.2 [72.2, 78.4]	75.3 [72.2, 78.1]	75.2 [73.4, 79.4]	0.424
ANB (degree)	4.9 [2.8, 6.7]	5.1 [2.9, 6.7]	4.4 [2.7, 6.1]	0.452
PAS (mm)	9.0 ± 3.1	9.1 ± 3.1	8.7 ± 3.0	0.163
AHI (events/hour)	52.7 (21.1)	58.7 [41.9, 73.6]	36.4 [26.3, 49.8]	<0.001
AI (events/hour)	34.1 [17.1, 60.2]	48.2 ± 20.5	12.1 ± 8.3	<0.001
HI (events/hour)	12.5 [4.0, 22.9]	7.6 [3.1, 16.4]	23.7 [19.1, 30.8]	<0.001
Positional OSA (*n*, %)				
Yes	31 (38.3%)	20 (31.1%)	11 (64.7%)	0.012
No	50 (61.7%)	44 (68.8%)	6 (35.3%)	
REM-related OSA (*n*, %)				
Yes	1 (1.2%)	0 (0)	1 (5.6%)	0.220
No	81 (98.8%)	64 (100%)	17 (94.4%)	
ODI (events/hour)	52.1 ± 21.3	56.5 ± 21.0	37.1 ± 15.1	<0.001
LSAT (%)	80 [73.0, 84.0]	79 [71.5, 84]	82 [78.0, 87.0]	0.165
ESS (score)	12.2 ± 6.1	13.0 ± 6.1	9.8 ± 5.8	0.138

Continuous data are presented as mean ± standard deviation or median [Q1, Q3]. Categorical data are presented as frequency and percentage. P values comparing AP and HP; $p < 0.05$ is considered statistically significant. AHI, apnea hypopnea index; AI, apnea index; ANB, angel form A-point to nasion to B-point; AP-group, apnea-predominant OSA group; BMI, body mass index; ESS, Epworth Sleepiness Scale; HI, hypopnea index; HP-group, hypopnea-predominant OSA group; OSA, obstructive sleep apnea; LSAT, lowest oxyhemoglobin saturation; ODI, oxygen desaturation index; PAS, posterior airway space; REM, rapid eye movement; SNA, angel from sella to nasion to A-point; SNB, angel from sella to nasion to B-point.

Baseline characteristics of AP-group versus HP-group

When comparing baseline characteristics between AP-group and HP-group, the percentage of patients who received previous upper airway surgery was significantly higher in AP-group compared to HP-group (*P*=0.034). The baseline AHI (*P*<0.001), AI (*P*<0.001), and ODI (*P*<0.001) were significantly higher in AP-group, while HI was significantly higher in HP-group (*P*<0.001). Additionally, the percentage of positional OSA was significantly higher in HP-group compared to AP-group (*P*=0.012). There was no significant difference between groups in the other baseline characteristics (Table 6.1).

MMA surgical outcome

In the total population, the mean degree of A-point advancement, mean degree of B-point advancement, and median degree of pog advancement were 7.3 ± 2.3 mm, 10.0 ± 4.3 mm, and 9.2 [6.6, 12.5] mm, respectively. No significant difference was found between AP-group and HP-group in the advancement degrees of A-point, B-point, and pog (Table 6.2).

Table 6.2 Surgical characteristics of the total population, AP-group and HP-group.

	Total Population (*n*=96)	**AP-Group (*n*=68)**	**HP-Group (*n*=28)**	***P*-Value**
A-point advancement (mm)	7.3 ± 2.3	7.2 ± 2.0	7.4 ± 2.9	0.746
B-point advancement (mm)	10.0 ± 4.3	9.8 ± 4.1	10.4 ± 4.9	0.548
Pog advancement (mm)	9.2 [6.6, 12.5]	9.1 [5.9, 12.2]	10.0 [7.5, 13.0]	0.408

Data are presented as mean ± standard deviation or median [Q1, Q3]. *P* values comparing AP-group and HP-group; *P*<0.05 is considered statistically significant. AP, apnea-predominant OSA group; HP, hypopnea-predominant OSA group; mm, millimeters.

For the AP-group, except for median HI, the median AHI (*P*<0.001), median AI (*P*<0.001), median ODI (*P*<0.001), and median LSAT (*P*<0.001) were all significantly improved after MMA. For the HP-group, the median AHI (*P*<0.001), median AI (*P*<0.001), median HI (*P*<0.001), median ODI (*P*<0.001), and median LSAT (*P*=0.005) were all significantly improved after MMA. An overview of preoperative and postoperative PSG variables of both groups are shown in Table 6.3.

Table 6.3 Preoperative and postoperative polysomnography values in AP-group and HP-group.

	Preoperative	**Postoperative**	***p*-Value**
AP-Group (*n*=68)			
AHI (events/hour)	58.7 [41.9, 73.6]	13.7 [7.3, 24.2]	<0.001
AI (events/hour)	46 [30.1, 64.4]	6.1 [1.9, 14.3]	<0.001
HI (events/hour)	7.6 [3.1, 16.4]	6.4 [3.8, 10.6]	0.308
ODI (events/hour)	56.9 [40.3, 74.9]	21.8 [10.9, 32.5]	<0.001
LSAT (%)	79 [71.5, 84]	85.5 [82, 89]	<0.001
HP-group (*n*=28)			
AHI (events/hour)	36.4 [26.3, 49.8]	9.9 [4.5, 18.9]	<0.001
AI (events/hour)	10.7 [5.3, 17.2]	1.5 [0.9, 6.8]	<0.001
HI (events/hour)	23.7 [19.1, 30.8]	5.3 [3.0, 15.5]	<0.001
ODI (events/hour)	37.1 ± 15.1	17.8 ± 11.7	<0.001
LSAT (%)	82 [78, 87]	87 [82, 88.8]	0.005

Data are presented as mean ± standard deviation or median [Q1, Q3]. *P* values comparing preoperative and postoperative values; *P*<0.05 is considered statistically significant. AHI, apnea hypopnea index; AI, apnea index; AP-group, apnea-predominant OSA group; HI, hypopnea index; HP-group, hypopnea-predominant OSA group; LSAT, lowest oxyhemoglobin saturation; ODI, oxygen desaturation index.

Surgical success was achieved in 39 of 68 patient (57.4%) in the AP-group and 23 of 28 patients (82.1%) in the HP-group. Surgical cure was achieved in 9 patients (13.2%) in

the AP-group and 10 patients (55.5%) in the HP-group. Both surgical success rate (*P*=0.021) and cure rate (*P*=0.012) were significantly higher in the HP-group. Multivariate logistic regression analysis showed no significant association between surgical success and gender (odds ratio [OR] =1.748, 95% confidence interval [CI]=0.486–6.287; *P*=0.393), age (OR=0.957, 95% CI=0.911–1.004; *P*=0.073), baseline BMI (OR=1.030, 95% CI=0.921–1.151; *P*=0.608), previous upper airway surgery (OR=0.735, 95% CI=0.293–1.845; *P*=0.512), and baseline AHI (OR=0.999, 95% CI=0.978-1.021; *P*=0.957).

Postoperative shift in apnea/hyponea predominance

Of the total population, 68 patients (70.8%) were apnea-predominant preoperatively, 37 of the 68 patients (54.4%) shifted to hypopnea- predominant after MMA. Twenty-eight patients (29.2%) were hypopnea-predominant preoperatively, 7 of them (25%) shifted to apnea-predominant postoperatively. After MMA, the percentages of apnea-predominant and hypopnea-predominant were 39.6% (n=38) and 60.4% (n=58), respectively.

Responders versus non-responders

In the responder group (n=62), 39 patients (62.9%) were apnea-predominant preoperatively. Twenty-six of preoperative apnea-predominance (66.7%) changed to postoperative hypopnea-predominance. Among the 23 hypopnea-predominance preoperatively (37.1%), 6 (26.1%) changed to apnea-predominance postoperatively (Figure 6.2).

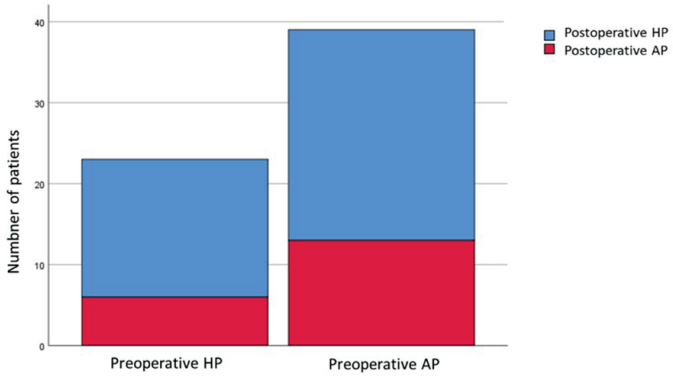


Figure 6.2 Distribution of apnea/hypopnea predominance in responders. AP, apnea-predominant; HP, hypopnea-predominant.

In the non-responder group (*n*=34), 29 patients (85.3%) were apnea-predominant preoperatively. Eleven of preoperative apnea-predominance (32.4%) shifted to hypopnea-predominance postoperatively. Only 5 patients (14.7%) were hypopnea-predominant preoperatively, 1 patient (20%) changed to apnea-predominance after MMA (Figure 6.3).

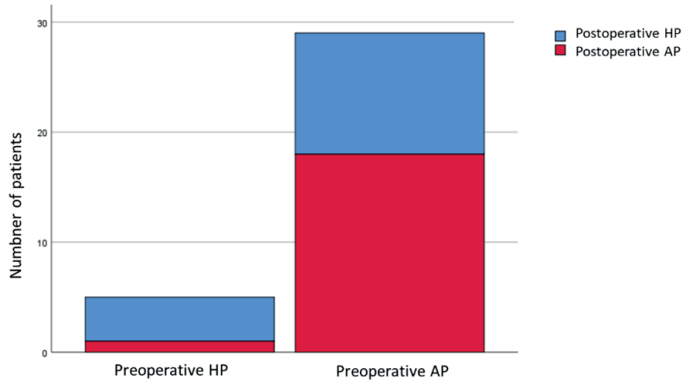


Figure 6.3 Distribution of apnea/hypopnea predominance in non-responders. AP, apnea-predominant; HP, hypopnea-predominant.

Excessive daytime sleepiness in apnea-predominant vs. hypopnea-predominant OSA

The ESS was preoperatively scored by a minority of participants (n=43) (Table 6.1). The mean preoperative ESS for the AP-group (n=32) and HP-group (n=11), was 13.0 ± 6.1 and 9.8 ± 5.8, respectively. When adjusting for potential confounders —such as age, gender, BMI, AHI, ODI, and LSAT— linear regression analysis showed that AP-group was significantly associated with a higher ESS (*P*=0.008).

Discussion

This study set out with the aim of assessing whether hypopnea-predominant OSA was more likely to achieve surgical success and to have better resolution of PSG parameters when compared to apnea-predominant OSA after MMA. The second aim in this study was to investigate whether MMA alters the presence of apnea-predominant OSA to hypopnea-predominant OSA or vice versa. As far as the authors are aware this is the first study that has specifically looked into these issues related to MMA outcome.

The most obvious finding to emerge from the analysis was that although MMA was able to significantly reduce the AHI in both the AP-group as well as the HP-group, MMA achieved a significantly better surgical success and cure rate in the HP-group compared to the AP-group. Additionally, MMA was able to significantly improve the median AHI, median AI, median HI, median ODI, and median LSAT in the HP-group. This might suggest that patients with hypopnea-predominant OSA might be more suitable candidates for MMA compared to patients presenting with apnea-predominant OSA. However, with a small sample size (28 patients in HP-group), caution must be applied here. Moreover, Mattew et al. found that a majority of extremely obese patients manifest with a preponderance of hypopneas[39]. When looking at the results of this study, this would propose that extremely obese patients would be more suitable candidates for MMA, which is in stark contrast to previous research, which established that a lower BMI was associated with a higher MMA success rate[19].

It was interesting to see that the number of patients who received previous upper airway surgery was significantly higher in the AP-group. Holty et al. reported in their review that they found that patient who underwent previous phase -1 surgery —uvulopalatopharyngoplasty— were less likely to achieve surgical cure after MMA[19]. The presence of apnea-predominant OSA in patients who received previous upper airway surgery, might explain why MMA is less successful in these patients. However, more research is necessary and needs to be carried out in order to confirm and possibly also explain this finding. It is important to bear in mind that many factors of course, may lead to MMA failure in patient who underwent previous phase -1 surgery. In contrast, Tang et al. looked into treatment outcome in apnea and hypopnea-predominant OSA patients undergoing adenotonsillectomy, and they found that there was no difference in outcome whether patients had apnea-predominant or hypopnea-predominant OSA[40]. This may be explained by the fact that non-anatomical factors (e.g., neuromuscular activation, ventilatory control, and arousal threshold) in children contribute significantly, and therefore anatomical airway factors might play a small role in the contribution to ventilatory instability and obstructive cycling of OSA[41].

Another important finding was that a majority of patients tended to shift from the AP-group prior to MMA to the HP-group after MMA. A possible explanation for this might be that MMA converted some apneas to hypopneas in these patients. There were 7 patients, which shifted from the HP-group prior to MMA to the AP-group after MMA. In all 7 patients, the AHI was significantly reduced postoperatively. While in these 7 patients MMA showed to be more effective in the reduction in the hypopneas than the apneas, 3 patients showed an increase in apneas after MMA. An analysis of non-anatomical factors (e.g., Pcrit, loop gain, muscle responsiveness, and arousal threshold) might shed more light on these different outcomes, the mechanisms responsible for

the different types of apneas and hypopneas, and it might explain the role of the apnea and hypopnea component in those patients, which were not successfully treated with MMA. A study on a non-framework surgery in patients with very severe OSA showed similar findings with our study. It was found that in addition to frequency, duration of hypopnea could also increase in patients —with AHI≥60 events/h— after one-stage multi-level sleep surgery[42]. These results emphasize the fact that MMA often not only improves the patient's severity of OSA, but also alters the patients type of OSA. Previous studies also highlighted this effect, by illustrating that MMA was able to alter the presence of positional dependency and percentage of central and mixed apnea index[23,24]. This observation suggests that it is likely that the mechanisms responsible for the different types of apneas overlap.

When looking at definition of the American Academy of Sleep Medicine for a apnea —decline of the peak signal excursion by ≥90% of pre-event baseline for ≥10 s— and hypopnea —decline of the peak signal excursions by ≥30% of pre-event baseline for ≥10 s in association with either ≥3% arterial oxygen desaturation or an arousal— one might hypothesize that patients presenting with apnea-predominant OSA might experience more OSA related burden compared to patients with hypopnea-predominant OSA[4,5,43]. In order to investigate this, we evaluated the ESS of patient prior to MMA, and divided them into an apnea-predominant and hypopnea-predominant OSA group. The results illustrate that apnea-predominant OSA is significantly associated with more excessive daytime sleepiness. When looking at the non-responders, it was found that 32% of patients shifted from apnea-predominant OSA to hypopnea-predominant OSA, the case can be made that even though these patients did not respond to MMA as one might have hoped for, MMA might still have alleviated some of these patients OSA burden by shifting them from apnea-predominant OSA to hypopnea-predominant OSA.

A note of caution is due here when interpreting the results of this study since there are several limitations. For one, the present study is a single-center retrospective cohort study. There are 12 patients who were excluded from the analysis due to the patient's rejection for the use of their data for research purposes or incomplete pre- and/or postoperative PSG data; therefore, there is an inherent concern for potential selection bias. Secondly, the study population could be regarded as small. With this small sample size, caution must be applied, due to the fact that this could potentially lead to sampling bias[44]. Thirdly, only 45% of the study participants completed the ESS, which therefore introduces the possibility for non-response bias[45]. Finally, there is some controversy surrounding hypopneas. This is partially based on the fact that there have been many different definitions for hypopnea over time[46]. Additionally, it is believed that scoring of hypopneas can be difficult and therefore lead to disagreements in

scoring of apneas vs. hypopneas[47]. Previous papers have also mentioned the fact that specifically for hypopneas it is difficult to distinguish between obstructive and central events[39]. These controversies and difficulties could have influenced the data collected for this study and therefore influenced our findings. Further research should be undertaken in order to confirm the present findings. The authors advocate for larger prospective multicenter studies, where specific attention is paid to the scoring for both apneas and hypopneas.

In addition to MMA, there are other evidence-based treatment options for OSA. Mandibular advancement device (MAD) is the most common oral appliance that offers a non-invasive option for the management of OSA. It needs to be noted that, in nature, MAD can only alleviate OSA-related symptoms, while MMA can treat OSA. Therefore, MMA can provide a solution for OSA patients who decline to accept lifelong treatment with MAD. Moreover, in order to further assist decision making in OSA treatment, further research on cost-effectiveness of MMA in OSA treatment is necessary.

In spite of its limitations, the authors strongly feel that the study adds to our understanding that specific characteristics of preoperative PSG —other than the AHI and in this case specifically apnea or hypopnea predominance— might be useful in predicting MMA outcome. This can aid physicians to better select candidates for MMA in order to increase surgical treatment successes, and better utilize the growing scarcity of medical resources.

Conclusion

Notwithstanding the study limitations, the findings suggest that patients presenting with hypopnea-predominant OSA might be associated with better surgical response after MMA. In addition, our results further support the concept that MMA is able to alter patients OSA phenotype.

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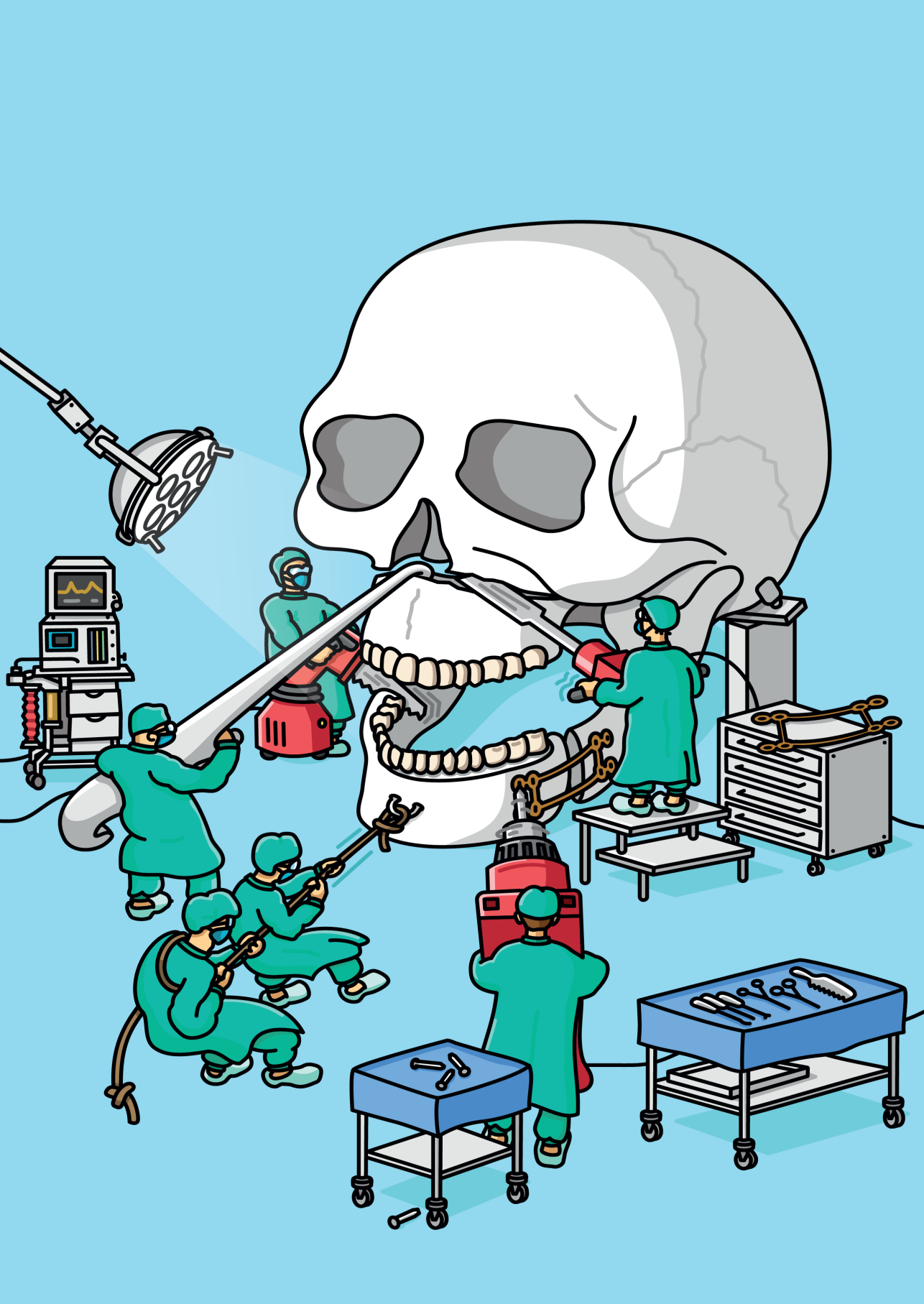
PART II

ISSUES RELATED TO SURGICAL FACTORS AND OUTCOME



Chapter 7

Splintless orthognathic surgery in edentulous patients — A pilot study

Jean-Pierre T.F. Ho, R Schreurs, F Baan, Jan de Lange. Alfred G. Becking

Chapter is based on the publication in:

International Journal Oral and Maxillofacial Surgery 2020;49(5):587-594

Abstract

The aim of this pilot study was to evaluate the accuracy and predictability of a splintless treatment protocol for edentulous patients undergoing orthognathic surgery in four consecutive cases. All operations were virtually planned, followed by computer-aided design of individual osteotomy guides and patient-specific fixation implants, which were three-dimensionally printed in titanium. In order to evaluate the discrepancy between the planned and the achieved postoperative result, the postoperative outcome was compared to the virtual treatment plan. Rotational and translational movement and discrepancies with the planned movements were quantified for the maxilla; the advancement was quantified for the mandible. For the maxilla, there was a mean translation discrepancy of 0.6 mm. With regard to rotation, there was a mean discrepancy of 1.9°, 0.1°, and 0.4° for pitch, yaw, and roll, respectively. The mean discrepancy in translation of the mandible was 0.4 mm. The results of this pilot study indicate that the splintless treatment protocol for orthognathic surgery in edentulous patients presented here is accurate and predictable.

Introduction

There has been a shift in orthognathic surgery from two-dimensional (2D) to three-dimensional (3D) imaging and virtual planning with the implementation of computer-assisted surgery (CAS) and 3D-printed splints[1,2]. A more recent innovation is splintless orthognathic surgery, in which computer-aided design and manufacturing (CAD/CAM) surgical cutting guides and patient-specific implant (PSI) fixation systems are used. This treatment protocol has been proven to be highly accurate in dentate patients[3-6]. To date, this has not been described for edentulous patients.

There is a population of edentulous patients who are eligible for orthognathic surgery for various indications such as facial asymmetry and obstructive sleep apnoea (OSA). In these patients, the treatment protocol often involves a Gunning splint, which is used as an intermediate and/or final splint for fixation[7-9]. These appliances are often not reliably fixed and even in those cases where the splints are screw-retained, the predictability and accuracy in these complex cases is thought to be reduced in comparison to dentate patients.

In this paper, a protocol for splintless orthognathic surgery in edentulous patients, with the use of patient-specific osteotomy guides and implants, is presented and assessed.

Materials and methods

Subjects

Four consecutive edentulous patients attending the Department of Oral and Maxillofacial Surgery, Amsterdam UMC (Academic Medical Centre location) between December 2017 and May 2018 were treated with the splintless orthognathic treatment protocol. Three patients were treated for severe OSA and received a maxillomandibular advancement osteotomy (MMA)[10,11]. One patient underwent a bilateral sagittal split osteotomy (BSSO) for the correction of facial asymmetry[12].

Clinical protocol

Preoperatively, all patients underwent a clinical evaluation. Facial profile and dimensions, chin and nose positions, asymmetries, and the occlusal relationship of the dentures were assessed. Patient photographs were obtained in conjunction with 3D stereophotogrammetry.

Computed tomography (CT) scans of all patients were acquired using a standardized scan protocol (Somatom Force; Siemens Medical Solutions, Erlangen, Germany): 120 kV, 300 mAs, field of view (FOV) 240 mm, pitch 0.55, slice thickness 1.0 mm, slice

increment 1.0 mm, image matrix 512 x 512, window W1600/L400, hard-tissue kernel Hr64. Patients with dentures in situ were scanned with the mandible in centric relation with the condyles seated in the glenoid fossa. Afterwards, the dentures of all patients were scanned individually in centric relation.
The clinical protocol was amended after the first patient (MMA). For the next three patients, an orientation screw was placed on both sides of the mandible body, each one placed distal to the mental foramen. This was done under local anaesthesia prior to acquisition of the CT scan.

Virtual planning and additive manufacturing workflow

The CT data were exported in Digital Imaging and Communications in Medicine (DICOM) format and imported into Materialise ProPlan CMF software version 3.0 (Materialise, Leuven, Belgium). A 3D virtual hard tissue model of the patient was reconstructed; the denture models were fused with the hard tissue model. The 3D virtual hard tissue models were aligned using the natural head position (NHP) concept, based on clinical assessment combined with patient photos (Figure 7.1a)[13].
The maxilla and/or the mandible were virtually osteotomized according to a Le Fort I osteotomy or BSSO, respectively. For the three MMA patients, the maxilla was virtually advanced and rotated counter clockwise to the planned final position. In these patients, the main objective was to decrease the apnoea and hypopnoea while still rendering an aesthetically acceptable result for both the patient and the surgeon (Figure 7.1b).
Consequently, the mandible was virtually advanced in centric relation (Figure 7.1c). The mandible of the patient only receiving a BSSO was virtually rotated to create facial skeletal and soft tissue symmetry (Figure 7.2). The mandibular rami were virtually rotated to align perfectly with the lower border of the two osteotomy segments.
Based on the planned final position of the maxilla and/or mandible, osteotomy guides with the design and location of the osteotomy were produced (Materialise, Leuven, Belgium). The screw hole positions for final fixation of the fixation PSIs were embedded in the osteotomy guides at easily reachable locations with adequate bone available for fixation (Figure 7.3a, c).
To ensure correct placement of the osteotomy guide on the mandible, a fixation screw hole was designed in the guide at the position of the orientation screw in the mandible. In the design of the fixation PSIs, the planned movement of the maxilla and/or mandible was embedded in the screw hole positions of the fixation PSI (Figure 7.3b, d). The osteotomy guides and the fixation PSIs were laser-sintered from pure grade 2 titanium (Materialise, Leuven, Belgium) (Figure 7.4).

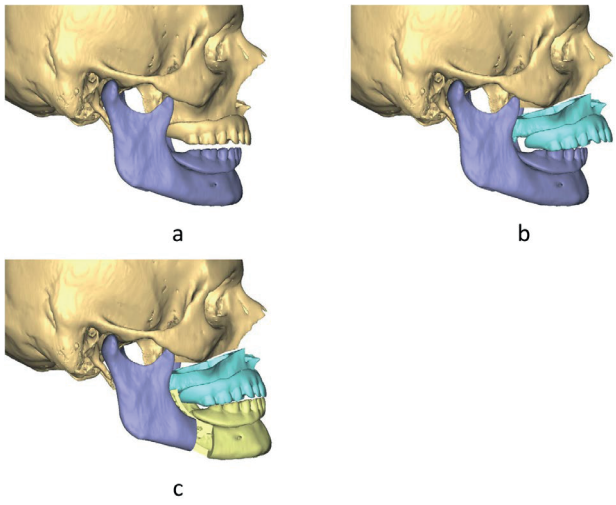


Figure 7.1 (a) Lateral view of a 3D hard tissue skull model with dentures of one of the MMA cases treated with the protocol described. The mandible, including the denture for the mandible, is shown in violet. (b) Lateral view illustrating a Le Fort I osteotomy. The maxilla (and dentures) was virtually repositioned to achieve the desired advancement. (c) Lateral view illustrating the planned position of the mandible after a virtual BSSO. The distal segment was advanced in centric relation. (MMA, maxillomandibular advancement; BSSO, bilateral sagittal split osteotomy).

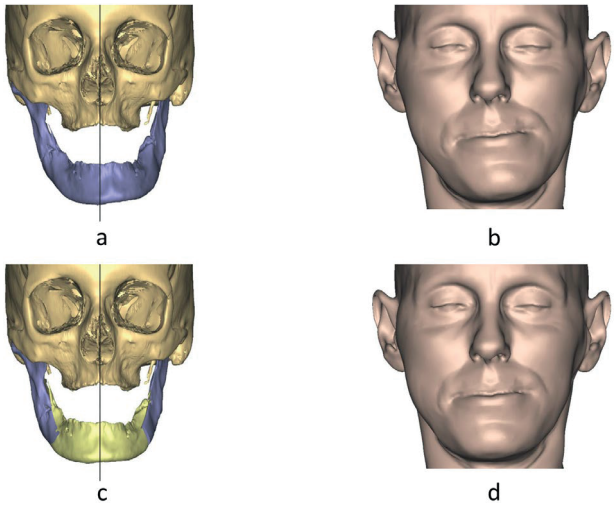


Figure 7.2 (a) Frontal preoperative view of the 3D hard tissue skull model of the patient receiving only a BSSO. The facial asymmetry is clearly visible. (b) Frontal preoperative view of the 3D soft tissue model. (c) The planned frontal view of the hard tissue after corrective BSSO, in which the mandible was virtually rotated to create facial skeletal and soft tissue symmetry. (d) The planned frontal view of the soft tissue after corrective BSSO. (BSSO, bilateral sagittal split osteotomy).

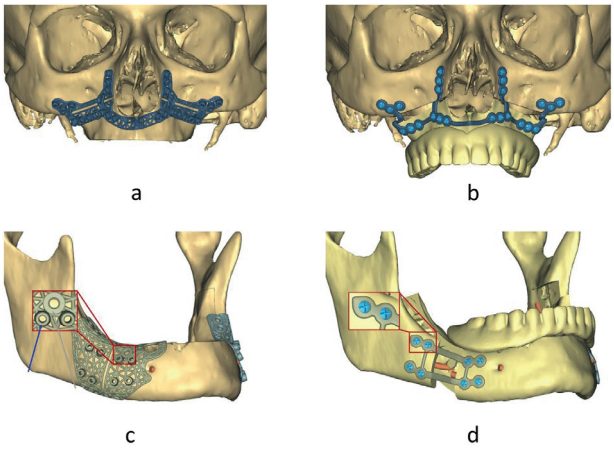


Figure 7.3 (a) 3D hard tissue skull model indicating where the CAD osteotomy guide for the maxilla (shown in blue) should be placed. (b) The CAD PSI (shown in dark blue) for the osteotomized maxilla (including the denture in yellow) containing the planned final position. The 24 screws (shown in light blue) for fixation are clearly indicated. (c) The two CAD osteotomy guides for the mandible situated bilaterally. The location of the drill hole for the fixation screw is clearly indicated (grey arrow). The pre-drilling cylinders with angulation control are also clearly shown (blue arrow). The most anterior and cranial screw hole in the osteotomy guide was designed to be used as a navigation hole to guide the osteotomy guide to the exact position in order to fixate the osteotomy guide with the orientation screw that was placed during the planning stages. (d) The CAD PSIs for the mandible containing the planned final position. In this design, the PSI consisted of two parallel straight plates, which were connected. The necessary eight screws (shown in light blue) are indicated. (CAD, computer-aided design; PSI, patient-specific implant).

Surgical technique

A buccal sulcus approach was utilized, followed by sub-periosteal dissection and elevation of the soft tissue and nasal mucosa. The osteotomy guides were positioned in best fit and temporarily fixed with at least four monocortical positioning screws (Figure 7.5a). A Le Fort I osteotomy cut dictated by the osteotomy guide was made and the 24 fixation screw holes were pre-drilled. Afterwards, the osteotomy guide was removed and the maxilla was down-fractured and mobilized with Rowe forceps (Figure 7.5b).
The fixation PSI was first fixed to the maxilla at the caudal pre-drilled screw holes. The maxilla and PSI were then aligned to the pre-drilled cranial screw holes and fixated. Due to the pre-drilled screw holes, the PSI could only be positioned and fixed in one position.

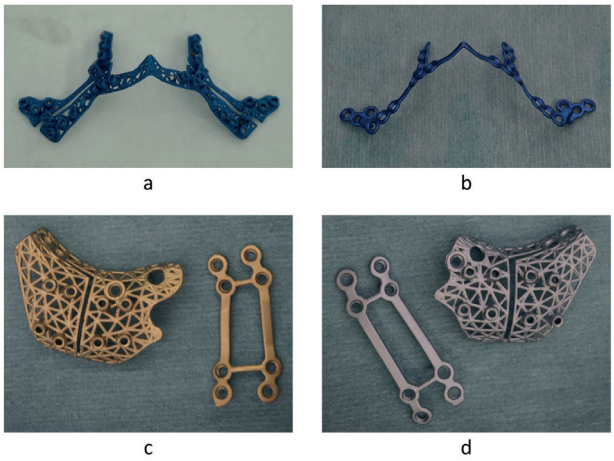


Figure 7.4 (a) The CAD/CAM titanium osteotomy guide for the maxilla. (b) The CAD/CAM titanium PSI for the maxilla. (c) The CAD/CAM titanium osteotomy guide and PSI for the right side of the mandible, coloured gold. In this design, the PSI consisted of two parallel straight plates, which were connected. (d) The CAD/CAM titanium osteotomy guide and PSI for the left side of the mandible, coloured silver. In this design, the PSI consisted of two parallel straight plates, which were connected. (CAD/CAM, computer-aided design and manufacturing; PSI, patient-specific implant).

In those cases where the maxilla and the fixation PSI could not be fixed tension-free, the fixation screws of the cranial screw holes were subsequently removed and further mobilization of the maxilla was performed with the Rowe forceps (Figure 7.5c), after which tension-free fixation was achieved in all three MMA cases (Figure 7.5d). An alar cinch suture and meticulous wound closure followed.

To approach the mandible, an extended vestibular incision was used, followed by sub-periosteal dissection and exposure of the mandible. The side-specific osteotomy guide was placed and temporarily fixed with positioning screws (Figure 7.6a, b). Next, the lower border osteotomy, the vertical osteotomy, and a portion of the oblique osteotomy were performed, dictated by the osteotomy guide. Eight screw holes were pre-drilled, through a transbuccal approach. In one case, multiple approaches were necessary. The osteotomy guide was removed, and the horizontal osteotomy and the remaining part of the oblique osteotomy were finalized. The segments were mobilized with the use of an osteotome, spreader and/or elevator. The same procedure was followed on the contralateral side. After mobilization of the segments on both sides, tension-free fixation was achieved with the side-specific fixation PSI in the pre-drilled screw holes (Figure 7.6c, d). Finally, wound closure was performed on both sides.

Antibiotics (amoxicillin–clavulanate (Augmentin); GlaxoSmithKline BV, Zeist, The Netherlands) were administered at the start of the procedure and were continued for 7 days.

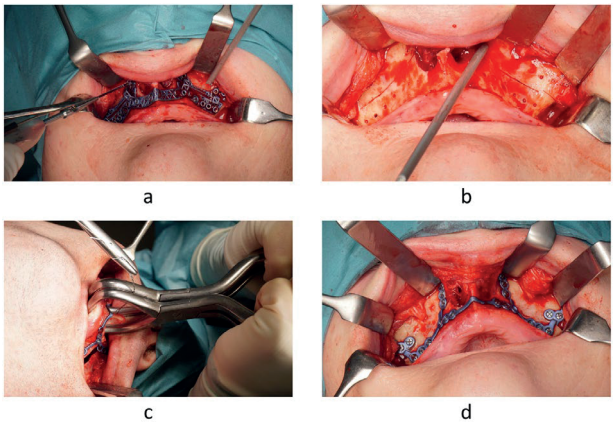


Figure 7.5 (a) Clinical picture showing the osteotomy guide perfectly positioned and fixated to the maxilla. The saw is already in place to perform the Le Fort I osteotomy cut on the right side. (b) The osteotomy guide has been removed and the osteotomy cuts have been placed. The pre-drilled screw holes are clearly visible caudal to the Le Fort I osteotomy cut. (c) A steel ligature with Murphy–Pean forceps is placed at the anterior nasal spine to help guide the maxilla to the planned position in order to fixate the PSI (including the maxilla) to the skull, where the fixation screw holes have already been pre-drilled. The PSI for the maxilla is fixated to the down-fractured maxilla. In this case, it could not be placed tension-free to the skull and as such could not be fixated; therefore, the maxilla needed to be mobilized further with the use of the Rowe forceps. (d) The PSI is perfectly placed and fixated. There is one screw hole not in use on each side of the maxilla; these are the fixation screw holes for the osteotomy guide. (PSI, patient-specific implant.).

Outcome evaluation

CT scans for evaluation were acquired within 7 days postoperatively using an identical scan protocol. Patients were scanned with the mouth closed in a relaxed jaw position and with the condyles seated in the fossa. Patients were not scanned with dentures.

In order to evaluate the result achieved, the DICOM data were imported into the Ortho Gnathic Analyser (OGA)[14]. In contrast to the original OGA protocol for dentate patients, three landmarks were placed on each bone segment in order to determine the position of the maxilla, distal mandibular segment, and both proximal segments, since the dental landmarks were obviously missing[14].

3D movement of the mandibular segment could not be determined. In order to measure mandibular advancement, the virtually planned osteotomy gap was measured and compared to the osteotomy gap achieved.

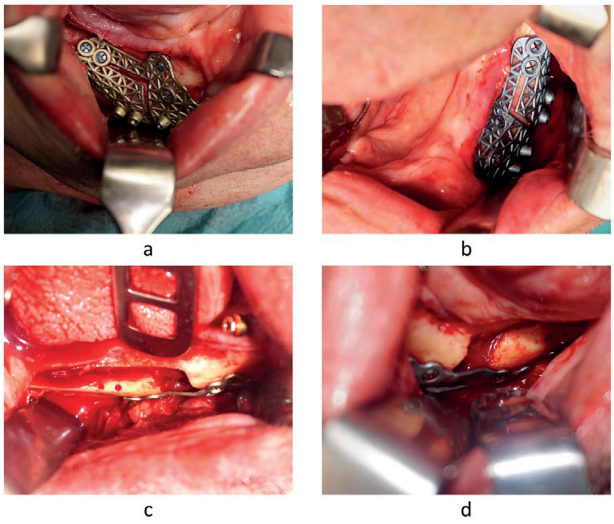


Figure 7.6 (a) Clinical picture showing the osteotomy guide (coloured gold) perfectly positioned and fixated to the right side of the mandible. The pre- drilled fixation hole cylinders are designed at more of an angle in order to pre-drill the fixation holes in the mandible with one transbuccal approach. (b) The osteotomy guide (coloured silver) perfectly positioned and fixated to the left side of the mandible. (c) The PSI (coloured gold) is perfectly placed and fixated on the right side of the mandible. (d) The PSI (coloured silver) is perfectly placed and fixated on the left side of the mandible. (PSI, patient- specific implant.). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Results

The study sample included two male and two female patients. Their mean age was 55 ± 7 years (range 48–62 years). The mean edentulous time was 11 ± 9 years (range 2-20 years).

The indication for three patients (two male and one female) was extreme OSA, with a mean apnoea–hypopnoea index (AHI) of 69.9 ± 20.1 (range 49.8–90.0). All three patients had previously been treated unsuccessfully for their OSA with a variety of different treatment modalities, including continuous positive airway pressure (CPAP). They were therefore referred by the otorhinolaryngologist for treatment with MMA.

The indication for the fourth patient was persistent facial asymmetry after two previous vertical ramus osteotomies (performed 25 and 13 years ago). The cause of the asymmetry was due to the fact that the patient had sustained a condylar fracture years before, with malformation and displacement of the condylar process.

All four patients were treated successfully with the protocol presented. The mean operating time was 238 ± 78.5 minutes (range 160–317 minutes). There were no postoperative complications such as bleeding, infection, loosening of the fixation PSIs,

or wound dehiscence. All three OSA patients were admitted for two post-operative nights and days before being discharged. The patient who underwent a BSSO stayed one postoperative night and day before being discharged. After 6 months, two patients complained of minor unilateral alveolar nerve impairment.

The planned translational and rotational movements of the maxilla and the postoperative outcomes are presented in Table 7.1. For the maxilla, the mean discrepancy of the translational outcomes was 0.6 mm. The mean discrepancy between the planned and achieved rotation for the maxilla was 1.9°, 0.1°, and 0.4° for pitch, yaw, and roll, respectively. For the mandible, the mean discrepancy of the osteotomy gap was 0.4 mm (Table 7.2).

Table 7.1 Planned translational and rotational movements of the maxilla in the MMA cases compared to the movements achieved (rounded to one decimal place). The discrepancy is the mean discrepancy between the planned and achieved movement.

	Maxilla 1		Maxilla 2		Maxilla 3		
Translation	**Planned (mm)**	**Achieved (mm)**	**Planned (mm)**	**Achieved (mm)**	**Planned (mm)**	**Achieved (mm)**	**Discrepancy (mm)**
Anterior - posterior	8.4	6.5	8.3	7.6	10.4	9.6	1.1
Right - left	0.2	-0.5	0.0	0.1	0.0	-0.3	0.3
Cranial - caudal	0.5	-0.5	0.8	0.8	1.4	1.0	0.5
Rotation	**Planned (degrees)**	**Achieved (degrees)**	**Planned (degrees)**	**Achieved (degrees)**	**Planned (degrees)**	**Achieved (degrees)**	**Discrepancy (degrees)**
Pitch	5.6	1.0	10.0	9.6	8.0	7.3	1.9
Yaw	-0.1	0.0	0.0	0.1	0.0	0.2	0.1
Roll	-0.6	-1.3	0.0	0.2	0.0	0.3	0.4

Table 7.2 Planned and achieved size of the right and left osteotomy gap of the mandible (in millimetres, rounded to one decimal place). The discrepancy is the mean discrepancy between the planned and the achieved gap size for the right and left sides respectively.

	Right side		Left side		Discrepancy	
Osteotomy gap	**Planned (mm)**	**Achieved (mm)**	**Planned (mm)**	**Achieved (mm)**	**Right side (mm)**	**Left side (mm)**
Mandible 1	-	-	-	-	-	-
Mandible 2	0.0	0.0	3.8	4.3	0.0	0.5
Mandible 3	11.3	12.0	14.9	14.5	0.7	0.4
Mandible 4	18.7	18.7	16.0	16.8	0.0	0.8

For the three OSA cases, the mean advancement of the maxilla was 9.35 ± 1.05 mm (range 8.3–10.4 mm), with a mean counterclockwise rotation of the maxillomandibular complex of 7.8 ± 2.2° (range 5.6–10.0°). The preoperative AHIs for these three OSA patients were 49.8, 83.0, and 90.0; the AHIs at 3 months postoperative were 16.2, 8.3, and 17.8, respectively. All three OSA patients were successfully treated according to the success criteria of Sher et al.[15]. Two patients (postoperative AHI 16.2 and 17.8 mainly in

supine position) were advised to start positional therapy. One patient (postoperative AHI 16.2) started positional therapy and the other (postoperative AHI 17.8) declined further OSA treatment, because of a lack of previous OSA complaints.
The patient receiving a BSSO for the correction of facial asymmetry was successfully treated in the opinion of both the patient and the surgeon. There was no clinically significant sign of soft tissue asymmetry.

Discussion

Orthognathic surgery in edentulous patients is not a procedure that is frequently encountered and performed. Such treatment is highly complex because of the lack of adequate reference points and the inability to create an optimal maxillomandibular fixation. In those cases where Gunning splints are used, these splints are usually of suboptimal fit, and inaccuracies are incorporated during surgery. These inaccuracies tend to be more extensive in larger advancements, such as in OSA cases treated with MMA.
Splintless orthognathic surgery has recently been reported extensively in orthognathic surgery for the dentate patient, with accurate and predictable results[3–6]. This study illustrated that a fully digital workflow with the use of CAD/CAM osteotomy guides and fixation PSIs is feasible and predictable for orthognathic surgery in edentulous patients.
A drawback that was experienced was the fact that multiple transbuccal accesses were required in case 1, due to the design of the cutting guides and fixation points. This is an inconvenience that may have considerable aesthetic repercussions. The design was optimized in the subsequent cases, with the screw holes designed more eccentrically to the mandibular surface (cases 2, 3 and 4). In these cases, all pre-planned fixation holes on each side of the mandible could be drilled through a single transbuccal approach (Figure 7.6a, b).
The orientation screws on both sides of the mandible body, which were used intraoperatively to achieve the exact position of the osteotomy guide, proved valuable in our experience (Figure 7.6a, b). The main benefit was correct positioning in the dorsoventral dimension. Improper positioning in the craniocaudal dimension is almost negligible, because the osteotomy guide embraces the mandibular body both cranially and caudally.
A second point of consideration is the size of the osteotomy guides (for both the maxilla and mandible), which results in the need for extensive soft tissue to be dissected compared to cases without osteotomy guides. Due to the need for more

extensive dissection and periosteal elevation, the use of a buccal sulcus approach was preferred here, as a crestal incision would require even more soft tissue dissection and elevation.

It should be noted that even though the osteotomy guides are of considerable size, the fixation PSIs are not significantly larger than conventional osteosynthesis implant material used in daily practice. In the design phase of the fixation PSI, extra attention was paid to prevent interference with the dentures postoperatively (Figure 7.3b, d). This was successful in all four patients: there was no need for removal of the fixation PSIs.

The PSIs were not significantly larger, but due to the specific 3D and interconnected design of the fixation PSIs, it is our opinion that these implants are more rigid than the commonly used osteosynthesis implant material. The fixated maxilla and mandible were found to be adequately stable in all cases. As a result of this, and specifically for the maxilla because of the counterclockwise rotation, there seemed to be adequate bony contact, which made bone grafting unnecessary.

A disadvantage that needs to be discussed is the cost of the technique presented. The costs of the osteotomy guides and fixation PSIs are much higher than those of traditional splints.

A disappointing finding in this study is the fact that movement of the mandibular segment could not be evaluated in 3D. The absence of the mandibular dentition unfortunately hampered CT comparison of the postoperative result with the mandible corresponding to its planned position relative to the cranial base. Correction of this position based on the position of the mandibular rami proved significantly prone to error. This made 3D postoperative evaluation using the OrthoGnathicAnalyser infeasible. A measurement of the gap was used to gauge mandibular advancement and compare it to the planned advancement. This is not ideal for evaluation purposes, but was the only feasible and reproducible method.

More empiric experience and a study with a larger sample size are needed. Randomized clinical trials are perhaps delusions in these rare situations. Due to the initial results of this study, the technique presented for orthognathic surgery in edentulous patients is believed to be superior to the traditional use of splints.

In conclusion, the edentulous population has not so far benefited to the same extent from new technologies in virtual planning. This paper presents a practical splintless orthognathic surgery protocol for edentulous patients requiring this type of surgery. With this treatment protocol, CAD/CAM osteotomy guides and PSIs are used to transfer and stabilize the desired final position of the edentulous maxilla and/or mandible. On comparison of the planned and achieved movements of the maxilla and mandible, the

protocol presented here was demonstrated to be accurate and predictable. A more rigorous method of evaluation for the mandible is recommended.

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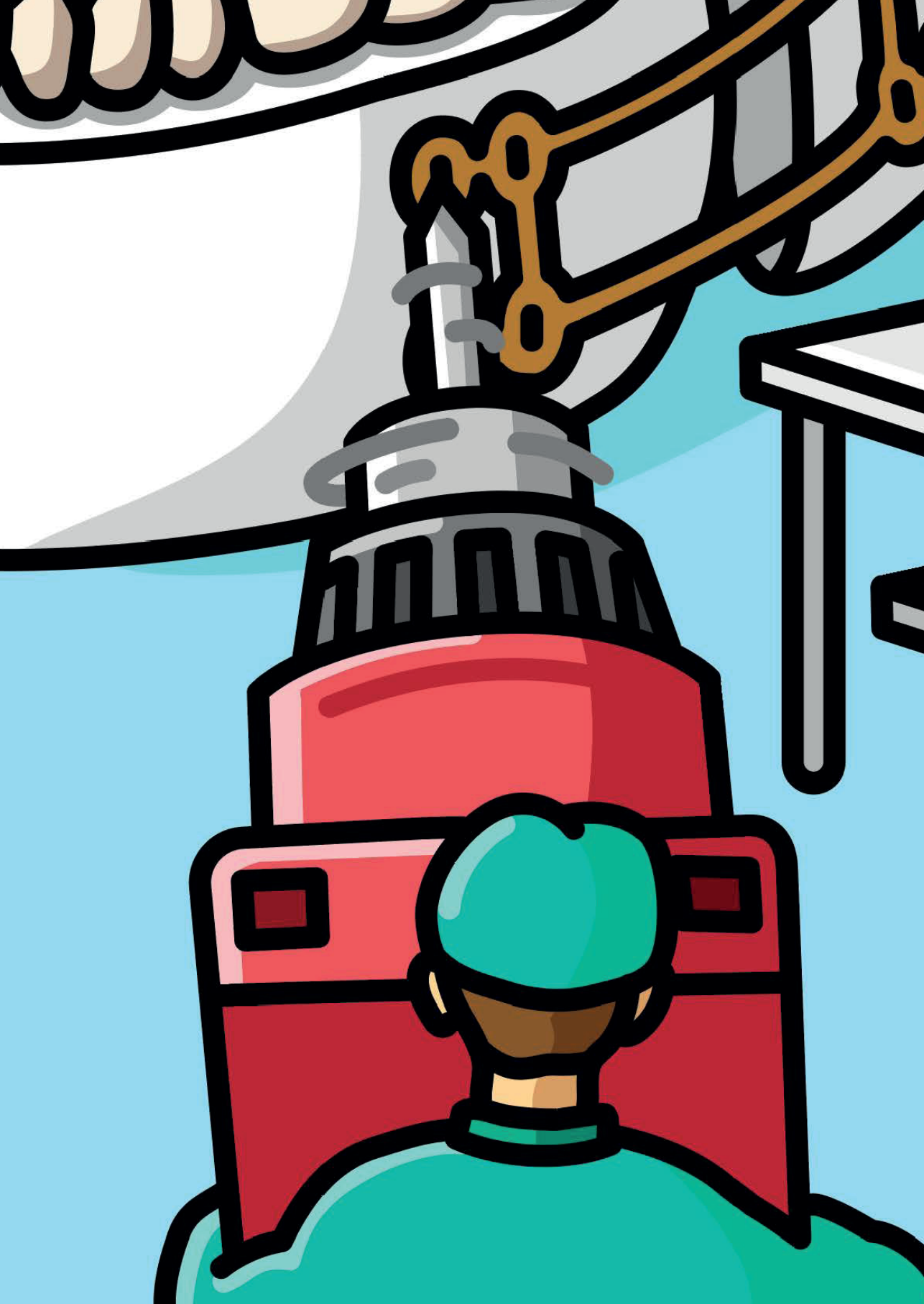

Chapter 8

Influence of surgeon experience on surgical outcome of maxillomandibular advancement for obstructive sleep apnea

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Chapter is based on the publication in:

Journal of Clinical Medicine 2023;12:3504.

Abstract

The primary aim of this study was to assess the association between clinical efficacy outcomes (i.e., polysomnography (PSG) results) of maxillomandibular advancement (MMA) and surgeons' experience. The second aim was to assess the association between the occurrence of postoperative complications of MMA and surgeons' experience. Patients treated with MMA for moderate to severe obstructive sleep apnea (OSA) were enrolled in this retrospective study. The patient population was divided into two groups based on two different surgeons performing MMA. The associations between surgeons' experience on the one hand and PSG results and postoperative complications on the other hand were investigated. A total of 75 patients were included. There was no significant difference in baseline characteristics between the two groups. The reductions in apnea-hypopnea index and oxygen desaturation index were both significantly greater in group-B than group-A (*P*=0.015 and 0.002, respectively). The overall success rate after MMA was 64.0%. There was a negative correlation between surgeon experience and surgical success (odds ratio: 0.963 [0.93, 1.00], *P*=0.031). No significant association was found between surgeon experience and surgical cure. Additionally, there was no significant association between surgeon experience and the occurrence of postoperative complications. Within the limitations of this study, it is concluded that surgeon experience may have little to no influence on the clinical efficacy and safety of MMA surgery in OSA patients.

Introduction

Obstructive sleep apnea (OSA) is a sleep breathing disorder where patients have repetitive episodes of partial or complete upper airway collapse and obstruction during sleep. This leads to absent and/or reduced respirations during sleep, which are called apneas and hypopneas, respectively[1]. It is estimated that globally, approximately 425 million adults between the ages of 30 and 69 have moderate to severe OSA[2]. OSA has been linked as an independent risk factor for cardiovascular, cerebrovascular, and metabolic diseases, reduced neurocognitive function, and increased mortality[3-8].

Since the inception of continuous positive airway pressure (CPAP) in 1981, it is currently still considered the first-line treatment of choice for moderate to severe OSA[9-11]. Nevertheless, patients and physicians may choose an alternative to CPAP due to, e.g., poor adherence to CPAP and the desire for a more tailor-made treatment based on patient preference, patient-reported outcome parameters, individual risk, and patient OSA phenotype[12-14].

Alternatives to CPAP therapy mainly include behavior strategies (e.g., weight loss), medical therapy (e.g., mandibular advancement devices (MADs)), and surgical therapy (e.g., upper airway surgery)[15]. Of the non-surgical alternative options to CPAP for the treatment of OSA, MADs are the most common modality. MADs advance the mandible in order to increase the airway volume and decrease the pharyngeal collapsibility[16]. There are different MAD designs, but a clear clinically relevant distinction in favor of one of the appliances cannot be drawn at this stage[16-19]. Given the variable efficacy and nature of life-long treatment with MADs, combined with potential side effects such as unwanted dental and skeletal changes, acceptance and adherence to MADs may decrease in OSA patients[17,20].

A surgical alternative with similar success rates to CPAP is maxillomandibular advancement (MMA)[14,21,22]. MMA is a skeletal surgery that addresses the entire upper airway[10]. It consists of surgical advancement of the maxilla and mandible — often combined with counterclockwise rotation of the maxillomandibular complex — by performing a combination of a Le Fort I osteotomy of the maxilla and a bilateral sagittal split osteotomy of the mandible[14,23]. Although there is only limited evidence on the association between the magnitude of advancement and reduction in AHI following MMA, a mandibular advancement of at least 10 mm has been recommended in MMA surgery for OSA[24,25]. By displacing the facial bones, MMA is able to enlarge multiple levels of the upper airway in both the medio-lateral and antero-posterior dimensions. In addition to enlarging the upper airway, MMA also increases tension and decreases collapsibility of the suprahyoid and velopharyngeal muscles[26,27].

Different aspects of MMA have been investigated in the past in order to see whether they are associated with a higher MMA success rate, e.g., certain patient

characteristics, specific comorbidities, particular polysomnography parameters, specific drug-induced sleep endoscopy findings, and certain surgical aspects[28-34].
However, one aspect that has not been investigated is whether MMA-related surgical experience has any bearing on the outcome after MMA. In many fields — such as general surgery or orthopedic surgery — it has been proven that operative results and health-related quality of life following surgery were significantly and positively correlated with surgeon experience and that outcomes of patients treated by less experienced surgeons were slightly worse than those treated by more experienced surgeons[35-38].
The aims of this study were (1) to assess the association between clinical efficacy outcomes (i.e., polysomnography (PSG) results) of MMA and surgeons' experience; and (2) to assess the association between the occurrence of postoperative complications of MMA and surgeons' experience. The hypothesis is that surgical outcomes after MMA are better when surgeons' MMA-related surgical experience increases.

Materials and methods

Ethical considerations

This study was deemed not to be subject to the Medical Research Human Subjects Act by the Medical Ethics Committee of the Amsterdam University Medical Centers (UMC), location Academic Medical Center (AMC) (reference number W23_017 # 23.041). A formal approval was therefore waived. Patients were sent a letter to inform them that their medical records, radiological images, and test results were going to be used for study purposes. They were given the option to object and opt out of inclusion in the study. This study was performed in accordance with the Declaration of Helsinki guidelines for human research, 1964, as amended in 2013 (64th WMA General Assembly, Fortaleza, Brazil). It was conducted at the Department of Oral and Maxillofacial Surgery of the Amsterdam UMC, The Netherlands.

Study participants

We performed a single-center retrospective study including a consecutive series of patients with OSA undergoing MMA surgery between January 2012 and March 2021 at the Department of Oral and Maxillofacial Surgery at the Amsterdam UMC, location AMC. Patients who met the inclusion criteria were eligible for this study.
The inclusion criteria were: (1) adults aged ≥18 years; (2) diagnosis of moderate to severe OSA (apnea-hypopnea index (AHI) ≥15 events/h) as determined by a preoperative overnight polysomnography (PSG); (3) continuous positive airway

pressure (CPAP) therapy failure or intolerance; and (4) presence of a follow-up PSG at least 3 months postoperatively. The exclusion criteria were: (1) no consent to the use of the patient record data for research purposes; (2) patients who underwent other adjunctive procedures at the time of MMA (e.g., multi-piece Le Fort osteotomy, temporomandibular joint reconstruction); (3) previous history of Le Fort I osteotomy or bilateral sagittal split osteotomy (BSSO); and (4) cleft palate and/or craniofacial syndromic patients.

The included medical records were reviewed, and data was collected. Preoperative (baseline) patient data included gender, age, and body mass index (BMI). The included patients were divided into two groups based on two different oral and maxillofacial surgeons (RA and JH), who performed the MMA surgery. Patients who were operated on by surgeon A were designated as group-A; patients who were operated on by surgeon B were designated as group-B.

Surgeon experience

Surgeon A started performing orthognathic and MMA surgery in March 2012; surgeon B first started performing orthognathic and MMA surgery in June 2017. For both surgeons, surgeon experience —i.e., MMA surgery-related experience— was calculated (in months) by subtracting the surgeon's starting date from the date on which MMA surgery was performed for each patient.

Maxillomandibular advancement surgery

All MMA procedures were completed using standardized surgical techniques by the two surgeons, which included a Le Fort I osteotomy for the maxilla in combination with a Hunsuck-Dal Pont modification of the Obwegeser BSSO for the mandible. Both the maxilla and mandible were advanced anteriorly and, whenever possible, counterclockwise rotated[23].

Prior to the availability of three-dimensional (3D) planning, patients were treated with a traditional two-dimensional (2D) planned surgical procedure using a standard surgical protocol with the goal of 8–10 mm advancement. Manually manufactured intraoperative occlusal splints were utilized in the planned 2D surgical procedure. After the availability of 3D planning, patients were virtually planned, and the degree of advancement was personalized based on multiple patient-related factors, including severity of OSA, skeletal pattern, dental occlusion, facial characteristics, prior upper airway surgery, and collapse pattern of the upper airway when pre-MMA drug-induced sleep endoscopy was available. Computer-aided design/computer-aided manufacturing of intraoperative occlusal splints were used in the 3D-planned surgical procedure[14].

Immediately postoperatively, all patients received extensive postoperative monitoring in either the intensive or medium care unit[39,40]. After being discharged from the intensive or medium care unit, the patients were transferred to a general post-surgery ward for further recovery[40].

Polysomnography

All patients underwent a level 1 or level 2 PSG preoperatively and at least 3 months postoperatively. PSG recordings were manually checked and scored according to the standards of the American Academy of Sleep Medicine (AASM) manual for the scoring of sleep and associated events[41]. The collected preoperative and post operative PSG variables included AHI, oxygen desaturation index (ODI), and lowest oxyhemoglobin saturation (LSAT).
Based on Sher's criteria, surgical success was defined as an AHI reduction of at least 50% and an AHI below 20 events/h postoperatively[42]. Surgical cure was defined as a postoperative AHI below 5 events/h[43].

Postoperative complication

Postoperative complications related to MMA surgery were assessed during the follow up for each patient. These were classified as minor or major complications according to the criteria of the "Accordion severity classification of postoperative complications" by Strasberg et al.[44].

Statistical analysis

All data were analyzed using SPSS software (version 27, IBM Corp., Armonk, NY, USA). A descriptive statistical analysis was performed for all demographic and outcome variables. Continuous variables were presented as mean and standard deviation (SD), and categorical variables were reported as frequency and percentage.
In order to compare baseline characteristics and surgical variables between group-A and group-B, the independent samples t-test was used. To determine how PSG values change from pre- to post-operative time between groups A and B, a two-way ANOVA test with one factor repeated was used. To investigate the association of surgeon experience with surgical success or cure, multivariate binary logistic regression analyses were used, with surgical success or surgical cure as dependent variables and surgeon experience as an independent variable, adjusted for surgeon groups (A and B), age, gender, baseline BMI, and baseline AHI. To investigate the association between surgeon experience and the AHI reduction after MMA, multivariate linear regression was used, with AHI reduction as the dependent variable and surgeon experience as the

independent variable, adjusted for surgeon groups (A and B), age, gender, baseline BMI, and baseline AHI. To analyze the correlation between surgeon experience and the occurrence of postoperative complications, multivariate ordinal regression was used with postoperative complications as the dependent variable and surgeon experience as the independent variable, adjusted for surgeon groups (A and B), age, gender, smoking, degree of mandibular advancement, degree of maxillary advancement, baseline BMI, and baseline AHI.

Results

At the department of Oral and Maxillofacial Surgery at the Amsterdam UMC, location AMC, a total of 80 patients underwent MMA for moderate to severe OSA either by surgeon A or surgeon B. Among these patients, two declined for their patient data to be used for research purposes; one was excluded due to the absence of available preoperative PSG data; and two were excluded because they underwent temporomandibular joint reconstruction in conjunction with MMA. Therefore, 75 patients were included in this study.

Baseline characteristics of group-A versus group-B

Group-A and group-B, consisted of 49 (65.3%) and 26 (34.7%) patients, respectively. In total, there were 64 males (85.3%) and 11 females (14.7%). The mean age was 50.7 ± 10.0 years, with a mean BMI of 30.2 ± 4.2 kg/m^2 for the total study population. There were 72 patients (96.0%) who presented with CPAP intolerance or failure prior to MMA. Additionally, 32 patients (42.6%) received a form of upper airway surgery for OSA prior to MMA. The mean preoperative AHI was 54.8 ± 21.3 events/h. There was no significant difference found between group-A and group-B in baseline characteristics. Baseline demographic characteristics and PSG values of the total population, group-A, and group-B are presented in Table 8.1.

Table 8.1 Baseline characteristics of the total population, group-A and group-B.

	Total Population (*n*=75)	**Group-A (*n*=49)**	**Group-B (*n*=26)**	***P*-value**
Male:female (*n*)	64:11	43:6	21:5	0.423
Age (years)	50.7 ± 10.0	50.7 ± 9.5	50.8 ± 11.0	0.969
BMI (kg/m^2)	30.2 ± 4.2	30.6 ± 4.4	29.5 ± 3.6	0.307
AHI (events/h)	54.8 ± 21.3	54.0 ± 21.6	56.2 ± 21.0	0.676
ODI (events/h)	54.8 ± 21.7	50.1 ± 20.9	62.3 ± 21.3	0.073
LSAT (%)	76.1 ± 11.0	76.6 ± 11.3	75.3 ± 10.6	0.634

Data presented as mean ± standard deviation. *P*-values comparing group-A and group-B. *P*-value <0.05 is considered statistically significant. AHI, apnea hypopnea index; BMI, body mass index; LSAT, lowest oxyhemoglobin saturation; ODI, oxygen desaturation index.

Surgical characteristics of group-A versus group-B

When comparing surgical variables between group-A and group-B, it was found that the degree of maxillary advancement, the degree of mandibular advancement, and the total operation time did not significantly differ between the 2 groups (*P*=0.260; *P*=0.078; *P*=0.051, respectively). Anticlockwise rotation of the maxillomandibular complex was performed in 20 patients in group-A (52.6%) and in 24 patients in group-B (96.0%). This difference between the two groups was, however, found to be statistically significant (*P*<0.001). The mean blood loss during surgery in group-A was significantly lower than that in group-B (347.6 ± 193.3 cubic centimeters [cc] vs. 455.6 ± 268.5 cc, *P*<0.001) (Table 8.2).

Table 8.2 Surgical characteristics of the total population, group-A and group-B.

	Total Population (*n*=75)	**Group-A (*n*=49)**	**Group-B (*n*=26)**	***P*-value**
Maxillary advancement (mm)	7.1 ± 2.4	7.4 ± 2.7	6.7 ± 1.9	0.260
Mandibular advancement (mm)	9.7 ± 4.4	8.9 ± 4.4	10.9 ± 4.1	0.078
Anticlockwise rotation of the jaw (%)	69.8	52.6	96.0	<0.001
Operation time (min)	222.2 ± 60.3	205.5 ± 60.1	253.8 ± 47.4	0.051
Blood loss (cc)	384.1 ± 225.6	347.6 ± 193.3	455.6 ± 268.5	<0.001

Data of maxillary advancement, mandibular advancement, operation time, and blood loss are presented as mean ± standard deviation. Data of rotation is presented as percentage. *P*-values compare surgical variables between group-A and group-B. *P*-value <0.05 considered statistically significant.

Postoperative outcomes of group-A versus group-B

The preoperative and postoperative PSG values are shown in Table 8.3. AHI, ODI, and LSAT were all significantly improved for both group-A and group-B (*P*<0.001) after MMA. In group-A the mean AHI decreased from 54.0 ± 21.6 to 20.0 ± 17.4 events/h, compared to a decrease from 56.8 ± 21.2 to 14.9 ± 15.7 events/h in group B, respectively. The improvement in AHI in group-B was significantly larger compared to that in group-A (*P*=0.015). The mean ODI decreased from 50.1 ± 20.9 to 28.7 ± 18.4 events/h in group-A, compared to a decrease from 62.3 ± 21.3 to 17.8 ± 11.8 events/h in group-B. The reduction of ODI in group-B was significantly larger than that in group-A (*P*=0.002). In contrast to the AHI and ODI, no significant difference was found between the two groups for the improvement of the LSAT after MMA (*P*=0.163).

Table 8.3 Preoperative and postoperative polysomnography values for group-A and group-B.

		Preoperative	Postoperative	*P*-value	Δ	*P*-value*
AHI (events/h)	Group A	54.0 ± 21.6	20.0 ± 17.4	<0.001	34.0 ± 23.2	0.015
	Group B	56.8 ± 21.2	14.9 ± 15.7	<0.001	41.9 ± 24.5	
ODI (events/h)	Group A	50.1 ± 20.9	28.7 ± 18.4	<0.001	21.4 ± 20.0	0.002
	Group B	62.3 ± 21.3	17.8 ± 11.8	<0.001	44.5 ± 25.1	
LSAT (%)	Group A	76.7 ± 11.6	85.1 ± 5.9	<0.001	8.3 ± 11.0	0.163
	Group B	75.0 ± 10.9	84.0 ± 7.3	<0.001	9.0 ± 8.4	
Success (*n*, (%))	Group A	-	29 (59.2)	-	-	0.065
	Group B		19 (73.1)			
Cure (*n*, (%))	Group A	-	12 (24.5)	-	-	0.151
	Group B		5 (19.2)			

Data presented as mean ± standard deviation. *P*-values compare preoperative and postoperative polysomnography values. *P*-value * compare Δ (preoperative and postoperative change) between group-A and group-B. *P*-value <0.05 is considered statistically significant. AHI, apnea hypopnea index; LSAT, lowest oxyhemoglobin saturation; ODI, oxygen desaturation index.

Correlation between surgeon experience and surgical outcome

In the total study population, surgical success was achieved in 48 patients (n=48/75; 64.0%). Surgical success was achieved in 29 patients (n=29/49; 59.2%) and in 19 patients (n=19/26; 76.0%), in group-A and group-B respectively. Surgical cure was achieved in 17 patients (n=17/75; 22.7%) in the total population, 12 patients (n=12/49; 24.5%) in group-A and 5 patients (n=5/26; 20.0%) in group B. The mean surgical experience of surgeon A was 34.0 ± 20.7 months, and the mean surgical experience of surgeon B was 23.4 ± 11.0 months. There was no significant difference found between the two-groups in surgical success (*P*=0.065) or surgical cure (*P*=0.151). The results of the binary logistic regression analyses — in order to investigate the correlation between surgeon experience and surgical cure or surgical success, adjusted for surgeon group (A and B), age, gender, baseline BMI, and baseline AHI — are shown in Table 8.4. There was a slightly negative correlation between surgeon experience and surgical success (odds ratio: 0.963 [0.93, 1.00], *P*=0.031). No significant correlation was found between surgeon experience and surgical cure (*P*=0.535).

Correlation between surgeon experience and AHI reduction

The results of the linear regression — in order to investigate the correlation between surgeon experience and AHI reduction — are shown in Table 8.5. There was no significant correlation found between surgeon experience and AHI reduction (*P*=0.489).

Table 8.4 Results of binary logistic regression for surgeon experience and surgical success and cure.

Variable	B	S.E.	Exp(B)	95% CI	*P*-value
Surgical Success					
Constant	6.958	3.527	1051.166	-	0.049
Surgeon experience (month)	−0.037	0.017	0.963	[0.931, 0.997]	0.031
Age (years)	−0.082	0.034	0.921	[0.863, 0.984]	0.015
Gender					
Female (Ref.)					
Male	−0.768	0.806	0.464	[0.095, 2.253]	0.341
Baseline BMI (kg/m^2)	−0.022	0.074	0.978	[0.847, 1.130]	0.766
Baseline AHI (events/h)	0.004	0.013	1.004	[0.979, 1.030]	0.750
Surgeon group	0.407	0.623	1.502	[0.443, 5.097]	0.514
Surgical cure					
Constant	0.717	3.417	2.049	-	0.834
Surgeon experience (month)	−0.012	0.019	0.989	[0.953, 1.025]	0.535
Age (years)	−0.038	0.033	0.962	[0.902, 1.026]	0.241
Gender					
Female (Ref.)					
Male	−1.077	0.867	0.340	[0.062, 1.863]	0.214
Baseline BMI (kg/m^2)	0.051	0.072	1.053	[0.914, 1.212]	0.476
Baseline AHI (events/h)	−0.004	0.014	0.996	[0.970, 1.024]	0.791
Surgeon group	−0.637	0.690	0.529	[0.137, 2.046]	0.356

The results are adjusted for age, gender, baseline BMI, and baseline AHI. *P*-value <0.05 is considered statistically significant. AHI, apnea hypopnea index; BMI, body mass index; CI, confidence interval for B; SE, standard error.

Table 8.5 Results of linear regression for surgeon experience and the AHI reduction after MMA.

Variable	B	S.E.	95% CI	*P*-value
AHI Reduction				
Constant	15.745	20.319	[−24.812, 56.303]	0.441
Surgeon experience (month)	−0.074	0.106	[−0.286, 0.138]	0.489
Age (years)	−0.417	0.186	[−0.787, −0.046]	0.028
Gender				
Female (Ref.)				
Male	−2.750	5.312	[−13.354, 7.854]	0.606
Baseline BMI (kg/m^2)	−0.035	0.451	[−0.935, 0.865]	0.938
Baseline AHI (events/h)	0.845	0.084	[0.678, 1.013]	<0.001
Surgeon group	4.527	3.924	[−3.305, 12.359]	0.253

The results are adjusted for age, gender, baseline BMI, and baseline AHI. *P*-value <0.05 considered statistically significant. AHI, apnea hypopnea index; BMI, body mass index; CI, confidence interval for B; SE, standard error.

Correlation between surgeon experience and occurrence of postoperative complications

Twenty-four of 75 patients (32%; 19 in group A and 5 in group B) did not experience any postoperative complications. Minor complications occurred in 25 patients (n=25/75;

33.3%) of the total study population; 11 patients (n=11/49; 22.4%) in group-A; and 14 patients (n=14/26; 53.8%) in group-B. Major complications occurred in 26 patients (n=26/75; 34.7%) of the total study population; 19 patients (n=19/49; 38.8%) in group-A; and 7 patients (n=7/26; 26.9%) in group-B (Table 8.6). The results of the correlation between surgeon experience and the occurrence of postoperative complications are shown in Table 8.7. There was no significant correlation found between surgeon experience and the occurrence of postoperative complications (*P*=0.656).

Table 8.6 Occurrence of postoperative complications for the total population, group-A and group-B.

Complications	**Number of Events (% of Population)**	**Group-A**	**Group-B**
Minor complication			
Neurosensory disturbance	38 (50.7)	18 (24.0)	20 (26.7)
Major complication			
Osteosynthesis infection	17 (22.7)	11 (14.7)	6 (8.0)
Malocclusion	5 (6.7)	5 (6.7)	0 (0)
Non-union	4 (5.3)	3 (4.0)	1 (1.3)
Complications	**Number of Subjects (% of Population)**	**Group-A**	**Group-B**
No complication	24 (32.0)	19 (25.3)	5 (6.7)
Any complication			
Minor complication	25 (33.3)	11 (14.7)	14 (18.7)
Major complication	26 (34.7)	19 (25.3)	7 (9.3)

Complications are categorized as major and minor complications. Complications are presented as number of events and number of patients for the total population, group-A, and group-B.

Table 8.7 Results of ordinal regression for surgeon experience and occurrence of postoperative complications.

Variable	**B**	**S.E.**	**Exp(B)**	**95% CI**	***P*-value**
Constant for Minor complications	−1.274	2.809	0.280	[0.001, 68.786]	0.650
Constant for Major complications	0.307	2.806	1.359	[0.006, 332.620]	0.913
Surgeon Experience (months)	−0.008	0.017	0.992	[0.960, 1.026]	0.656
Age (years)	0.026	0.027	1.026	[0.974, 1.081]	0.333
Gender					
Female	−0.957	0.835	0.384	[0.075, 1.974]	0.252
Male (Ref.)	-	-	-	-	-
Baseline BMI (kg/m^2)	−0.018	0.064	0.982	[0.866, 1.114]	0.776
Baseline AHI (events/h)	−0.005	0.013	0.995	[0.969, 1.022]	0.734
Mandibular advancement (mm)	0.139	0.094	1.149	[0.956, 1.381]	0.139
Maxillary advancement (mm)	−0.059	0.188	0.943	[0.652, 1.362]	0.753
Smoking (no smoking)	−1.672	0.845	0.188	[0.036, 0.984]	0.048
Smoking (<10 p/week)	−1.504	0.961	0.222	[0.034, 1.462]	0.118
Smoking (>10 p/week) (Ref.)	-	-	-	-	-
Surgeon group	0.108	0.68	1.114	[0.293, 4.233]	0.874

The results are adjusted for age, gender, smoking, baseline BMI, baseline AHI, mandibular advancement, and maxillary advancement. *P*-value <0.05 is considered statistically significant. AHI, apnea hypopnea index; BMI, body mass index; CI, confidence interval for B; SE, standard error.

Discussion

This study was set out with the aim of assessing whether surgeon experience influences the surgical outcomes of MMA. In order to do so, clinical efficacy outcomes (i.e., polysomnography (PSG) results) and postoperative complications of MMA surgeries — performed by two oral and maxillofacial surgeons with different surgical experiences — were analyzed. As far as the authors are aware, this is the first study that has specifically looked into these issues related to MMA outcomes.

The study results show that, in contrast to general and orthopedic surgery literature, which has shown that surgeon experience is correlated with surgical outcomes, surgeon experience was slightly negatively associated with surgical success and was not associated with surgical cure[35-38]. To further investigate this finding, we investigated whether surgeon experience has any correlation with AHI reduction to complement the effect of surgeon experience on MMA. This, however, was also found not to be the case. This might be explained by the fact that more experienced surgeons might have strived to treat the more complicated OSA cases. A different possible explanation for these results might be the inherent complexity of OSA itself. Other authors have previously stated that in addition to anatomical factors, non-anatomical factors — e.g., critical closing pressure, loop gain, muscle responsiveness, and arousal threshold — might play an important role in OSA phenotyping and the treatment outcome of the OSA patient[31,34,45-49]. These features are, of course, independent of surgeon experience and could therefore explain these findings.

Although no correlation was found between surgeon groups (A and B) and surgical outcomes, when evaluating the preoperative and postoperative PSG values between the two-groups, it was found that the decreases in AHI and ODI were significantly greater in group-B compared to group-A. A possible explanation for this might be that the preoperative AHI and ODI in group-B were slightly higher compared to group-A. As a result, a greater reduction in AHI and ODI following MMA was possible. Another explanation could be the difference in surgical techniques between the two surgeons. As the use of anticlockwise rotation of the jaw was significantly higher and the degree of mandibular advancement tended to be larger in group-B, this may have contributed to a more favorable effect on the upper airway[23]. Hence, sufficient jaw advancement may be an important factor associated with MMA treatment outcome, which needs to be further investigated in future research.

Additionally, the results showed that surgeon experience was not associated with the occurrence of postoperative complications after MMA. Similar to the reported literature, this study's results illustrate that plate infection and removal, which is considered a major complication, is the main indication requiring readmission and/or

reoperation[21,44]. When looking at the minor complications, these study results also show that neurosensory disturbance proved to be the most reported (minor) complication after MMA[21,22].

When interpreting the results of this study, one should bear in mind that there are several factors that must be taken into consideration in addition to certain limitations of this study. Due to the retrospective study design, there is, of course, a possibility for selection bias[50]. Secondly, the sample size of the two-groups could be considered quite small, which could therefore potentially lead to sampling bias[51]. When looking at the size of the two-groups, there could be a potential for selection bias[50]. However, when looking at the baseline characteristics for the two-groups, no significant difference was found, and these could be regarded as homogenous. Thirdly, the same previous argument can be made for the limited number of surgeons (n=2) evaluated in this study. Fourthly, the overall success rate in this study is lower than reported elsewhere in the literature[21,25]. This could be due to the fact that MMA in our center is mainly indicated for more severe to extreme OSA patients (mean AHI of 54.8 events/h), whereas other studies also include more moderate to less severe OSA patients[52,53]. In addition to a higher preoperative AHI, the average age among patients included in this study was also higher compared to other studies on the surgical outcome of MMA[21]. These findings could potentially not be extrapolated to all patients and therefore be limited to this specific patient profile. Fourth, PSG variables and complications might be insufficient to address our research question. Finally, comparable to earlier papers, this study defined surgeon experience as the number of months of practice[35,38,54]. Some might argue that experience might be better measured in case volume[37,38]. When looking at the number of cases between the two-groups, surgeon A almost had twice as many cases as surgeon B; nevertheless, the study results exhibited that this difference in volume between the two surgeons proved to have no bearing on surgical outcome or the occurrence of complications between the two surgeons. It should be noted that many factors are involved in a surgeon's experience, such as the number of surgeries he/she performed during training, additional training — for example, fellowships — and the experience level of the training surgeon's tutor, which are not taken into account in this study.

In order to better investigate the association between the surgeon's experience and MMA surgical outcome, as part of the standards of MMA surgery care for patients with OSA, the authors do recommend that prospective studies with a large sample size be executed. In addition, more research is necessary on different aspects of MMA, such as surgical techniques, quality of life, and long-term outcome[55-57]. In addition to MMA, other alternatives to CPAP, such as MADs and hypoglossal nerve stimulation, have shown promising outcomes in well-selected OSA patients[15]. Therefore, for OSA patients

who refuse CPAP therapy, alternative treatments should be considered based on both patient phenotypes and patient preferences.
In spite of the limitations of this study and the fact that no association was found between surgeon experience and surgical outcome, the authors still feel that the study is relevant and provides insight into factors that might and might not notably contribute to the surgical outcome after MMA.

Conclusions

Within the confines of the study limitations, the findings reject the hypothesis that surgical outcome after MMA is better — with regards to surgical success, surgical cure, and lower occurrence of complications — when the surgeons' experience increases.

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Chapter 9

Assessment of surgical accuracy in maxillomandibular advancement surgery for obstructive sleep apnea: A preliminary analysis

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Chapter is based on the publication in:

Journal of Personalized Medicine 2023;13:1517

Abstract

This retrospective study aimed to: (1) investigate the surgical accuracy of maxillomandibular advancement (MMA) in obstructive sleep apnea (OSA) patients, with a specific focus on maxillary and mandibular advancement and counter-clockwise rotation and (2) investigate the correlation between the amount of achieved advancement and the reduction in the relative apnea hypopnea index (AHI). Sixteen patients, for whom a three-dimensional virtual surgical plan was generated preoperatively and a computed tomography scan (CT) or cone-beam computer tomography (CBCT) was acquired postoperatively, were included. The postoperative CT or CBCT was compared to the virtual surgical plan, and differences in the mandibular and maxillary advancement and counterclockwise rotation were assessed. Maxillary and mandibular advancement (median 3.1 mm, *P*=0.002 and 2.3 mm, *P*=0.03, respectively) and counter-clockwise rotation (median 3.7°, *P*=0.006 and 4.7°, *P*=0.001, respectively) were notably less than intended. A significant correlation was found between the planned maxillary advancement and the difference between the planned and actual maxillary advancement (*P*=0.048; adjusted R^2=0.1979) and also between the planned counterclockwise rotation and the difference between the planned and actual counter-clockwise rotation for the mandible (*P*=0.012; adjusted R^2=0.3261). Neither the maxilla-first nor the mandible-first surgical sequence proved to be superior in terms of the ability to achieve the intended movements (*P*>0.45). Despite a significant reduction (*P*=0.001) in the apnea hypopnea index (AHI) from a median of 62.6 events/h to 19.4 events/h following MMA, no relationship was found between the extent of maxillary or mandibular advancement and AHI improvement in this small cohort (*P*=0.389 and *P*=0.387, respectively). This study underlines the necessity for surgeons and future research projects to be aware of surgical inaccuracies in MMA procedures for OSA patients. Additionally, further research is required to investigate if sufficient advancement is an important factor associated with MMA treatment outcome.

Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by repeated partial or complete obstruction of the upper airway, leading to hypopneas or apneas[1]. Patients frequently suffer from excessive daytime sleepiness, fatigue, tiredness, snoring, gasping, and morning headaches[2]. Risk factors for OSA mainly include older age, male sex, obesity, smoking, alcohol use, family history of OSA, and craniofacial and upper airway morphology[3–5].

For decades, the preferred first-line treatment option for moderate-to-severe OSA has been nonsurgical 'continuous positive airway pressure' (CPAP)[6–8]. Another common non-invasive option for OSA treatment is the use of a mandibular advancement device (MAD)[9]. A disadvantage of CPAP and MAD is suboptimal long-term adherence. Surgical therapy provides a solution for OSA patients who have difficulties accepting lifelong treatment with CPAP or MAD. In an American Academy of Sleep Medicine clinical practice guideline, it is recommended that clinicians discuss and/or refer adult OSA patients with a body mass index (BMI) <40 kg/m^2 who are intolerant or unaccepting of positive airway pressure (PAP) to a sleep surgeon for an alternative treatment option, as part of a patient-oriented solution[10].

Maxillomandibular advancement surgery (MMA) has proven to be the most effective surgical treatment for OSA—aside from tracheostomy—with a success rate of approximately 85%[8,11–13]. The surgical procedure consists of a combination of a Le Fort I osteotomy for the maxilla and a bilateral sagittal split osteotomy (BSSO) for the mandible. The maxilla and mandible are both significantly advanced and rotated counter-clockwise to enlarge the upper airway's volume and reduce upper airway soft tissue collapsibility[13–15]. Virtual surgical planning (VSP) is used for preoperative simulation of the MMA, and 3D-printed surgical splints are generated from the VSP to transfer the plan to the surgical setting[16]. Since large maxillomandibular complex advancement and counterclockwise rotation contribute to a decrease in the apnea hypopnea index (AHI) and therefore treatment success, achieving these planned movements accurately during surgery is essential[12,17]. Previous research has shown that the planned surgical movements are often not accurately achieved in standard orthognathic surgery, especially in cases with larger movements[18]. Given the extensive movements involved in MMA, it is reasonable to expect that the planned movements in MMA might be even less accurately achieved compared to standard orthognathic surgery. Surprisingly, no prior studies have investigated the extent to which planned—specifically sagittal—movements are accurately achieved in MMA procedures.

The primary aim of this study was to investigate the extent to which planned advancement and counter-clockwise rotation, the two most relevant movements for surgical success in MMA for OSA surgery, are accurately achieved. The secondary aim of

this study was to investigate the correlation between realized maxillary and mandibular advancement and relative AHI reduction.

Materials and methods

Study participants

Patients treated for OSA with MMA in the Department of Oral and Maxillofacial Surgery of the Amsterdam University Medical Centers (UMC) between November 2017 and March 2020 were considered for inclusion in this study. The inclusion criteria were: (1) adults aged 18 years or older; (2) diagnosed with OSA through polysomnography (PSG); (3) CPAP therapy failure or intolerance; (4) PSG conducted at least 3 months postoperatively; (5) preoperative three-dimensional (3D) virtual surgical planning of MMA; and (6) availability of a spiral computed tomography (CT) or cone-beam computer tomography (CBCT) scan after surgery. Exclusion criteria were: (1) patients undergoing other additional procedures during MMA (e.g., multi-piece Le Fort osteotomy, temporomandibular joint (TMJ) reconstruction); (2) previous Le Fort I osteotomy or BSSO; (3) cleft palate or syndromic patients; and (4) insufficient image quality for postoperative analysis. The study design was a retrospective cohort study.
This study was conducted and performed in accordance with the Declaration of Helsinki guidelines for human research. Patients were sent a letter to inform them that their medical records, polysomnography results, and radiological images were anonymously going to be used for study purposes. The option was provided to opt out of inclusion in the study. Included patients' medical records were reviewed and data were collected. Preoperative (baseline) patient characteristics included gender, age, and body mass index (BMI).
The Medical Ethics Committee of the Amsterdam UMC decided that this study was waived for the Medical Research Human Subjects Act (W22_042 # 22.07).

Imaging protocol

CT (Somatom Force, Siemens Medical Solutions, Erlangen, Germany) or CBCT (Planmeca Promax, Planmeca OY, Helsinki, Finland) scans were acquired 1 to 6 weeks preoperatively using a standardized protocol (120 kV, 300 mAs, field of view (FOV) 240 mm, pitch 0.55, slice thickness 1.0 mm, image matrix 512 × 512, window W1600/L400, hard-tissue kernel (Hr64)) or CBCT scan (84–96 kV, 100 mAs, FOV 230 mm × 170 mm (diameter × height), slice thickness 0.4 mm, image matrix 575 × 575, window/level 2500/596, pixel size 0.4 mm). Scanned patients were instructed to remain still, relax, and place the bite in a retruded contact position.

Baseline two-dimensional skeletal patterns and relationships were obtained on lateral cephalometric radiographs between 1 and 6 weeks preoperatively. Steiner radiographic cephalometric analyses were performed in Viewbox (version 4; dHAL Software, Kifissia, Greece).

Virtual surgical planning

Preoperative CT or CBCT data were exported in digital imaging and communications in medicine (DICOM) format and imported into the Maxilim software (Medicim NV, Mechelen, Belgium) (until April 2017) or IPS CaseDesigner (KLS Martin, Tuttlingen, Germany) (from May 2017 onwards). A 3D virtual patient model was reconstructed and aligned with the patient's natural head position (NHP) based on clinical assessment and standardized patient photos[19]. The maxilla and mandible were virtually osteotomized according to a Le Fort I osteotomy and BSSO, respectively (Figure 9.1). Based on the planned maxillary and mandibular position, intermediate and final splints were designed and 3Dprinted for either maxilla-first or mandible-first treatment sequence based on the surgeon's preference.

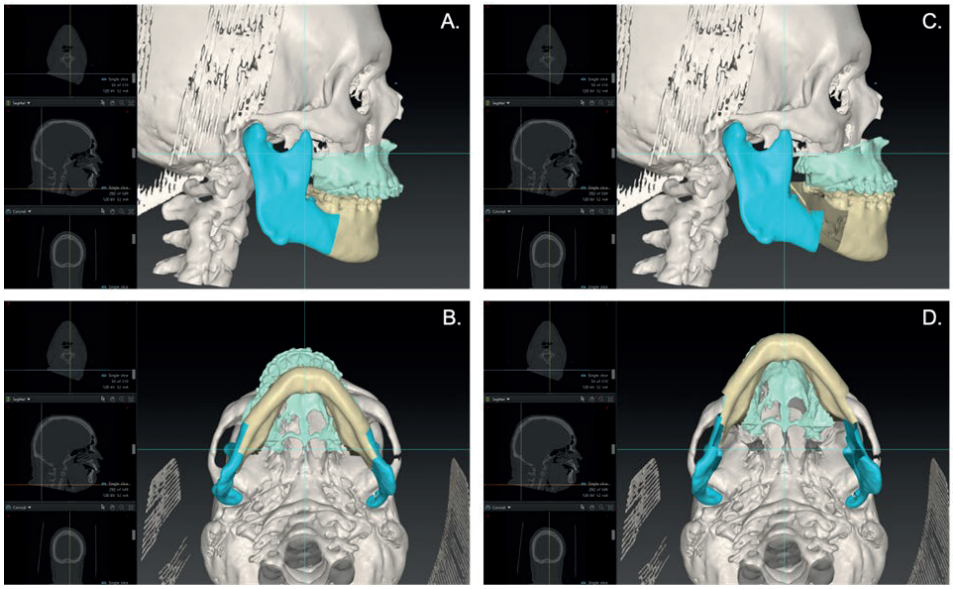

Figure 9.1 An example of a virtual plan of an MMA case. Lateral (**A**) and caudal (**B**) view of the preoperative 3D virtual hard-tissue skull model of the patient in IPS (KLS Martin, Tuttlingen, Germany). Lateral (**C**) and caudal (**D**) view of the postoperative 3D virtual hard-tissue skull model, where the maxilla and mandible are virtually osteotomized according to a Le Fort I osteotomy and BSSO. The maxilla and mandible are advanced and counter-clockwise pitched.

Surgical technique

Le Fort I osteotomy

A gingivobuccal incision was made, apical, from the first molar on the right to the first molar on the left. Subperiosteal dissection and elevation of the oral soft tissue and nasal mucosa were performed. A Le Fort I osteotomy was performed using a reciprocating saw from the pterygoid processes towards the piriform rims. A glabella reference marker was placed. Down-fracturing and mobilization of the maxilla was performed with a bone hook and Rowe's forceps. A surgical splint was used to position the maxilla in the intended planned position after the removal of interferences. Temporary maxillomandibular fixation was performed using power chains or steel wire ligatures. Rigid fixation was applied with an array of titanium miniplates and monocortical screws. Wound closure followed with absorbable sutures.

Bilateral Sagittal Split Osteotomy (BSSO)

A mucosal incision was made with subperiosteal dissection and elevation of the oral soft tissue along the anterior border on one side of the ramus and continued inferiorly, along the external oblique ridge. A horizontal, oblique, and vertical osteotomy was placed with either a burr or reciprocating saw according to the Hunsuck modification of the Obwegeser and Dal Pont BSSO technique[20]. The bone segments were separated with osteotomes and a bone spreader. The same procedure was applied on the contralateral side. A surgical splint was used to position the mandible in the planned position, and rigid fixation was applied with an array of titanium miniplates and monocortical or bicortical screws after putting the maxillomandibular complex into temporary maxillomandibular fixation with power chains or steel wire ligatures. Wound closure followed with absorbable sutures.

In the maxilla-first surgical protocol, the Le Fort I osteotomy was performed before the BSSO, and in the mandible-first protocol, the BSSO was performed before the Le Fort I osteotomy. Antibiotics (Augmentin, GlaxoSmithKline BV, Zeist, The Netherlands) were administered at the start of the procedure and continued for 7 days postoperatively. All patients were monitored for at least one night in the intensive care or medium care unit[21].

Outcome evaluation

In order to evaluate the accuracy of the achieved postoperative result, the preoperative and postoperative DICOM data were imported into 3D MedX (3D Lab Radboudumc, Nijmegen, the Netherlands) to assess the surgical result with the OrthoGnathicAnalyser

workflow[18,22]. This is a validated evaluation tool, which is able to calculate the transformation between the planned and achieved maxilla and mandible and express the deviation in clinically relevant parameters: (1) front–back translation (posteroanterior axis); (2) right–left translation (lateromedial axis); (3) up–down translation (superoinferior axis); (4) roll; (5) pitch; and (6) yaw (Figure 9.2). The main goal in MMA surgery is to adequately advance the maxilla and mandible and rotate them counter-clockwise in order to enlarge the upper airway. It is therefore essential to achieve the planned advancement and counter-clockwise rotation; thus, these were the parameters that were investigated in this study.

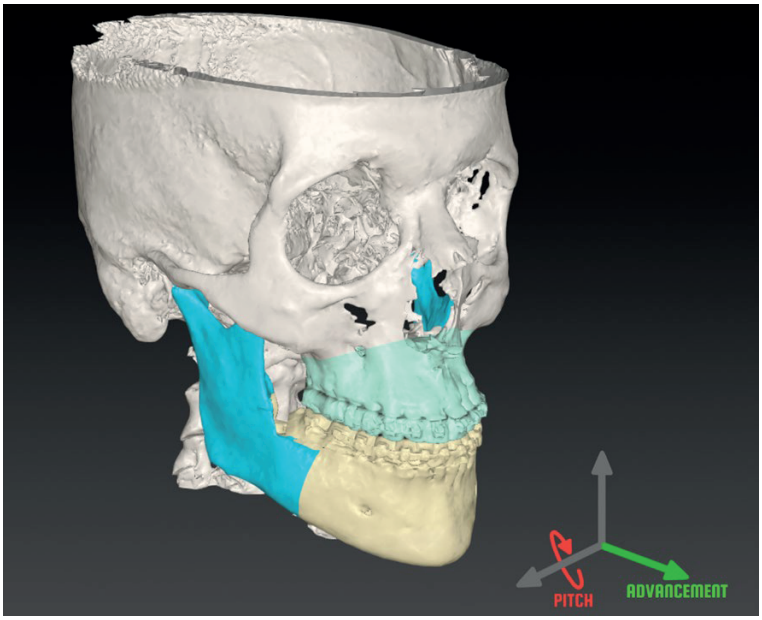

Figure 9.2 Maxillomandibular complex positioning frame. The back to front (advancement) translation in green and pitch rotation in red around the reference axes are visualized.

Patients received a full-night level 1 (in lab) or 2 (at home) PSG prior to MMA surgery and at least 3 months after surgery (Somnoscreen; SOMNOmedics GmbH, Randersacker, Germany). To assess sleep stages, EEG (F3, F4, C3, C4, M1, M2, O1, O2), EOG, and submental EMG were used. Nasal airflow was measured with a cannula/pressure transducer. Oronasal thermal flow determined airflow and mouth breathing. Arterial oxyhemoglobin was monitored via pulse oximetry. Thoracoabdominal excursions were measured qualitatively with respiratory belts. A position sensor determined body position, and limb movements were detected with

tibial EMG. Cardiac events were scored via ECG, and snoring was recorded with a snore sensor. A clinical neurophysiologist specialized in scoring sleep studies interpreted and scored the sleep studies based on the updated 2007 criteria from the American Academy of Sleep Medicine[23]. Included PSG parameters consisted of the preoperative and postoperative apnea hypopnea index (AHI), 3% oxygen desaturation index (ODI), and lowest oxygen saturation (LSAT). According to Sher's criteria, surgical response was defined as "at least 50% AHI reduction following MMA and a postoperative AHI<20"[24].

Sample size

Due to the nature of retrospective design, the sample size was not estimated prior to the study. A post hoc power analysis was performed for the primary outcome variables (i.e., observed differences between planned and achieved movements) using G*Power (Version 3.1.9.6, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany).

Statistical analysis

Statistical analysis was performed using SPSS (version 29.0; IBM Corp., Armonk, NY, USA) and R (R Development Core Team, Vienna, Austria). Descriptive statistics were calculated for all demographic and outcome variables. Mean, standard deviation, median, interquartile range (IQR), and/or range were used to report the continuous variables, and frequency and percentage were used for summarizing categorical variables. Normality was tested using the Shapiro–Wilk test. To compare the paired continuous values, the paired-samples t-test (for data with a normal distribution) or Wilcoxon's signed-rank test (for non-normal data) were used. To compare continuous values between the maxilla-first and mandible-first surgical sequence group, the independent-samples t-test was used when data were normally distributed, and the Mann–Whitney U test was used when data were not normally distributed. Linear regression analysis was performed to investigate the association between the planned movement and the difference between the planned and achieved movement. Adjusted R-squared (R^2) value was used to quantify the proportion of the variance that could be explained by the planned movement in the linear regression model. The relative AHI improvement was calculated, and a Pearson correlation analysis was used to investigate its relationship with the amount of maxillary and mandibular advancement. For all analyses, a *P*-value <0.05 was considered statistically significant.

Results

Study participants

In total, 27 patients underwent MMA for OSA in the Department of Oral and Maxillofacial Surgery, Amsterdam UMC, between November 2017 and March 2020. One patient opted out of the study, and ten patients were excluded due to the fact that the 3D-imaging protocol was not followed correctly, which was mostly due to the absence of a CT or CBCT scan after surgery (n=7). Therefore, 16 patients were included in this study; 10 were male and 6 were female. The mean age was 53 ± 9 years (range 36–69 years) (Table 9.1). Among the included sixteen patients, all patients (100%) had treatment failure or intolerance to CPAP, twelve patients (75%) had treatment failure or intolerance to MAD, and seven patients (44%) had other type(s) of upper airway surgery prior to MMA.

Table 9.1 Baseline characteristics of the study population.

Total population (N=16)		**mean ± SD**	**range**
Male (n (%))	10 (62.5)		
Age (years)		52.9 ± 9.3	36-69
BMI (kg/m²)		27.1 ± 3.9	18.0 — 32.4
∠SNA (degrees)		80.40 ± 3.9	69.6 — 88.1
∠SNB (degrees)		73.9 ± 7.4	52.0 — 83.8
∠ANB (degrees)		6.1 ± 5.0	-0.1 — 17.7
∠OP-SN (degrees)		20.8 ± 12.0	5.0 — 59.9
∠MP-SN (degrees)		42.5 ± 16.3	13.6 — 90.5

Gender is presented as number of patients and percentage. Age, BMI, ∠SNA, ∠SNB, ∠ANB, ∠OP-SN, and ∠MP-SN are presented in years, kg/m², and degrees. ∠ANB, angle between the A/nasion plane and the nasion/B plane; BMI, body mass index; cm, centimeters; kg/m², kilograms per square meter; ∠MP-SN, angle between the mandibular plane and the sella/nasion plane; ∠OP-SN, angle between the occlusal plane and the sella/nasion plane; SD, standard deviation; ∠SNA, angle between the sella/nasion plane and the nasion/A plane; ∠SNB, angle between the sella/nasion plane and the nasion/B plane. *P*-value <0.05 was considered statistically significant.

Planned vs. realized movements

The median planned advancement of the maxilla was 9.5 mm (range 6.0–12.0 mm), and the median planned advancement for the mandible was 11.2 mm (range 4.9–18.4 mm). The planned median counter-clockwise rotation for the maxilla and mandible were 6.2° (range 0.0–10.2°) and 7.8° (range 1.2–25.4°), respectively. For both the maxilla and mandible, the achieved advancement and counter-clockwise rotation were significantly smaller than the planned advancement and rotation (P<0.05) (Table 9.2). The study revealed that a larger advancement corresponded to a larger difference between the

planned and realized advancement for both the maxilla and mandible. Notably, this difference was only found to be statistically significant for the maxilla (P=0.048; adjusted R^2=0.20) and not for the mandible (P=0.06; adjusted R^2=0.18) (Figure 9.3). A larger counter-clockwise rotation was associated with a significantly greater difference between the planned and realized counter-clockwise rotation for the mandible (P=0.012; adjusted R^2=0.33) but not for the maxilla (P=0.9; adjusted R^2=0.07) (Figure 9.4).

Table 9.2 Comparison between planned and achieved advancement (B-F translation) and counter-clockwise rotation (anticlockwise pitch) for maxilla and mandible.

		Planned			Achieved			Difference			*P*-value
		median	IQR	range	median	IQR	range	median	IQR	range	
Counter-clockwise rotation (degrees)	Maxilla	6.2	3.9–7.7	0.0–10.2	2.6	0.7–5.6	4.8–13.7	3.7	1.7–6.2	-6.1–7.9	0.006
	Mandible	7.8	6.3–11.0	1.2–25.4	4.5	2.6–6.2	-5.7–14.9	4.7	1.2–8.2	-0.8–10.5	0.001
Advancement (mm)	Maxilla	9.5	7.9–11.9	6.0–12.0	6.7	5.7–8.2	1.4–9.5	3.1	2.1–4.3	0.6–12.0	0.002
	Mandible	11.2	8.7–13.3	4.9–18.4	8.7	7.9–9.9	1.7–16.9	2.3	0.3–4.6	-3.1–6.4	0.03

Translations are presented in mm. Rotations are presented in degrees. B-F translation, translation from back to front; mm, millimeters; IQR, interquartile range = quartile 3 – quartile 1. *P*-value <0.05 was considered statistically significant.

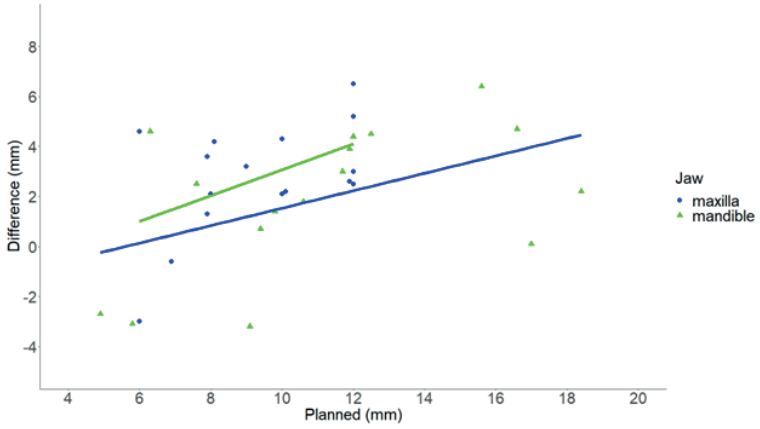

Figure 9.3 Scatter plot illustrating the relation between the planned advancement and the difference between planned and realized advancement. The X-axis illustrates the planned advancement in mm. The Y-axis illustrates the difference between planned and realized advancement in mm. Each green triangle depicts an individual maxilla and each blue dot depicts an individual mandible. The green and blue line illustrates the linear regression of the maxilla and mandible data, respectively. Mm, millimeters. *P*-value <0.05 was considered statistically significant.

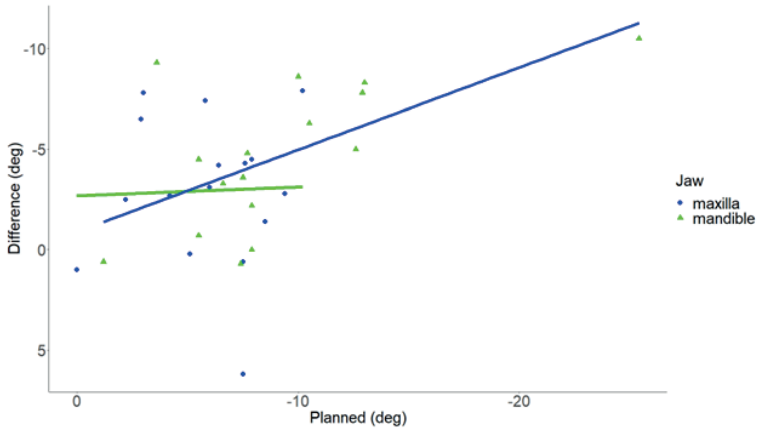

Figure 9.4 Scatter plot illustrating the relation between the planned counter-clockwise rotation and the difference between planned and realized counter-clockwise rotation. The X-axis illustrates the planned pitch in deg. The Y-axis illustrates the difference between planned and realized counter-clockwise rotation in deg. Each green triangle depicts an individual maxilla and each blue dot depicts an individual mandible. The green and blue line illustrates the linear regression of the maxilla and mandible data, respectively. Deg, degree. *P*-value <0.05 was considered statistically significant.

Maxilla-first surgical-sequence vs. mandible-first treatment sequence

In the comparative analysis between the maxilla-first surgical sequence and the mandible-first treatment sequence, Table 9.3 serves to demonstrate their collective inability to achieve the intended movements accurately. In the analysis, the discrepancies between the planned and achieved movements between the maxilla-first and mandible-first surgical sequences were all not statistically significantly (*P*>0.45).

Table 9.3 Comparison of discrepancy between planned and achieved sagittal movements in maxilla-first vs. mandible-first surgical sequences.

		Maxilla-first (N=7)			Mandible-first (N=9)			*P*-value
		median	IQR	range	median	IQR	range	
Counter-clockwise rotation (degrees)	Maxilla	4.3	2.5 – 6.5	0.3 – 7.8	2.8	1.2 – 6.8	0.6 – 7.9	0.71
	Mandible	4.5	3.3 – 8.7	0.8 – 9.2	4.8	0.7 – 7.3	0.0 – 10.5	0.50
Advancement (mm)	Maxilla	3.1	2.1 – 4.3	2.1 – 5.1	2.6	1.7 – 4.1	0.6 – 6.5	0.66
	Mandible	1.8	1.4 – 4.6	0.1 – 4.6	3.1	2.4– 4.3	0.7 – 6.4	0.45

Rotations are presented in degrees. Translations are presented in mm. Mm, millimeters; IQR, interquartile range = quartile 3 – quartile 1. *P*-value <0.05 was considered statistically significant.

Amount of advancement and the relative AHI improvement

The median AHI was significantly reduced from 62.6 (6.4–84.0) events/h to 19.4 (3.9-47.0) events/h (*P*=0.001). Overall success was achieved in 63% of the cases (Table 9.4).

Table 9.4 PSG results before and after MMA for total population.

	Total population (N=16)				
	mean	**SD**	**median**	**IQR**	**range**
Pre-op AHI (events/h)	49.8	23.8	62.6	43.5 — 77.7	6.4 — 84.0
Post-op AHI (events/h)	17.3	12.8	19.4	10.8 — 29.9	3.9 — 47.0
Pre-op ODI (events/h)	50.9	25.8	64.7	45.6 — 75.8	2.2 — 93.4
Post-op ODI (events/h)	21.0	13.9	19.5	10.5 — 31.8	3.0 — 51.1
Pre-op LSAT (%)	74.7	12.0	76	63 — 80	52 — 92
Post-op LSAT (%)	82.4	8.8	85	75 — 87	64 — 92
Success (%)	10/16 (62.5)				
Cure (%)	3/16 (18.8)				

PSG results are presented as events/hour or percentage. Success and cure are presented as percentage. AHI, apnea-hypopnea index; events/h, events per hour; Post-op, after MMA; Pre-op, prior to MMA; N, number of patients; LSAT, lowest oxygen saturation; MMA, maxillomandibular advancement; ODI, oxygen desaturation index; PSG, polysomnography; IQR, interquartile range = quartile 3 – quartile 1; SD, standard deviation. *P*-value <0.05 was considered statistically significant.

No association was found between the amount of realized maxillary and mandibular advancement and the relative AHI improvement (*P*=0.389 and *P*=0.387 respectively) (Figure 9.5).

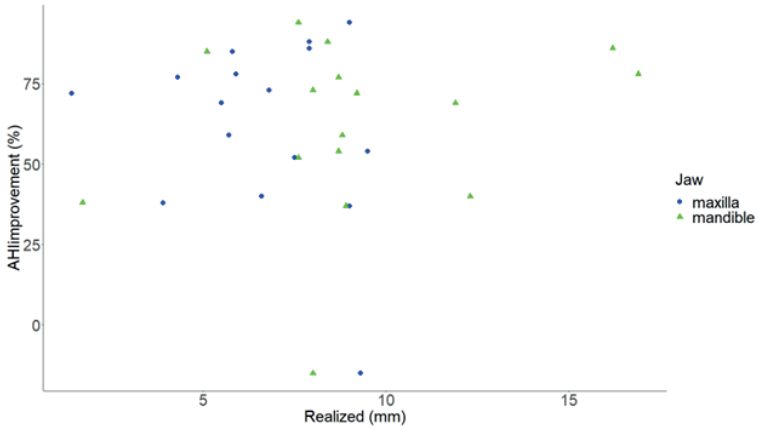

Figure 9.5 Scatter plot illustrating the relation between the realized maxillary and mandibular advancement and the percentage of AHI improvement. The X-axis illustrates the realized advancement in mm. The Y-axis illustrates the AHI improvement in %. Each green triangle depicts an individual maxilla and each blue dot depicts an individual mandible. AHI, apnea hypopnea index; mm, millimeters; %, percentage. *P*-value <0.05 was considered statistically significant.

Discussion

Previous studies have looked into the accuracy of orthognathic surgery[18,22,25,26]. However, as far as the authors are aware of, none have explored the extent to which planned surgical movements are accurately achieved in MMA procedures[17,18]. Therefore, the present study aimed to investigate the extent to which preoperative planned advancements and counter-clockwise rotations were achieved during MMA surgery for OSA patients.

One of the main findings of this preliminary study is the consistent trend of underachievement of the desired advancements in the MMA cases. This is well in line with findings in traditional orthognathic surgery for the correction of dentofacial discrepancies[22]. Notably, these discrepancies may be attributed to various factors, for example altered seated position of the condyle as a result of different muscular tone and patient positioning intraoperatively[22,27].

In addition to the difference found between the planned and realized advancement, the results also show that the realized counter-clockwise rotation for both the maxilla and mandible were consistently less than planned. Liebregts et al. found a similar difference between the planned and realized counter-clockwise rotation in bimaxillary osteotomies in traditional orthognathic surgery[18]. The possible reasons for this might be positioning errors intraoperatively due to interfering bone segments between the osteotomized maxilla and the pterygoid plates or a non-centric relation of the mandible during temporary maxillomandibular fixation with the use of intraoperative surgical splints[18,22].

Both findings emphasize that although virtual surgical planning and CAD/CAM intraoperative surgical splints are utilized for MMA nowadays, it is still difficult to accurately achieve the planned advancement and counter-clockwise rotation. The relatively large surgical splints that are frequently used in MMA surgery, due to the large planned displacements, might be a significant factor in decreasing surgical accuracy. This might explain the results of this study, which showed that the surgical accuracy was further reduced when the planned advancements and counter-clockwise rotations increased. The paper by Liebregts et al. and Stokbro et al. also alluded to this finding[18,28].

The mandible-first sequence has been proposed as a solution to address issues with centric relation and, consequently, to enhance the predictability of achieving the intended position[29]. However, no significant beneficial effect could be demonstrated in this small sample size. The choice between the maxilla-first and mandible-first surgical sequences is often influenced by surgeon preferences[30,31]. In cases of OSA, concerns about achieving the desired maxillary advancement due to limitations in soft tissue

(e.g., through scarring due to previous upper airway surgery) might be present. In our hospital, a strategic approach is often used that is only possible within the maxilla-first sequence. It involves the use of two intermediate splints: one for larger advancement (e.g., 12 mm) and another for a slightly lesser advancement (e.g., 10 mm) as a precautionary 'back-up'.

Multiple studies have reported the association between MMA success and the amount of advancement[12,17], but others have reported no association between the amount of planned advancement and AHI improvement after MMA[32,33]. A possible explanation for these inconsistent findings could be that the planned advancement instead of the realized advancement has been used, or because there is variation in the use of twodimensional and three-dimensional imaging methods[17,34,35].

As a secondary objective, this study investigated the correlation between the realized advancement and the relative AHI reduction, but no significant correlation was found. This lack of correlation may be attributed to the low number of patients included and the extensive complexity of OSA, where treatment success or improvement depends on various interacting factors, including demographic characteristics, anatomical hard-tissue and soft-tissue parameters, PSG specifics, and surgical characteristics[35–39]. This finding raises the question of whether or not more accurate achievement of the planned advancement and counter-clockwise rotation is actually necessary through, for example, a splintless surgical workflow[40–43]. This is especially true when looking at the finding that the median AHI was significantly reduced from approximately 63 events/h to 19 events/h despite consistently not achieving the planned displacements. Some cases still showed a significant relative AHI reduction despite a small advancement, as seen in Figure 9.5.

The amount of advancement and counter-clockwise rotation necessary for surgical success remains unknown. A major advantage of the present study is the fact that a validated workflow and tool, the OrthoGnathicAnalyser, was used in order to measure the discrepancy between the planned and the realized result in three dimensions with the use of CT and CBCT. The argument could be raised that an error distribution between the CT and CBCT-based registration could have influenced the outcome of this study. However, based on the validated findings of Eggers et al. this can be considered as negligible[44]. Although the OrthoGnathicAnalyser tool is able to accurately measure all translational and rotational movements, the main focus in this study was on the advancement and the counter-clockwise rotation of the maxilla and the mandible, as these are essential factors contributing to the relief of patients' OSA[14,45–48]. However, caution is warranted in interpreting the results because of the study limitations (small population, potential biases in retrospective design, and low inclusion rate). In the present study, the powers of the primary outcomes (i.e., maxillary advancement,

mandibular advancement, maxillary counter-clockwise rotation, and mandibular counter-clockwise rotation) were 1, 0.7, 0.8, and 1, respectively. This indicated that except for mandibular advancement, all other primary outcome variables had sufficient power in the statistical analyses. It is recommended that future studies—preferably prospective studies in large cohorts—should be undertaken to verify the current findings, especially since the literature on the topic is scarce. Additional future research should further investigate which factors in MMA surgery contribute most to surgical success and to optimize surgical planning for individual patients.

Conclusions

This study emphasizes the importance of acknowledging the presence of surgical inaccuracies in MMA procedures for patients with OSA and underscores the need for heightened awareness among surgeons and future research endeavors. Furthermore, our findings propose that the extent of maxillomandibular complex advancement may not hold paramount significance in determining the outcome of MMA treatment. Therefore, further investigations and refinements in surgical techniques are imperative to optimize the efficacy of MMA procedures.

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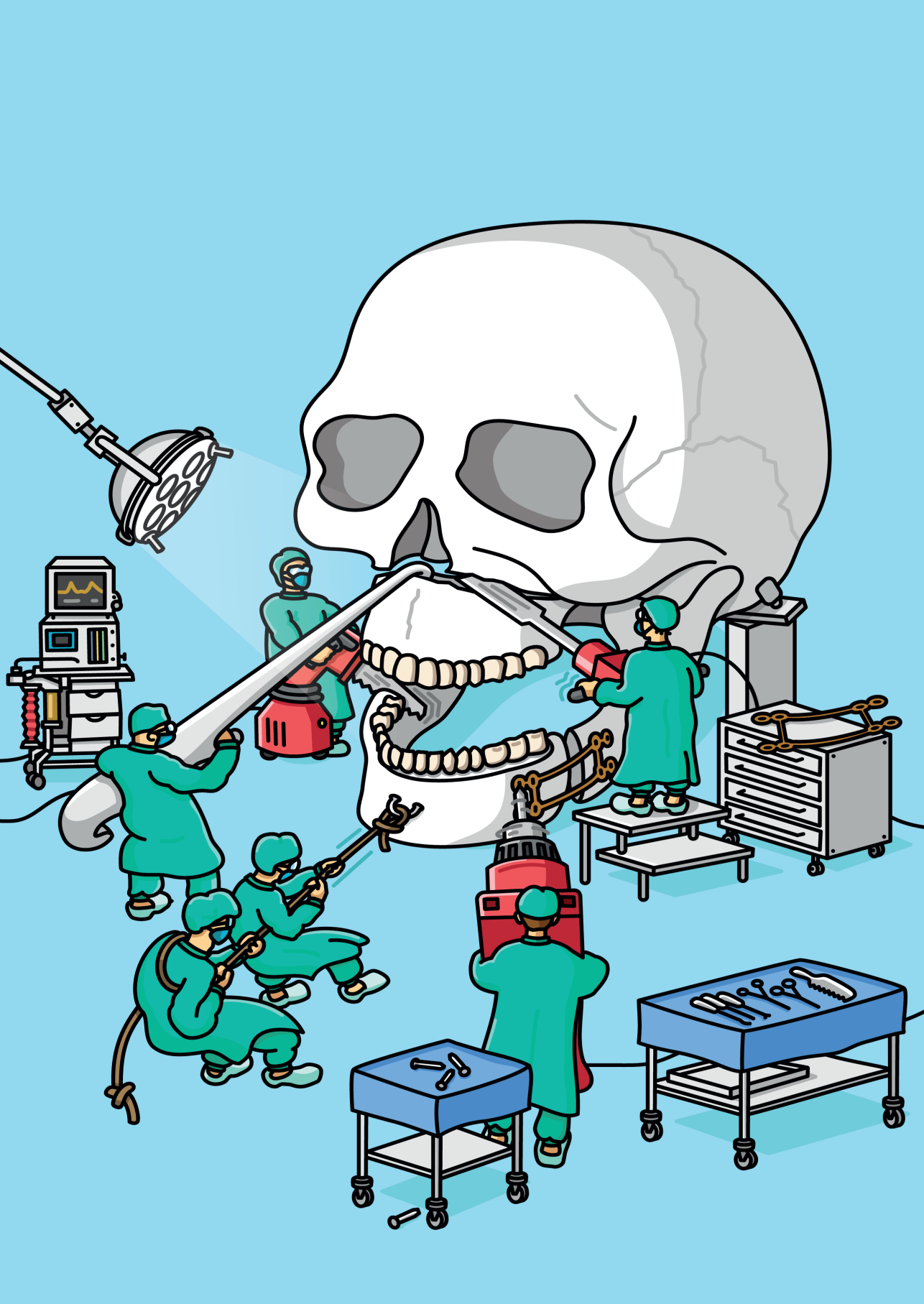

Chapter 10

General discussion

General discussion

The purpose of this thesis was to perform an in-depth investigation of various aspects related to maxillomandibular advancement (MMA) and its application in treating obstructive sleep apnea (OSA), including its efficacy, predictors of success, patient phenotypes, alternative surgical techniques, and the influence of surgeon experience and surgical accuracy.

To accomplish these goals, this thesis compared two surgical approaches to MMA: the commonly performed multilevel surgery (MLS) and a promising alternative, upper airway stimulation (UAS). Additionally, specific polysomnography findings were evaluated, such as central apneas and mix apneas – and specifically the presence of a high percentage of central and mixed apnea index in the total apnea-hypopnea index (CMAI%) –, as well as apnea-predominant and hypopnea-predominant OSA, as potential predictors of surgical response to MMA. Furthermore, a study was performed investigating whether readily available clinical data, including patient-related, polysomnographic, cephalometric, and surgical variables, could serve as predictors for MMA outcome. The study also delved into the accuracy and predictability of an alternative treatment protocol for MMA in edentulous OSA patients. Moreover, the association between the clinical efficacy outcomes of MMA and surgeons' experience was explored to ascertain whether surgeons' expertise plays a significant role in MMA outcomes. Finally, the thesis assessed the surgical precision of the advancement and counter-clockwise rotation of the maxillomandibular complex during MMA in obstructive sleep apnea patients.

Key findings

Comparing multilevel surgery and upper airway stimulation to maxillomandibular advancement

A wide range of surgical therapies exists for OSA[1,2]. Three such therapies are multilevel surgery (MLS), upper airway stimulation (UAS), and maxillomandibular advancement (MMA), all of which target various levels of upper airway obstruction in OSA patients. MLS has been a popular choice for OSA treatment worldwide over the past 35 years[2]. On the other hand, UAS, though relatively new with over a decade of practice, remains highly promising[3]. Both MLS and UAS focus on multiple levels of soft tissue obstruction, whereas MMA involves skeletal surgery and also addresses multiple sites of upper airway obstruction[4,5].

Among these surgical options, only UAS has strict exclusion criteria, including apnea hypopnea index (AHI) <15 and >65 events/hour, CMAI≧25%, presence of complete concentric collapse at the palate (CCCp) during drug-induced sleep endoscopy (DISE), and often a body mass index (BMI)of ≧32[6]. MLS and MMA lack such specific exclusion criteria, leaving a group of patients – with moderate to severe OSA, who have tried and failed or cannot tolerate positive airway pressure (PAP), show multiple levels of upper airway collapse during DISE, and do not specifically meet UAS exclusion criteria – which may be candidates for MLS, UAS, or MMA. However, due to limited literature directly comparing MLS, UAS, and MMA, practitioners often face a dilemma in selecting the most suitable surgical option for their patients.

A systematic review and meta-analyses in chapter 2, where MLS and MMA were compared in which both surgeries were pooled separately due to the absence of direct comparison studies – e.g., randomized controlled trials (RCTs) – indicated that both MMA and MLS are effective treatments for OSA. MMA demonstrated greater improvements in OSA parameters but also showed a higher complication rate compared to MLS.

In chapter 3, a systematic review compared MMA to UAS, but a meta-analysis was not feasible due to dissimilar patient populations in the included studies. The findings suggested that both MMA and UAS are effective and safe therapies for OSA. However, direct comparison of their efficacy and safety could not be performed, limiting the results, which should be interpreted with caution.

As of now, no studies directly compare MLS, UAS, and MMA using an comparative study design. To make a more informed decision on the best surgical option for OSA patients eligible for all three procedures, future research should focus on conducting such studies. Additionally, research should aside from investigating efficacy and morbidity also explore quality of life and cost-effectiveness to aid practitioners and patients in the decision-making process.

Predictors for maxillomandibular advancement success and failure

MMA exhibits remarkable efficacy as a surgical treatment for OSA patients, boasting success rates of around 85%[7]. However, there is still potential for further enhancement. By identifying predictors of MMA surgical response, we can proactively devise treatment plans tailored to more accurately predicted therapeutic outcomes. Emerging from the results in chapter 4, the presence of cardiovascular disease, a higher central apnea index, and a larger superior posterior airway space are all three associated with a less favorable surgical response to MMA. Furthermore, among the notable findings in chapter 4, perhaps the most striking observation is that no significant differences were found between responders and non-responders concerning the amount of surgical

advancement, the presence of previous upper airway surgery, and the level of the AHI. These results contradict previously reported literature[7].

The findings presented in chapter 5 reveal that in addition to improving the AHI and lowest oxyhemoglobin saturation, MMA also leads to significant enhancements in the central and mixed apnea indexes. Interestingly, contrary to UAS, the presence of a high percentage of central and mixed apnea index should not be considered a predictor for failure or a contraindication for MMA. This suggests that potential candidates currently excluded from UAS based on the CMAI%≧25% criterion might consider MMA as a phase 1 treatment to remove this exclusion criterion, allowing them to proceed to UAS as a phase 2 treatment if needed.

The AHI, calculated by the number of apneas and hypopneas per hour of sleep, varies between patients, and some may present with either a more hypopnea-predominant or apnea-predominant OSA. Chapter 6 demonstrates that preoperative hypopnea-predominant OSA patients are more suitable candidates for MMA, as they showed significantly higher surgical success and cure rates after the procedure.

Both chapter 5 and 6 indicate that MMA can alter the type of sleep apnea, leading to the emergence of CMAI%≧25% after MMA and a shift from apnea-predominant to hypopnea-predominant OSA patients, and vice versa. This phenomenon of shifting from one type of OSA to another has also been reported by other authors[8].

As alluded to earlier, certain results in chapter 4 appear to be inconsistent with previously reported findings. Consequently, future studies addressing the current topic are necessary and strongly recommended. Since many studies, including this thesis, predominantly focus on polysomnography outcomes, particularly the highly criticized AHI, it might be argued that achieving more consistent findings in the future could involve shifting the focus towards utilizing alternative outcome measures, such as patient satisfaction measures.

Alternative surgical technique for maxillomandibular advancement

The prevalence of OSA is higher among elderly individuals, who are also more likely to be edentulous[9–11]. Edentulism can exacerbate the presentation of OSA, leading to a relatively higher indication for MMA in edentulous patients[12,13]. Conventional gunning splints have been traditionally used as intermediate and/or final splints for aligning and stabilizing the osteotomized maxilla and mandible in edentulous patients[14–17]. However, this traditional approach is known for its arduousness and has been criticized for its lack of predictability and precision. Chapter 7 introduces an innovative alternative protocol utilizing individual osteotomy cutting guides and patient-specific fixation implants for edentulous patients, demonstrating both accuracy and predictability. Based on the promising initial results, this technique is considered superior to the traditional use of

splints. Further empirical experience and studies with larger sample sizes are warranted to strengthen our understanding.

Surgical experience and maxillomandibular advancement outcome

Extensive evidence has demonstrated a significant and positive correlation between surgeon experience and operative outcomes as well as health-related quality of life after surgery. Patients treated by highly experienced surgeons consistently achieved better results compared to those treated by less experienced counterparts[18–21]. However, chapter 8 has been unable to demonstrate this association. In contrast to previous studies, the findings suggest that surgeon experience has little influence on the clinical efficacy and safety of MMA. One should bear in mind that the surgeon experience was determined by calculating the duration (in months) between the date of the surgeons' respective board registration date and the date the surgeon performed the MMA surgery for each patient. This might have impacted the outcome.
To gain deeper insights into the relationship between the surgeon's experience and the surgical outcomes of MMA in OSA patients, the authors strongly advocate conducting prospective studies with a substantial sample size.

Surgical accuracy of maxillomandibular advancement

Significant factors contributing to the reduction of the apnea-hypopnea index (AHI) and, consequently, treatment success in MMA include substantial maxillomandibular complex advancement and counterclockwise rotation[7,22]. Achieving the planned sagittal movements is crucial to ensure treatment efficacy. Surprisingly, no prior study has yet investigated the extent to which the intended sagittal movements are actually achieved in MMA to date. Chapter 9, illustrates that the achieved maxillomandibular complex advancement and counterclockwise rotation were smaller than the planned movements. Interestingly, a larger planned advancement for the maxilla was associated with a greater discrepancy between the planned and actual achieved advancements, and a similar trend was observed for the mandibular counterclockwise rotation. Despite this discrepancy, MMA demonstrated effectiveness as an OSA treatment, with a notable reduction in the AHI. However, no significant correlation was identified between the amount of maxillary and mandibular advancement and the relative improvement in AHI.

These findings raise several important points:

1. There is a clear need for further studies to validate and corroborate these observations.
2. The significant discrepancy between planned and achieved movements highlights the importance of enhanced surgical precision in MMA procedures.
3. It prompts the question whether additional accuracy in the surgical approach, including greater advancement and counterclockwise rotation, is truly necessary for optimal outcomes.
4. Further investigations are warranted to gain a better understanding of the relationships between surgical accuracy, advancement, counterclockwise rotation, and treatment effectiveness in MMA for OSA patients.

Future perspectives for obstructive sleep apnea and maxillomandibular advancement

Improved surgical techniques

In the last decade, significant advances in surgical techniques have emerged, incorporating virtual surgical planning, computer-assisted designing, and computer-assisted manufacturing of intra-operative splints[23–25]. Additionally, as discussed in chapter 7 of this thesis, a novel alternative protocol employing individual osteotomy cutting guides and patient-specific fixation implants has been reported. Wider adoption of this technique, combined with the potential integration of navigation systems and robotics, holds the promise of more personalized treatment plans based on each patient's unique craniofacial anatomy and achieving greater precision and more minimally invasive procedures. This, in turn, could lead to reduced surgical risks, shorter recovery times, and ultimately improved outcomes for OSA patients.

Enhanced patient selection and personalized treatment

As our understanding of OSA, craniofacial structures, and associated abnormalities, as well as MMA continues to advance, a wealth of improved predictors for treatment success and failure are anticipated to emerge. This progress will contribute to the development of more precise patient selection criteria, thereby identifying the most suitable candidates for MMA and ultimately leading to enhanced success rates and treatment outcomes. While certain phenotypes have been explored in this thesis, the ongoing discovery of additional phenotypes will further refine patient selection.
Moreover, specific endotypes, such as collapsibility, muscle responsiveness, ventilatory stability, and arousal threshold, may also play pivotal roles as predictors. Biomarkers, although currently underexplored and underutilized in OSA screening, diagnostics, and

treatment indication, hold great potential as quick, non-invasive, and cost-effective tools[26,27]. Consequently, it is imperative to dedicate more attention and research to comparing the specificity and sensitivity of various biomarkers against the current gold standard, polysomnography. This investigation should encompass both non-invasive treatments and surgical interventions, such as MMA. Additionally, wearables present another avenue for consideration in this context.

Moving towards a more personalized approach, artificial intelligence and machine learning are poised to play a vital role[28]. Big-data studies and advanced analytics are foreseeable in future research, providing crucial insights for patient and treatment selection, as well as facilitating patient-specific operation planning. This paradigm shift in personalized treatment strategies holds significant promise for optimizing outcomes and revolutionizing the field of OSA management, including MMA.

Multidisciplinary approach

Obstructive sleep apnea (OSA) represents a heterogeneous and complex condition, influenced by various etiological factors and offering numerous treatment options[1,2]. The multifaceted nature of this disorder, coupled with the involvement of multiple healthcare providers, adds to the challenge of determining the most appropriate treatment for individual patients. To address this, a structured and systematic approach is advocated, involving a multidisciplinary team[29]. This approach should encompass relevant specialties, incorporating clinicians and physiologists responsible for the sleep service, such as respiratory physicians, neurologists, otolaryngologists, dentists, maxillofacial surgeons, clinical neurophysiologists, psychologists, CPAP technologists, dietitians, and bariatric surgeons. By fostering case discussions under audit conditions, this collaborative approach facilitates the prospective delivery of evidence-based treatments, ensuring optimal patient care. Embracing a comprehensive team effort not only aids in selecting the most suitable treatment options for OSA patients but also enhances the overall management of this complex condition.

Additionally, MMA surgery is often performed in conjunction with other treatments for sleep apnea, such as continuous positive airway pressure (CPAP) therapy and orthodontic interventions. In the future, a more integrated and multidisciplinary approach involving sleep medicine specialists, oral and maxillofacial surgeons, orthodontists, and other healthcare professionals – e.g., speech therapist, orofacial physiotherapist, and nutritionist – may further optimize MMA patient care and long-term outcomes.

Considering the complexity of OSA, as mentioned above, and the multitude of treatment options available, a compelling approach would involve providing specialized education to OSA surgeons, potentially through a fellowship program. This initiative

aims to cultivate a group of surgeons with a keen interest, comprehensive education, and substantial experience in diagnosing, treating, and counseling OSA patients. Candidates for this program may possess backgrounds in otolaryngology, maxillofacial surgery, or general surgery, thereby enhancing their expertise in addressing the unique challenges of OSA cases.
All of these might improve patient care and surgical outcomes for OSA patients.

Research and innovation

Ongoing OSA and MMA research should be focused on refining surgical techniques, improving patient outcomes, and exploring alternative treatments. Continued innovation and scientific discoveries may result in new surgical approaches, materials, or devices that enhance the effectiveness and safety of surgically treated patient, which is of course not exclusive to patient receiving MMA. It's important to note that medical advances take time to develop and implement, and the future of MMA surgery will depend on continued research, clinical trials, and the evolution of medical technology.

Shared discission making

Finally, it is strongly advocated that in the future, increased attention should be given not only to informed decision-making but also to shared decision-making. As physicians, our primary focus is to provide treatment options to patients based on their efficacy. However, it is essential to recognize that each patient is unique, and what may be the most effective treatment option in general may not always align with the individual preferences and values of a specific patient.
Therefore, it is crucial to offer patients the opportunity and freedom to express their priorities and values, which may influence their choice of treatment. Engaging in open and respectful discussions with patients allows for shared decision-making, where patients actively participate in the treatment planning process, considering both medical evidence and their personal preferences. This patient-centered approach promotes better patient satisfaction, improved adherence to treatment, and ultimately leads to more successful treatment outcomes. By fostering a collaborative and patient-oriented environment, we can optimize the care provided and enhance patient experiences throughout their treatment journey.

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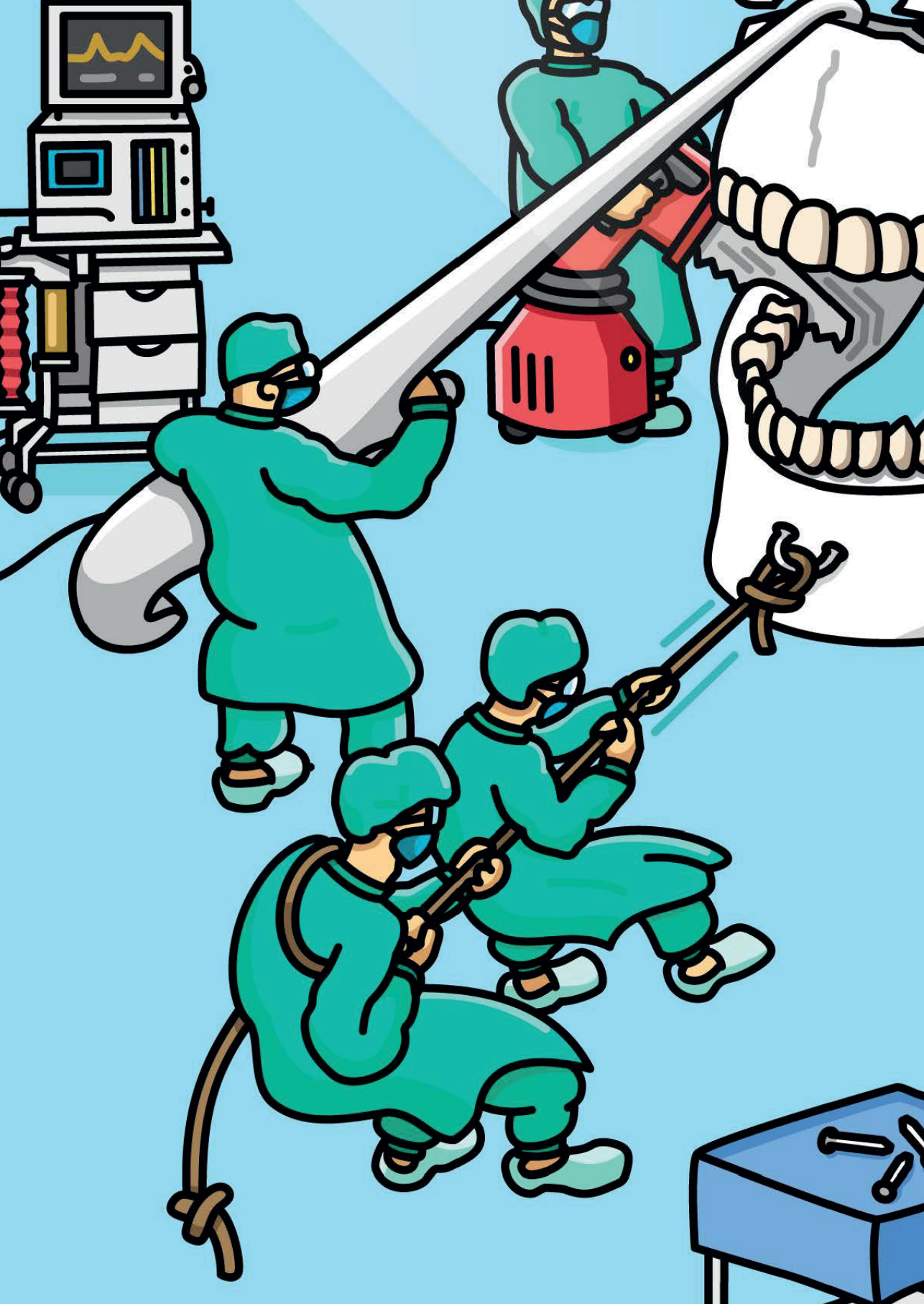


Chapter 11

Summary in English and Dutch

Summary

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by recurrent partial or complete airway obstruction during sleep, leading to interrupted breathing and reduced oxygen levels. It affects individuals of all ages, impacting their overall health and quality of life. The hallmark of OSA is frequent apneas and hypopneas during sleep, causing disrupted sleep patterns and preventing restorative deep sleep stages. This results in excessive daytime sleepiness, impaired cognitive function, reduced quality of life, and an increased risk of accidents. The prevalence of OSA has been steadily increasing in recent years, attributed to various factors such as the rise in obesity rates, sedentary lifestyles, and an aging population. It is estimated that OSA affects approximately of 9% to 38% of the general adult population.

Diagnosing OSA typically involves a comprehensive evaluation, including a thorough clinical history, physical examination, and objective assessment of sleep using polysomnography (PSG) or polygraphy. The diagnosis of OSA is typically based on the frequency and severity of apnea-hypopnea events per hour of sleep, as measured by the apnea-hypopnea index (AHI).

The management of OSA encompasses both non-pharmacological and pharmacological approaches. Lifestyle modifications, including weight loss, regular exercise, and avoidance of alcohol and sedatives, are often recommended as initial steps. Continuous positive airway pressure (CPAP) therapy is the most commonly prescribed treatment for OSA. It involves the use of a mask that delivers pressurized air to the upper airway, effectively maintaining its patency during sleep. Other treatment options include mandibular advancement devices, positional therapy, and a wide array of surgical interventions which address different sites of obstruction.

Maxillomandibular advancement (MMA) is a surgical procedure that has emerged as one of the most effective treatment option for obstructive sleep apnea (OSA). It involves repositioning the maxilla and mandible anteriorly and rotating them counter clockwise to enlarge the upper airway and to reduces the collapsibility of the soft tissues of the upper airway.

While MMA has been proven to be generally effective and has been extensively studied in the previous decades – to date – there are still issue related to MMA that remains unclear. Therefore, the main objective of this thesis was to investigate different issues related to MMA in order to gain more insight into OSA – as a whole – and MMA as a treatment option for OSA. Each chapter addresses a specific aspect related to MMA.

Chapter 2 presents a systematic review and meta-analyses in which the clinical efficacy and safety of MMA and multilevel surgery (MLS) for treating obstructive sleep apnea (OSA) are compared. The results indicated that both procedures were effective in improving OSA, but MMA showed greater improvements in OSA parameters. However, MMA also had a higher complication rate compared to MLS.

In **chapter 3** a systematic review evaluates the efficacy and safety of MMA and upper airway stimulation (UAS) for OSA treatment. The findings suggested that both MMA and UAS were effective and safe therapies for OSA, but direct comparison between the two procedures was limited due to the available evidence.

Chapter 4 describes a retrospective study aiming to identify potential predictors of surgical response to MMA in OSA patients. The presence of cardiovascular disease, higher central apnea index, and larger superior posterior airway space were independently associated with a less favorable surgical response to MMA.

The study in **chapter 5** evaluates the efficacy of MMA for OSA patients with a high percentage of central and mixed apnea index in the total apnea-hypopnea index. MMA proved to significantly improve various OSA parameters, including apnea-hypopnea index, lowest oxyhemoglobin saturation, and central and mixed apnea indexes. The results showed that the presence of a high percentage of central and mixed apnea index should not be considered a contraindication for MMA.

Chapter 6 reports on a retrospective cohort study comparing the outcomes of MMA in patients with apnea-predominant OSA versus hypopnea-predominant OSA. The results suggested that preoperative hypopnea-predominant OSA patients may be more suitable candidates for MMA, as they demonstrated higher surgical success and cure rates. Additionally, MMA had a greater impact on shifting patients from apnea-predominant to hypopnea-predominant OSA.

In **chapter 7** a pilot study is presented in which the accuracy and predictability of a splintless treatment protocol for edentulous patients undergoing orthognathic surgery is assessed. The results indicate that the protocol, which included virtual planning and patient-specific guides and implants, was accurate and predictable.

A retrospective study is described in **chapter 8**, investigating the association between surgeons' experience and the clinical efficacy and safety outcomes of MMA in OSA

patients. The findings suggested that surgeon experience had little influence on the clinical efficacy and safety of MMA.

Finally, **chapter 9** presents a retrospective study evaluating the surgical accuracy of the performed MMA in OSA patients. The results indicate that the desired advancement and counter-clockwise rotation in MMA cases were not accurately achieved, suggesting the need for further studies to confirm these findings.

This thesis highlights the clinical efficacy, safety, predictors of response, and surgical accuracy of MMA for obstructive sleep apnea patients. The findings contribute to the understanding of MMA as an effective treatment option for OSA, with considerations for patient selection and surgical outcomes.

Samenvatting

Obstructieve slaapapneu (OSA) is een veelvoorkomende slaap gerelateerde ademhalingsstoornis, gekenmerkt door terugkerende episoden van gedeeltelijke of volledige obstructie van de bovenste luchtwegen, wat leidt tot verstoringen in de ademhaling en daaropvolgend daling van het zuurstofgehalte. Deze aandoening treft mensen van alle leeftijden en geslachten, en heeft significante gevolgen voor hun algehele gezondheid en kwaliteit van leven. Het kenmerk van OSA is het optreden van apneus (complete afwezigheid van de luchtpassage) en hypopneus (gedeeltelijke afwezigheid van de luchtpassage) tijdens de slaap, wat leidt tot herhaalde ontwakingen en gefragmenteerde slaappatronen. De terugkerende aard van deze gebeurtenissen verstoort de normale slaaparchitectuur, waardoor mensen geen herstellende diepe slaapfasen kunnen bereiken, met als gevolg onder andere overmatige slaperigheid overdag, verminderde cognitieve functie, verminderde kwaliteit van leven en een verhoogd risico op ongevallen.

De prevalentie van OSA neemt de laatste jaren gestaag toe als gevolg van verschillende factoren zoals de stijgende obesitaspercentages, zittend en passieve levensstijl en vergrijzing van de bevolking. Naar schatting lijdt ongeveer 9% tot 38% van de volwassen bevolking aan OSA.

De diagnose van OSA omvat doorgaans een uitgebreide evaluatie, waaronder een grondige medische voorgeschiedenis, lichamelijk onderzoek en objectieve beoordeling van de slaap met behulp van polysomnografie (PSG) of polygrafie. De diagnose van OSA is meestal gebaseerd op de frequentie en ernst van apneu-hypopneu-gebeurtenissen per uur slaap, zoals gemeten door de apneu-hypopneu-index (AHI).

De behandeling van OSA omvat zowel niet-farmacologische als farmacologische benaderingen. Aanpassingen in levensstijl, zoals gewichtsreductie, regelmatige lichaamsbeweging en het vermijden van alcohol en slaapmiddelen, worden vaak aanbevolen als eerste stap. Continue positieve luchtwegdruk (CPAP) therapie is de meest voorgeschreven behandeling voor OSA. Hierbij wordt gebruik gemaakt van een masker dat onder druk lucht naar de bovenste luchtwegen levert, waardoor deze tijdens de slaap openblijven. Andere behandelopties omvatten bijvoorbeeld mandibulair repositie apparaat, positie therapie en verschillende chirurgische ingrepen die verschillende niveaus van obstructie aanpakken.

Maxillomandibulaire advancement (MMA) chirurgie blijkt een van de meest effectieve chirurgische opties voor OSA te zijn. Hierbij worden de bovenkaak (maxilla) en onderkaak (mandibula) naar voren verplaatst en tegen de klok in gedraaid om de bovenste luchtweg te vergroten en de collapsibiliteit van de zachte weefsels in de bovenste luchtwegen te verminderen.

Hoewel MMA over het algemeen effectief is gebleken en er meerdere studies onderzoek hebben gedaan naar MMA de afgelopen decennia, zijn er nog steeds onderwerpen met betrekking tot MMA die onduidelijk zijn. Daarom was het belangrijkste doel van dit proefschrift om diverse onderwerpen met betrekking tot MMA te onderzoeken om niet alleen meer inzicht te krijgen in OSA als geheel, maar om ook meer inzicht te krijgen in MMA als behandeloptie voor OSA. Elk hoofdstuk richt zich op een specifiek aspect met betrekking tot MMA.

Hoofdstuk 2 presenteert een systematische review en meta-analyses waarin de klinische werkzaamheid en veiligheid van MMA en multilevel chirurgie (MLS) voor de behandeling van OSA worden vergeleken. De resultaten geven aan dat beide procedures effectief waren bij het verbeteren van OSA, maar MMA liet grotere verbeteringen zien in OSA-parameters. MMA had echter ook een hoger complicatierisico in vergelijking met MLS.

In **hoofdstuk 3** evalueert een systematische review de werkzaamheid en veiligheid van MMA en stimulatie van de bovenste luchtwegen (UAS) voor de behandeling van OSA. De bevindingen suggereren dat zowel MMA als UAS effectieve en veilige therapieën waren voor OSA, maar directe vergelijking tussen de twee procedures was beperkt vanwege het beperkte beschikbare bewijs.

Hoofdstuk 4 beschrijft een retrospectieve studie gericht op het identificeren van mogelijke voorspellers van chirurgisch succes bij MMA voor OSA-patiënten. De aanwezigheid van hart- en vaatziekten, een hogere centrale apneu-index en een grotere superior posterieure luchtwegruimte werden geassocieerd met een minder gunstig chirurgisch resultaat bij MMA.

De studie in **hoofdstuk 5** evalueert de werkzaamheid van MMA bij OSA-patiënten met een hoog percentage centrale en gemengde apneu-index in de totale apneu-hypopneu-index. MMA bleek aanzienlijke verbeteringen te geven in verschillende OSA-parameters, waaronder de apneu-hypopneu-index, laagste oxyhemoglobine saturatie en centrale en gemengde apneu-indexen. De resultaten tonen aan dat de aanwezigheid

van een hoog percentage centrale en gemengde apneu-index geen contra-indicatie is voor MMA.

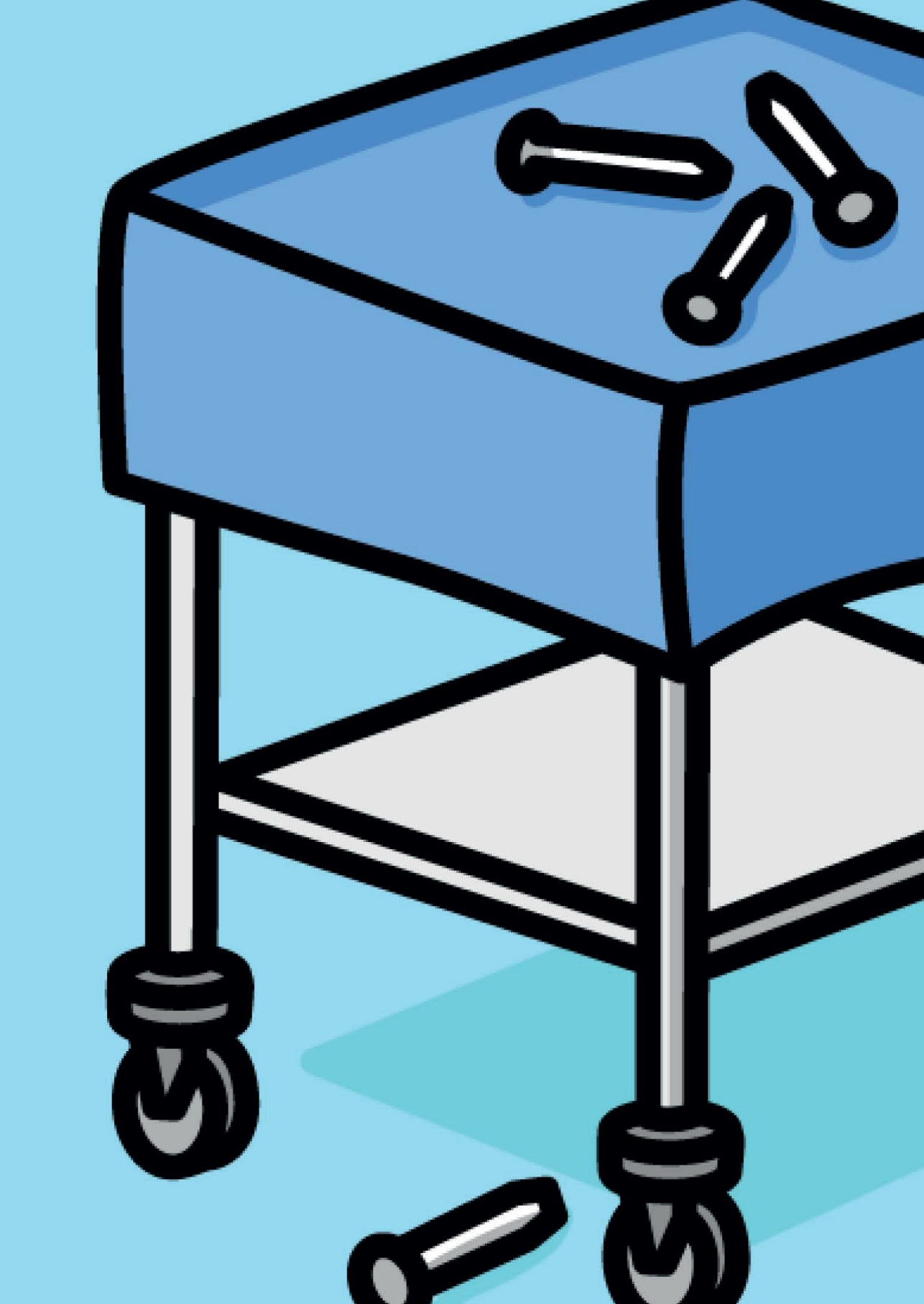
Hoofdstuk 6 rapporteert over een retrospectieve cohortstudie waarin de resultaten van MMA worden vergeleken bij patiënten met apneu-dominante OSA versus hypopneu-dominante OSA. De resultaten suggereren dat patiënten met preoperatieve hypopneu-dominante OSA, in vergelijking met apneu-dominante OSA, mogelijk geschiktere kandidaten zijn voor MMA, omdat zij hogere chirurgische succes- en genezingspercentages vertoonden. Bovendien had MMA een grotere impact op het verschuiven van patiënten van apneu-dominante naar hypopneu-dominante OSA.

In **hoofdstuk 7** wordt een pilotstudie gepresenteerd waarin de nauwkeurigheid en voorspelbaarheid van een orthognathisch behandelprotocol, waarbij er geen gebruik van wafer(s) wordt gemaakt, voor edentate patiënten wordt beoordeeld. De resultaten geven aan dat het protocol, dat gebruik maakt van virtuele planning en patiëntspecifieke boor-, zaagmallen en implantaten, nauwkeurig en voorspelbaar is.

Een retrospectieve studie wordt beschreven in **hoofdstuk 8**, waarin de associatie tussen de ervaring van chirurgen en de klinische efficiëntie en veiligheidsresultaten van MMA bij OSA-patiënten wordt onderzocht. De bevindingen suggereren dat de ervaring van de chirurg weinig invloed had op de klinische efficiëntie en veiligheid van MMA.

Tot slot presenteert **hoofdstuk 9** een retrospectieve studie waarin de chirurgische nauwkeurigheid van uitgevoerde MMA bij OSA-patiënten wordt geëvalueerd. De resultaten geven aan dat de gewenste voorwaartse verplaatsing en tegen de klok in rotatie tijdens MMA niet nauwkeurig werden bereikt, wat suggereert dat verder onderzoek nodig is om deze bevindingen te bevestigen.

Dit proefschrift benadrukt enkele aspecten van MMA, namelijk de klinische efficiëntie, veiligheid, voorspellers van respons en chirurgische nauwkeurigheid van MMA voor patiënten met obstructieve slaapapneu. De bevindingen dragen bij aan het begrip van MMA als een effectieve behandeloptie voor OSA, met aandacht voor patiëntenselectie en resultaten.



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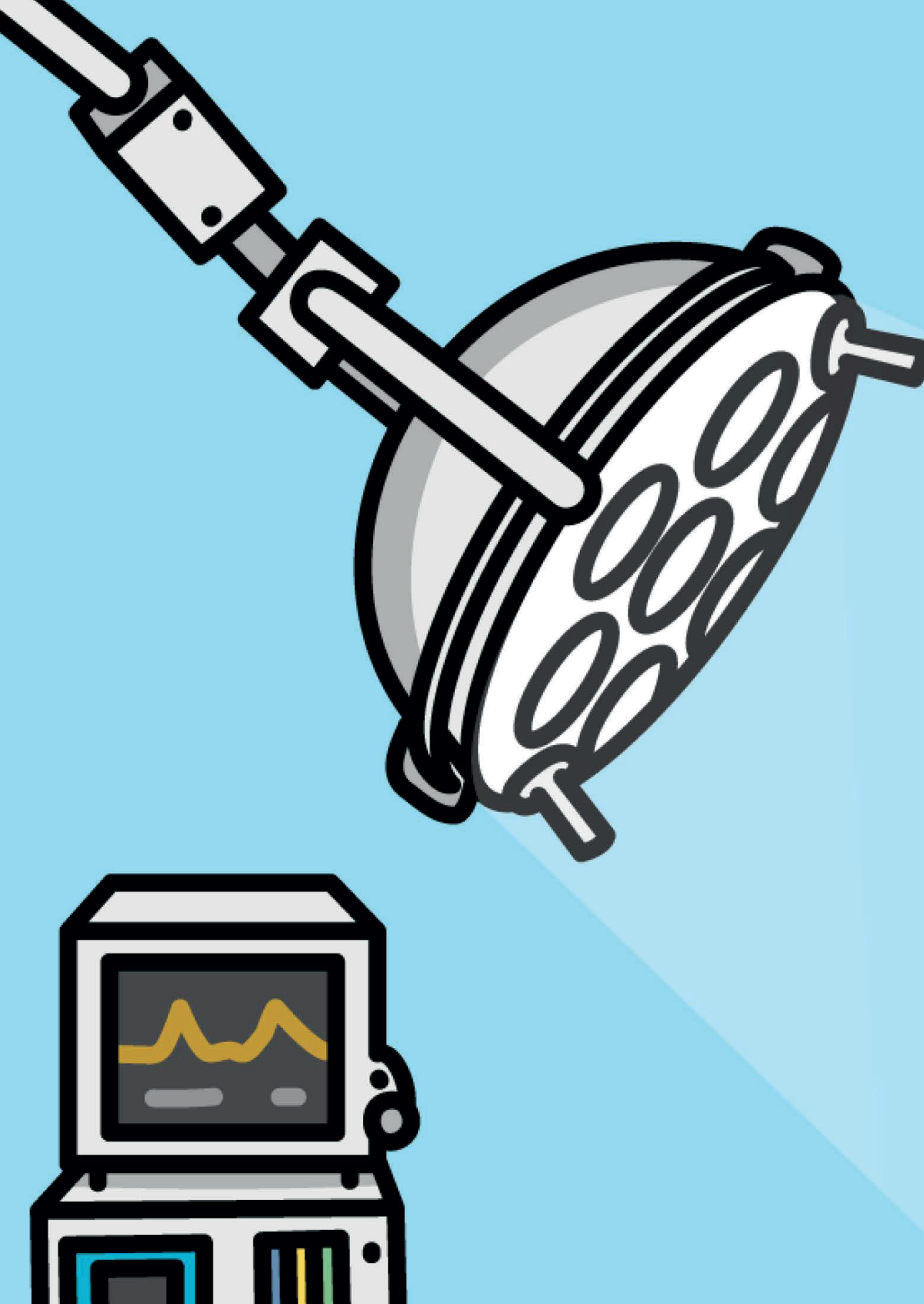

Chapter information

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Chapter 2

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

Published in:
Sleep Medicine Reviews, 2021

Authors:
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Conduct of study:	JH, NZ, ZH
Collection of data:	JH, NZ, ZH
Analysis and management of data:	NZ
Drafting of manuscript and/or critical revision:	JH, NZ, ZH, RSp, NV, GA, FL, MR, JL

Funding sources:
Department and institutional funds.

Conflicts of interest:
None

Chapter 3

Published as:
Maxillomandibular Advancement and Upper Airway Stimulation for Treatment of Obstructive Sleep Apnea: A Systematic Review

Published in:
Journal of Clinical Medicine, 2022

Authors:
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Conduct of study:	JH, NZ
Collection of data:	JH, NZ
Analysis and management of data:	JH, NZ
Drafting of manuscript and/or critical revision:	JH, NZ, ZH, RSp, NV, GA, FL, MR, JL

Funding sources:
Department and institutional funds.

Conflicts of interest:
None

Chapter 4

Published as:
Maxillomandibular advancement for obstructive sleep apnea: a retrospective prognostic factor study for surgical response

Published in:
Sleep and Breathing, 2022

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Funding sources:
Department and institutional funds.

Conflicts of interest:
None

Chapter 5

Published as:
Central and mixed sleep apnea related to patients treated with maxillomandibular advancement for obstructive sleep apnea: A retrospective cohort study

Published in:
Journal of Cranio-Maxillofacial Surgery, 2022

Authors:
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Funding sources:
Department and institutional funds.

Conflicts of interest:
None

Chapter 6

Published as:
Obstructive Sleep Apnea Resolution in Hypopnea-Predominant versus Apnea-Predominant Patients after Maxillomandibular Advancement

Published in:
Journal of Clinical Medicine, 2022

Authors:
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Study design:	JH, NZ, JL
Conduct of study:	JH, NZ
Collection of data:	JH, NZ
Analysis and management of data:	JH, NZ
Drafting of manuscript and/or critical revision:	JH, NZ, JL

Funding sources:
Department and institutional funds.

Conflicts of interest:
None

Chapter 7

Published as:
Splintless orthognathic surgery in edentulous patients-a pilot study

Published in:
International Journal of Oral & Maxillofacial Surgery, 2019

Authors:
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Author contributions:

Study design:	N/A
Conduct of study:	JH
Collection of data:	JH, RSc, FB
Analysis and management of data:	JH, RSc
Drafting of manuscript and/or critical revision:	JH, RSc, FB, JL, AB

Funding sources:
Department and institutional funds.

Conflicts of interest:
None

Chapter 8

Published as:
Influence of Surgeon Experience on Surgical Outcome of Maxillomandibular Advancement for Obstructive Sleep Apnea

Published in:
Journal of Clinical Medicine, 2023

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Collection of data:	JH, SÖ, NZ
Analysis and management of data:	JH, SÖ, NZ
Drafting of manuscript and/or critical revision:	JH, SÖ, NZ, RA, AB, JL

Funding sources:
Department and institutional funds.

Conflicts of interest:
None

Chapter 9

Submitted as:
Assessment of Surgical Accuracy in Maxillomandibular Advancement Surgery for Obstructive Sleep Apnea: A Preliminary 3D Analysis Study

Authors:
J.P.T.F. Ho, N. Zhou, T.C.T. van Riet, R. Schreurs, A.G. Becking, J. de Lange

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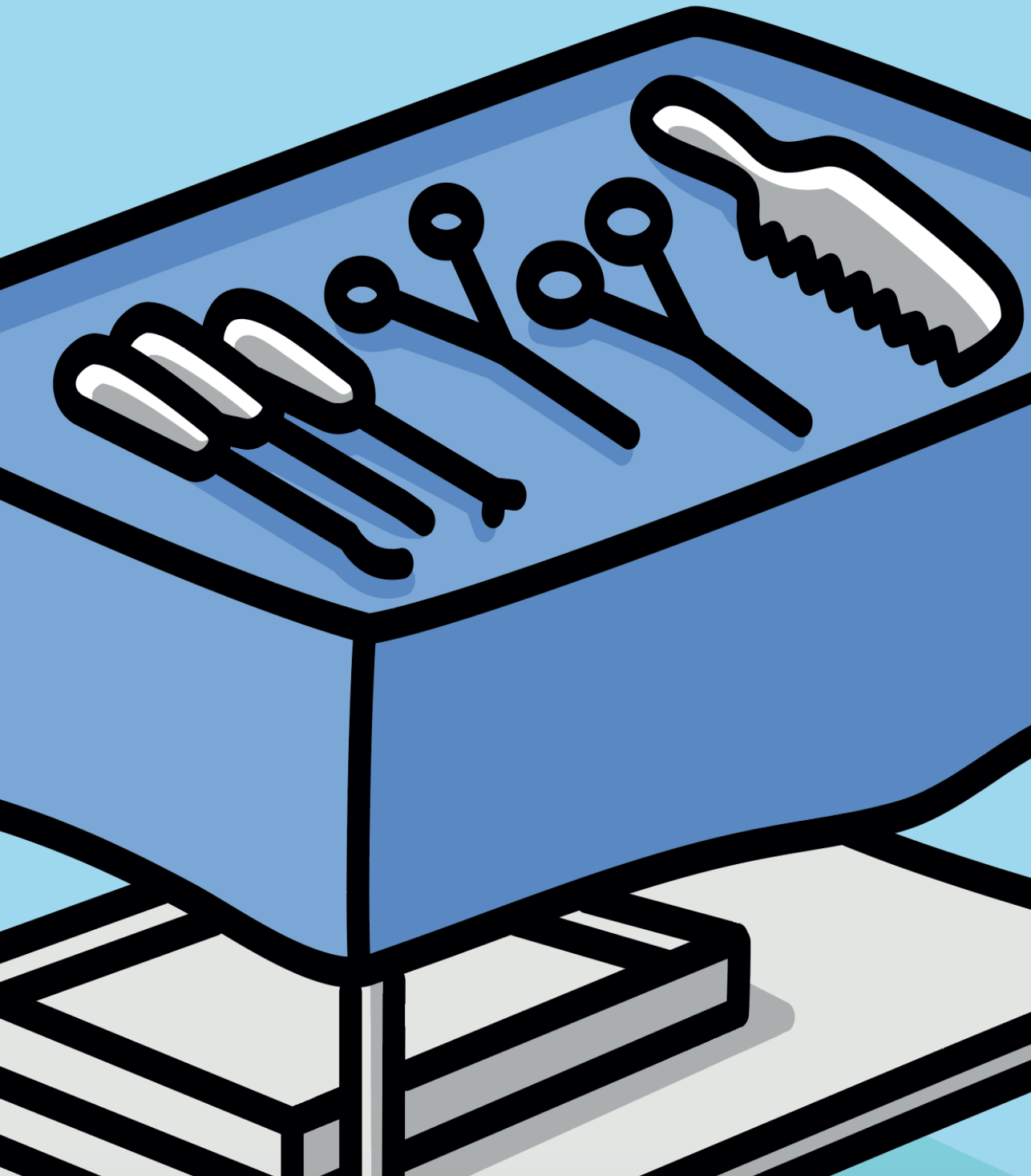
Collection of data:	JH, NZ, RSc
Analysis and management of data:	JH, NZ, TR, RSc
Drafting of manuscript and/or critical revision:	JH, NZ, TR, RSc, AB, JL

Funding sources:
Department and institutional funds.

Conflicts of interest:
None



List of publications

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Peer-reviewed publications

Publications in this thesis

- Zhou N, Ho JTF, Huang Z, Spijker R, de Vries N, Aarab G, Lobbezoo F, Ravesloot MJL, de Lange J. Maxillomandibular advancement versus multilevel surgery for treatment of obstructive sleep apnea: A systematic review and meta-analysis. Sleep Medicine Reviews 2021;*57:*101471. https://doi.org/10.1016/j.smrv.2021.101471
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- van Riet TCT, Chin Jen Sem KTH, Ho JTF, Spijker, R., Kober, J., & de Lange, J. Robot technology in dentistry, part two of a systematic review: an overview of initiatives. *Dental Materials* 2021;*37*(8):1227–1236. https://doi.org/10.1016/j.dental.2021.06.002

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- 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. International Journal of Oral and Maxillofacial Surgery 2023;52(3): 343-352.
  https://doi.org/10.1016/j.ijom.2022.08.012
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- Kuik K, Al Jaja ML, Schreuder WH, Peferoen LAN, Ho JPTF. Een pasgeborene met een zwelling in de mondbodem [A neonate with a swelling in the floor of the mouth]. Nederlands Tijdschrift voor Tandheelkunde 2023;130(1):11–16.
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- Tan ML, Ho JPTF, Tuk JGC, de Lange J, Lindeboom JAH. Impact of maxillomandibular advancement on oral health related quality of life in patients with obstructive sleep apnea: A longitudinal study of the oral health impact profile (OHIP-14). Advances in Oral and Maxillofacial Surgery 2023;9:100398.
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- Beuling MG, Agterbos PCG, van Riet TCT, Ho JPTF, de Vries R, Kober J, de Lange J. Forces and movements during tooth extraction: A scoping review. Advances in Oral and Maxillofacial Surgery 2023;9:100391.
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- Su N, Donders MHCM, Ho JTF, Vespasiano V, de Lange J, Loos BG. Development and external validation of prediction models for critical outcomes of unvaccinated COVID-19 patients based on demographics, medical conditions and dental status. Heliyon 2023;9(4):e15283. https://doi.org/10.1016/j.heliyon.2023.e15283
- Kuik K, Tan ML, Ho JTF, Lindeboom JAH, de Lange J. Subjective Efficiency Evaluation after Maxillomandibular Advancement Surgery in Obstructive Sleep Apnea Patients. Journal of Clinical Medicine 2023;12(12):4023. https://doi.org/10.3390/jcm12124023
- Karagozoglu KH, Mahraoui A, Bot JCJ, Cha S, Ho JTF, Helder MN, Brand HS, Bartelink IH, Vissink A, Weisman GA, Jager DHJ. Intraoperative Visualization and Treatment of Salivary Gland Dysfunction in Sjögren's Syndrome Patients Using Contrast-Enhanced Ultrasound Sialendoscopy (CEUSS). Journal of Clinical Medicine 2023;12(12), 4152. https://doi.org/10.3390/jcm12124152

Non-peer-reviewed publications

Other publications from the same author

- JPTF Ho. Rubriek: Röntgenraadsels. Een radiologische toevalsbevinding. QP Tandheelkunde. Juni 2017 | nummer 6 | jaargang 12 | www.qualitypractice.nl
- MC Donders, JPTF Ho. Rubriek: Röntgenraadsels Multipele radio-opaciteiten bij patiënte met darmpoliepen. QP Tandheelkunde. December 2017 | nummer 2 | jaargang 13 | www.qualitypractice.nl
- JPTF Ho. Droge mond en speeksel Sialo-endoscopie: kijken in de speekselklier en nog veel meer. QP Tandheelkunde. December 2019 | nummer 2 | jaargang 15 | www.qualitypractice.nl
- TR van Velzen, JPTF Ho. Complicaties na toediening van tandheelkundige lokale anesthesie | QP Tandheelkunde | jaargang 17 | nr. 3 | QP Mondhygiëne | nummer 4 | jaargang 14 | www.qualitypractice.nl
- JM Duininck, JPTF Ho. Computergestuurde lokale anesthesie, een update | QP Tandheelkunde | jaargang 17 | nr. 3 | QP Mondhygiëne | nummer 4 | jaargang 14 | www.qualitypractice.nl

Contribution to textbook

Role of Epiglottis in Obstructive Sleep Apnea. Editors: M. Delakorda, N.de Vries. Springer Nature Switzerland.EAN 9783031349911. Chapter 25. Maxillomandibular Advancement. N Zhou, JPTF Ho, J de Lange.

PhD Portfolio

PhD Portfolio

Conferences (national and international)

- AMC-themasymposium voor verwijzers: Implantologie - voorspelbaarheid maakt betrouwbaar 2012
- AMC-themasymposium voor verwijzers: Dentoalveolaire chirurgie op de poli MKA 2013
- AMC-themasymposium voor verwijzers: Speekselklierpathologie 2013
- M3 in gekanteld perspectief 2013
- AMC-themasymposium voor verwijzers: Traumatologie 2013
- NVMKA-najaarscongres 2013
- ITI Kadavercursus pre-implantologie hands-on 2014
- NVMKA-voorjaarscongres 2014
- Nobel Biocare Zygoma implants course 2014
- NVMKA-najaarscongres 2014
- AMC-themasymposium voor verwijzers: Implantologie in het kort en het klein 2014
- Lambert de Bont Conferentie 2014
- The Global Postlaryngectomy Rehabilitation Academy Course 2014
- AOCMF BASIC PRINCIPLES (Davos) Course 2014
- New opportunities in implant dentistry course (BIOMET 3i) 2014
- AMC-themasymposium voor verwijzers: Medicatie in relatie tot de tandheelkunde 2015
- AMC-themasymposium voor verwijzers: Implantologie en tandtechniek digitaal de toekomst in 2015
- Mini around the nose course 2015
- Master Course in Prevention and Management of Esthetic Implant Failures 2015
- Evidence Based Medicine cursus Isala Academie 2015
- 12th International Course on Diagnostics and Surgery of Salivary Gland Diseases in Consideration of New Techniques 2015
- NVMKA-najaarscongres 2015
- MMV Congres: Samen leren, samen werken 2015
- AMC-themasymposium voor verwijzers: Zin en onzin van antibioticaprofylaxe 2016
- De MKA-chirurg als hoofdaannemer in de implantologie 2016

- S.O.R.G. Course: Basic Principles in Core Oral and Maxillofacial Surgery 2016
- Symposium Optimization in CMF trauma care 2016
- NVMKA-voorjaarscongres 2016
- AOCMF Seminar-Advances in Computer-Assisted Microvascular Craniomaxillofacial Reconstruction (hands-on) 2016
- EACMFS: John Lowry Trainee Study Day From Then Until Now Milestones of Craniomaxillofacial Surgery & Reconstructions 2016
- 23rd Congress of the European Association for Cranio Maxillo-Facial Surgery (Ancient and Modern – Surgery Meets Technology) 2016
- NVMKA-najaarscongres 2016
- NKI/AVL, AMC en KNMT-themasymposium: 2016
- Symposium: Medical 3D Printing 2016
- Royal College of Surgeons: Emergency Skills in Oral & Maxillofacial Surgery 2016
- Lambert de Bont Conferentie 2016
- Cursus "Stralingshygiënisch geschoold Beroepsbeoefenaar – Conebeam CT voor MKA-chirurgen (4A/M) 2016
- Cursus ‘Indicatiestelling implantologie in de algemene praktijk’ 2017
- S.O.R.G. Course: Updates and Controversies in Advanced Oral and Maxillofacial Surgery 2017
- AMC-themasymposium voor verwijzers: Samewerken bij schisis, groei en ontwikkeling 2017
- AMC-themasymposium voor verwijzers: Prothetische nascholing voor verwijzers; The dentist in controle! 2017
- AMC-themasymposium voor verwijzers: Refereeravond voor orthodontisten 2017
- Biennial Symposium Surgical Orthodontics (BSSO) Pre-Conference Course ‘Esthetic & Functional Surgery of the Facial Structures Revisited’ by Federico Hernández-Alfaro & Domingo Martin 2017
- Biennial Symposium Surgical Orthodontics (BSSO) 2017
- Astra Tech Implant System Educational Experience 2018
- Lambert de Bont Conferentie 2018
- AASM SLEEP 2018 32nd Annual Meeting of the Associated Professional Sleep Societies 2018

- AMC-themasymposium voor verwijzers: TMJ functie en dysfunctie — 2018
- 24rd Congress of the European Association for Cranio Maxillo-Facial Surgery — 2018
- 2018 Annual Meeting of the American Association of Oral and Maxillofacial Surgeons, 100th Anniversary of AAOMS — 2018
- NVMKA-najaarscongres — 2018
- AMC-themasymposium voor verwijzers: Snurken en Obstructieve Slaap Apneu Syndroom — 2018
- 2019 International Surgical Sleep Society Annual Meeting in New York — 2019
- AMC-themasymposium voor verwijzers: Cosmetische tandheelkunde, orthodontie en chirurgie — 2019
- Dentsply Sirona Connects You To The Future: Digital Workflow in Implant Dentistry — 2019
- NVMKA-najaarscongres — 2019
- Biennial Symposium Surgical Orthodontics (BSSO) — 2019
- Biennial Symposium Surgical Orthodontics (BSSO) Post-Conference Course 'Ryder Cup, techniques in theatre' — 2019
- Lambert de Bont Conferentie — 2020
- 2020 Annual Meeting of the American Association of Oral and Maxillofacial Surgeons virtual conference — 2020
- The 2021 Virtual American Academy of Dental Sleep Medicine (AADSM)Annual Meeting virtual conference — 2021
- 25th Congress of the European Association for Cranio Maxillo-Facial Surgery — 2021
- Teach the Teacher NWZ Academie "EPA gericht opleiden" — 2021
- Teach the Teacher NWZ Academie "toetsen, beoordelen en feedback geven" — 2021
- EMEA - BioSkills: Temporomandibular Joint Replacement — 2021
- Lambert de Bont Conferentie — 2022
- 14e NVTS Congres — 2022
- 2022 American Academy of Dental Sleep Medicine (AADSM) 30th Anniversary Meeting — 2022
- 1st International Course on COMPREHENSIVE OSA TREATMENT OSA Academy — 2022

- Teach the Teacher 2022
  NWZ Academie “toetsen, beoordelen en feedback geven”
- Teach the Teacher 2022
  NWZ Academie “De innerlijke criticus & feedback”
- 26th Congress of the European Association for 2022
  Cranio Maxillo-Facial Surgery
- Verwijzersavond MKA-chirurgie Noord-Holland Noord: 2022
  Aangezichtstrauma met bijzonder aandacht voor dento-alveolair trauma
- International Osteology Symposium Barcelona 2023 2023
- 15e NVTS Congres 2023
- 25th International Conference on Oral and Maxillofacial Surgery 2023
- Biennial Symposium Surgical Orthodontics (BSSO) 2023
- Herfstsymposium NVDMFR 2023 2023
- Diagnostiek van cariës tot kaakgewricht 2023

Webinar

- Webinar S.O.R.G. 2020
  Overview of TMJ disorders (23-04-2020)
- Webinar KLS Martin (30-04-2020) 2020
  Maximizing the safety of OMF patients and OMF
  teams during the Corona pandemic disorders
- Webinar KLS Martin (14-05-2020) 2020
  Individual patient-specific solutions for midface reconstruction
- Webinar KLS Martin (02-05-2020) 2020
  Individual patient-specific solutions for secondary orbital reconstruction
- Webinar KLS Martin (10-06-2020) 2020
  Individual patient - specific solutions for the mandible
- Webinar S.O.R.G. (03-06-2020) 2020
  New concepts for preprosthetic reconstruction Subperiosteal
  and patient - specific solutions disorders
- Webinar S.O.R.G. (09-06-2020) 2020
  Surgical therapy for OSA patients
- Webinar S.O.R.G. (18-06-2020) 2020
  The different approaches to the TMJ\
- Webinar S.O.R.G. (23-06-2020) 2020
  Craniofacial microsomia
- Webinar KLS Martin (24-06-2020) 2020
  Emerging technologies for orthognathic surgery

- Webinar KLS Martin (25-06-2020) 2020
  Individual patient-specific solutions for secondary orbital reconstruction
- Webinar S.O.R.G. (15-07-2020) 2020
  Ballistic facial injuries - Early and secondary management
- Webinar S.O.R.G. (23-07-2020) 2020
  Individual patient-specific solutions in orthognathic surgery
- Webinar AMSJI masterclass 2nd (14-09-2020) 2020
  2nd Additively Manufactured Subperiosteal Jaw Implant masterclass
- Webinar S.O.R.G. (15-09-2020) 2020
  Diagnosis and treatment of vascular anomalies
- Webinar S.O.R.G. (21-10-2020) 2020
  TMJ arthroscopic disc repositioning techniques
- Webinar KLS Martin (05-11-2020) 2020
  The role of customized implants in corrections of jaw deformities
- Webinar S.O.R.G. (18-02-2021) 2021
  The history of orthognathic surgery, 1849 – 2021
- Webinar S.O.R.G. (25-02-2021) 2021
  Diagnosis, Evaluation and Treatment Planning - Surgical diagnosis
- Webinar S.O.R.G. (04-03-2021) 2021
  Limits in orthodontic treatment. Orthodontic alternatives to surgery
- Webinar S.O.R.G. (11-03-2021) 2021
  Diagnosis, Evaluation and Treatment Planning –
  Indications, patient selection | Orthognathic Surgery
- Webinar S.O.R.G. (01-04-2021) 2021
  Surgical Technical Planning – Virtual surgical planning –
  updated basic concept | Orthognathic Surgery
- Webinar S.O.R.G. (22-04-2021) 2021
  Surgical Treatment - Mandibular osteotomies | Orthognathic Surgery
- Webinar S.O.R.G. (29-04-2021) 2021
  Surgical Treatment - Genioplasty | Orthognathic Surgery
- Webinar S.O.R.G. (11-05-2021) 2021
  Outcomes - Complications | Orthognathic Surgery
- ANZAOMS 2021 (11-11-2021) 2021
  Patient Specific Solutions in Non-Augmentative Preprosthetic Restoration
- Webinar S.O.R.G. (10-02-2022) 2022
  Pathophysiology in TMJ Disorders
- Webinar S.O.R.G. (17-02-2022) 2022
  TMJ Arthroscopy - From Simple to Complex

- Webinar S.O.R.G. (24-02-2022) 2022
  Imaging of the TMJ
- Webinar NVTS (08-03-2022) 2022
  'Doel en fysiologie van de slaap'
- Webinar S.O.R.G. (17-03-2022) 2022
  Management of Inflammatory Arthritis of the TMJ (Adults)
- Webinar S.O.R.G. (31-03-2022) 2022
  TMD and Dentofacial Deformity/Orthognathic Surgery
- Webinar S.O.R.G. (28-04-2022) 2022
  The 10 Most Relevant Queries about TMJ Minimally Invasive Surgery
- Webinar S.O.R.G. (05-05-2022) 2022
  Alloplastic Replacement in TMJ Surgery
- Webinar S.O.R.G. (25-05-2022) 2022
  Complications in TMJ Surgery
- Webinar NVTS (10-10-2022) 2022
  'Ontwikkelingen OSA, De revisie van de richtlijn en de dagelijkse praktijk'
- Webinar S.O.R.G. (10-11-2022) 2022
  Patient-Specific Preprosthetic Dental Implants -
  New Non-Augm. Treatment of the Severely Def. Maxilla
- Webinar S.O.R.G. (10-11-2022) 2022
  IPS CaseDesigner® Version 2.2 | New Features (EN)
- Webinar NVTS (23-05-2023) 2023
  'De rol van de KNO-arts bij patiënten met slaapapneu klachten'

Scientific oral presentation

- Symposium Optimization in CMF trauma care (international) 2016
  A contemporary three-dimensional method using mirroring and surface based matching techniques for measuring zygomatic complex symmetry
- 23rd Congress of the European Association for 2016
  Cranio Maxillo-Facial Surger
  A contemporary three-dimensional method using mirroring and surface based matching techniques for measuring zygomatic complex symmetry
- 24rd Congress of the European Association 2018
  or Cranio Maxillo-Facial Surgery
  Splintless Surgery To Increase The Predictability Of Orthognathic Surgery In Edentulous Cases – A Technical Note
- NVMKA-najaarscongres 2018
  Precisie en voorspelbaarheid van splintloze orthognatische chirurgie

bij edentate patienten

- Landelijke opleidingsdag AIOS MKA-chirurgie 2020
  Diagnostiek; anamnese, aanvullend onderzoek (polysomnografie)
- Landelijke opleidingsdag AIOS MKA-chirurgie 2020
  Mandibulair Repositie Apparaat (MRA)
- Landelijke opleidingsdag AIOS MKA-chirurgie 2020
  Perioperatieve management bimaxillaire osteotomie voor OSA
- Quality Practice Mondhygiëne congres (nationaal) 2020
  Medicijn gerelateerde osteonecrose van de kaak
- American Academy of Dental Sleep Medicine (AADSM) 2021
  "Splintless Maxillomandibular Advancement for
  Obstructive Sleep Apnea in Edentulous Patients: A Pilot Study"
- Postacademisch onderwijs 2021
  Afdeling Orthodontie ACTA
  Klinische les: Obstructieve slaap apneu syndroom (OSAS)
  25th Congress of the European Association for 2021
  Cranio Maxillo-Facial Surgery
  Central and mixed apnea in obstructed sleep apnea patient treated with
  maxillomandibular advancement surgery
- 25th Congress of the European Association for 2021
  Cranio Maxillo-Facial Surgery
  SORG satellite online event – Obstructive Sleep Apnea Management
  Patients related outcomes of MMA therapy
- American Academy of Dental Sleep Medicine (AADSM) 2022
  "Comparison of the effects of maxillomandibular advancement on
  respiratory function and facial esthetics between obstructive sleep apnea
  patients with and without maxillomandibular deficiency"
- 1st International Course on COMPREHENSIVE 2022
  OSA TREATMENT OSA Academy "Orthognathic Surgery for OSA"
- ACTA Dental Education B.V. 2022
  QP-congres: Chirurgie in de algemene praktijk
  Tandheelkundige lokale anesthesie: relevante anatomie en complicaties
- Nederlandse vereniging voor orthodontie 2022
  Najaarscongres: Next level OSAS en het belang van
  een interdisciplinaire aanpak!
- 26rd Congress of the European Association for 2022
  Cranio Maxillo-Facial Surgery
  Maxilla-first versus mandible-first surgical sequence in

maxillomandibular advancement surgery for obstructive sleep apnea

- 25th International Conference on Oral and Maxillofacial Surgery 2023
  Influence of Surgeon Experience on Surgical Outcome of Maxillomandibular Advancement for Obstructive Sleep Apnea
- 25th International Conference on Oral and Maxillofacial Surgery 2023
  Obstructive Sleep Apnea Resolution in Hypopnea-Predominant Versus Apnea-Predominant Patients after Maxillomandibular Advancement
- Herfstsymposium NVDMFR 2023 2023
  De rol van beeldvorming bij benigne TMJ-pathologie: van diagnostiek tot therapie.

Poster presentation

- American Acadamy of Dental Sleep Medicine (AADSM) 2021
  “Splintless Maxillomandibular Advancement for Obstructive Sleep Apnea in Edentulous Patients: A Pilot Study”

Grant/funding

- BOOA-research grant van de NVMKA 2014
  Therapeutische en economische evaluatie van twee behandelmogelijkheden voor persisterende periradiculaire laesies.
- Dentsply sponsored study 2018
  “Mandibular Advancement Device (MAD) therapy in Edentulous Patients with obstructive sleep apnea: dental implant retained MAD therapy - MADE-study”, I-OT-18-031
- Amsterdam UMC Innovatie-impuls 2021
  Onderwijsvernieuwing op het gebied van de extractieleer
- Aanmoedigingsprijs BOOA-research grant van de NVMKA 2021
  Ontwikkeling en valideren van een predictiemodel voor maxillomandibulaire advancement osteotomie als behandeling van het obstructief slaap apneu syndroom
- Subsidieaanvraag (R34) bij de NIH/NIAID 2022
  (Phase I/IIa Clinical Trial Using Localized and Systemic Delivery of the P2X7 Receptor Antagonist AZD9056 for the Treatment of Salivary Gland Dysfunction in Sjögren's Syndrome Patients)

- Aanmoedigingsprijs BOOA-research grant van de NVMKA 2022
  Chirurgische navigatie bij de positionering van een TMJ fossa prothese en het gebruik van orientatie schroeven bij de positionering van de mandibulaire condyle prothese ter bevodering van de accuratesse
- Amsterdam UMC Innovatie-impuls 2022
  Anesthesia related mandibular advancement device: innovatie voor perioperatieve zorg bij patiënten met OSAS
- KLS Martin sponsored study 2023
  "CADFEM/KLS Martin Docq OSA project proposal"
- NVTS research grant 2023
  Een mandibular advancement device voor patiënten met OSAS na een operatie
- NVTS research grant 2023
  Slimme MRA's bij obstructief slaapapneu: een systematisch literatuuronderzoek
- SORG Maxime Champy Research Grant 2023
  Complex issues related to alloplastic TMJ replacement: A review and recommendations based on a consensus meeting
- Aanmoedigingsprijs BOOA-research grant van de NVMKA 2023
  Velopharyngeale insufficiëntie na een maxillomandibulaire advancement bij patiënten met obstructief slaap apneu syndroom

Awards

- AADSM Clinical Excellence Award 2021
  In. Recognition of Research Excellence in Dental Sleep Medicine and The Most Outstanding Clinical Research

PhD training

- Basic course on Regulations and Organization for clinical investigators 2018
  (The eBROK course of the NFU Brokacademy)
- Scientific Writing in English for Publication 2020
  Scientific writing course UvA
- Research Integrity - Biomedical sciences 2021
  Course ACTA
- Stanford introduction to statistics course 2021
  Scientific online Coursera course
- Basic course on Regulations and Organization for clinical investigators 2021
  (The eBROK recertification course of the NFU Brokacademy)

Bachelor thesis supervisor

- P. van Leeuwen & M. van Maastrigt 2015
  Quantitative diagnostics: methodology validation by determining the accuracy and effectiveness of identifying zygomaticomaxillary complex fractures based-on a novel 3D mirroring model technique
- S. Aydi & R. Rezai 2016
  A three-dimensional analysis of zygomaticomaxillary symmetry in unfractured patients

Master thesis supervisor

- T. Remmelts 2015
  Advanced diagnostics: effectiveness of a mirroring tool for zygomatic symmetry
- S. Aydi 2019
  A Ten-Year Retrospective Inquiry of Zygomaticomaxillary complex fractures
- R. Rezai 2019
  Development and validation of a software package to analyse zygoma fractures
- L. Yohannes 2020
  Oral Health-related quality of life after coronectomy in the first postoperative week
- L. van Ewijk 2020
  A comparison of two different techniques for temporary intra-operative maxillomandibular fixation during orthognathic surgery
- R. van Ommeren 2020
  An overview and evaluation of orthodontic appliances during orthognathic surgery - A cross-sectional study
- K. Chin Jen Sem 2020
  Robots in Dentistry: a scoping review
- Y. Afrian 2021
  Adverse effects following dental local anesthesia: a literature review
- C. Robles de Medina 2021
  Current knowledge of congenital granular cell epulis: a scoping review
- R. Simons 2021
  Early root migration after a mandibular third molar coronectomy
- P. Agterbos 2022

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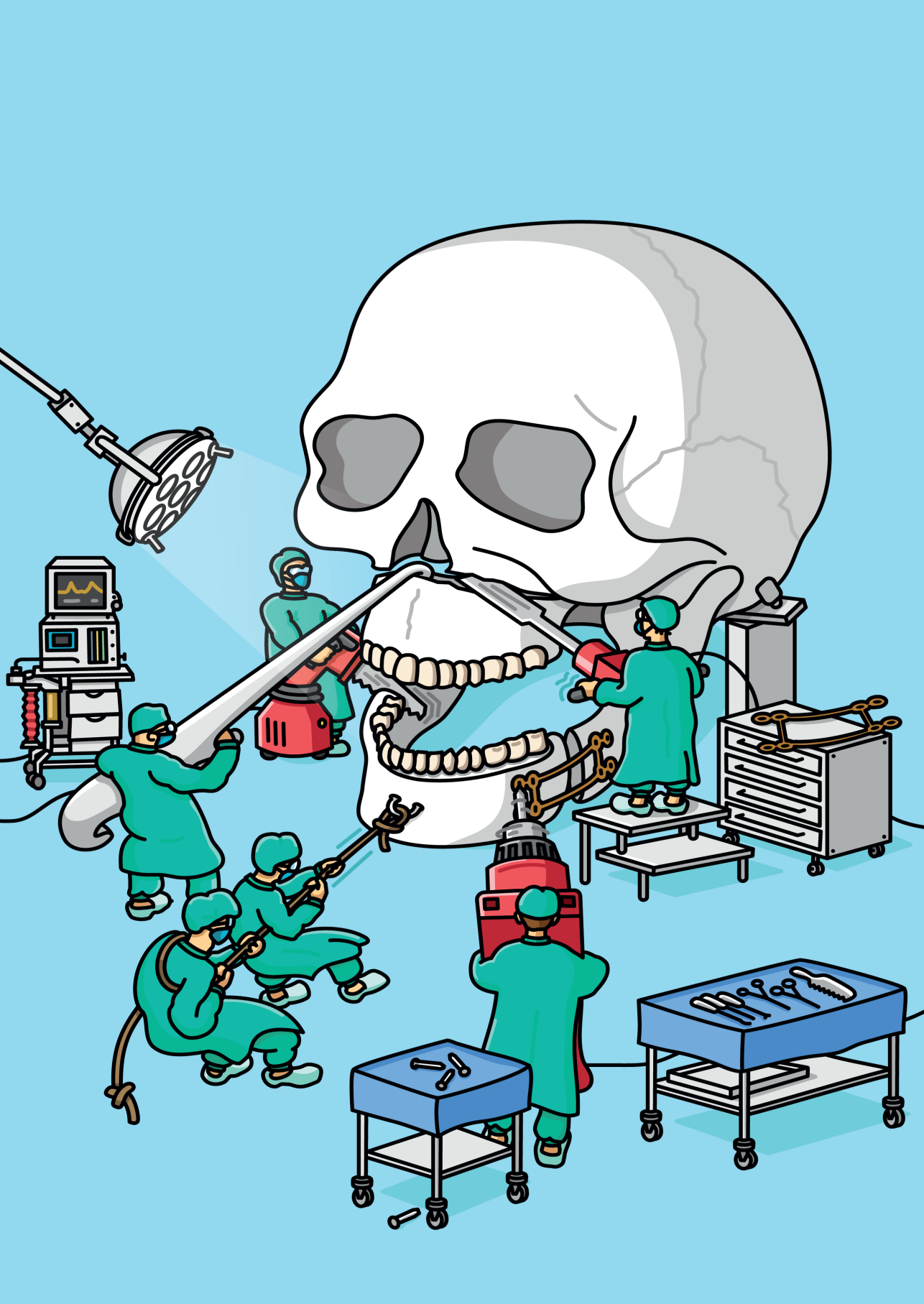
- R. Buenting 2022
  Confidence of dental students in application of local anesthesia: development and validation of a questionnaire
- A. Dobber 2023
  Evaluation of tooth extraction education: a scoping review
- M. Al-Hussein 2023
  A comparison between nonsurgical and surgical treatment of oroantral communications: A systematic review
- S. Klee 2023
  Short-term postoperative outcome in patients with obstructive sleep apnea undergoing maxillomandibular advancement
- M. Soffner 2023
  De psychologische status van patiënten die een TMJ reconstructie hebben ondergaan

Honor student supervisor

- L. Bidar 2020
  Maxillomandibular Advancement as a treatment for Obstructive Sleep Apnea: a systematic review (pre-analysis)
- M. Al Jaja 2022
  Een pasgeborene met een zwelling in de mondbodem
- S. Özkan 2022
  Comparison of surgical outcome of maxillomandibular advancement between two surgeons

Foreign student supervisor

- J. Yang (Harvard University, Boston USA) 2023
  Non-sleep related outcome of maxillomandibular advancement: a systematic review
- J. Yang (Harvard University, Boston USA) 2023
  Smart mandibular advancement devices for obstructive sleep apnea: a systematic literature review



Acknowledgments / Dankwoord

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In dit dankwoord wil ik graag mijn oprechte waardering uitspreken voor eenieder die heeft bijgedragen aan het succesvol afronden van mijn promotietraject. Deze reis was gevuld met persoonlijke successen, maar ook uitdagingen en tegenslagen.

Prof. dr. J. de Lange, hooggeleerde promotor, beste Jan. Door de jaren heen is mijn relatie met jou voortdurend aan verandering onderhevig geweest. Eerst was jij mijn afdelingshoofd, opleider, promotor en nu collega. De dagen dat wij samen opereren zijn vaak ontspannen, gevuld met humor en anekdotes, ongeacht de complexiteit van de ingreep. Op de vraag van AIOS vanwaar het komt dat wij zo vaak samen opereren, beantwoord ik met een knipoog: "De professor durft me niet alleen te laten en houdt mij liever dichtbij zich om mij zodoende in de gaten te kunnen houden." Maar stiekem hoop ik dat jij net zo graag met mij opereert als ik met jou. Het is bekend dat promovendi zich vaak afvragen of ze hun proefschrift wel zullen voltooien, en in mijn geval was dat geen geheim, immers velen hebben getwijfeld hieraan. Het besluit om te stoppen met het zygoma-project was moeilijk, maar jij hebt mij hierin gesteund en daar ben ik je dankbaar voor. Jaren geleden vroeg jij mij om in het AMC te blijven werken en het deelgebied OSA op te pakken, met de woorden: "OSA is the gift that keeps on giving." Destijds kon ik me niet voorstellen dat ik ooit op dit onderwerp zou promoveren, maar zoals vaker het geval is had je ook hierover gelijk. Met veel dankbaarheid en respect wil ik mijn waardering uitspreken voor jouw bijdrage aan mijn academische groei en succes. Dank voor je steun, begeleiding en de vrijheid die je me gaf om mijn eigen ideeën te verkennen en deze promotie op een geheel eigen wijze in te vullen. Ik hoop dat we samen nog veel succes zullen behalen, zowel in de wetenschap, klinische zorg als daarbuiten

Prof. dr. A.G. Becking, hooggeleerde promotor, beste Eddy. Ook aan jou ben ik veel dank verschuldigd. Met name in de begin jaren van mijn promotie was je van enorm grote waarde. Jouw enthousiasme, deskundigheid en begeleiding in die jaren van het zygoma-project hebben ervoor gezorgd dat de eerste twee onderzoeken in korte tijd waren gepubliceerd. Helaas verliep het vervolg van het project minder voortvarend. In die periode toonde je vaak begrip, zelfs tijdens de meest uitdagende momenten. Ik ben dankbaar voor de vele momenten van overleg en brainstormsessies, vaak tijdens een coffee-run. Ook jij hebt mij de ruimte geboden om deze promotie geheel zelfstandig te kunnen invullen en vorm te geven. Ik vraag mij achteraf af of jij en Jan ooit een wedje hebben gemaakt hoelang het zou duren voordat het tweede project zou falen. If so, zou het in ieder geval niet aan jou hebben gelegen. Jouw passie voor ons vakgebied is aanstekelijk en heeft mijn eigen passie versterkt. Ik kijk met bewondering naar het

grote netwerk aan contacten die jij door de jaren heen hebt opgebouwd. Je hebt altijd wel iemand in jouw netwerk waar ik terecht kan voor hulp en advies, ongeacht het onderwerp. Ik kijk met trots terug op onze samenwerking en alles wat wij samen hebben kunnen realiseren.

Ook de leescommissie wil ik bedanken voor de tijd en de moeite die zij hebben genomen om dit proefschrift kritisch te beschouwen en te beoordelen. Het is een voorrecht om tegenover u te mogen staan en om met u van gedachten te wisselen over de inhoud van dit proefschrift.

Mijn coauteurs van de publicaties die hebben bijgedragen aan dit proefschrift, ik wil u allen bedanken voor uw bereidwilligheid om de samenwerking met mij aan te gaan. Ik ben iedere coauteur afzonderlijk zeer dankbaar voor zijn of haar tijd, inspanningen, waardevolle ideeën, adviezen en kritische houding vanaf het opzetten van het onderzoek tot aan het schrijven van het manuscript. In het bijzonder wil ik twee coauteurs toch even extra benoemen, namelijk:
R.C. Apperloo, beste Ruub, voor degenen die het niet weten, jij hebt de OSAS in het AMC groot gemaakt. Jij hebt ook veel van de patiënten geopereerd die in dit proefschrift voorkomen. Velen net als ik hebben de techniek van de MMA van jou geleerd, en daarom is het volgende op jou van toepassing: "The mark of an outstanding surgeon isn't just in their hands but in their ability to cultivate excellence in the hands of others" (hoofdstuk 8).
Dr. N. Zhou, dear Ning, the past few years we have been on a crazy OSA and MMA journey. We have spent countless hours examining and deliberating on the MMA data. It has been a pleasure and honor working with you. Hope we can continue our scientific journey together. Remember, both you and Zhengfei are always welcome in Krista's and my home.

Mijn paranimfen op deze bijzondere dag, ook jullie beiden wil ik kort individueel benoemen en bedanken.
V.T. Akkerman, beste Vollie, je was tijdens de opleiding mijn oudste AIOS. Een betere zou ik niet kunnen wensen. Ook na de opleiding zien en spreken wij elkaar nog zeer regelmatig. Daarnaast bezoeken wij samen congressen en cursussen zowel in Nederland als daarbuiten. Het is altijd lachen vanaf het moment dat wij in de auto of vliegtuig stappen tot aan het moment dat wij weer thuis zijn. Wij gaan uiteraard altijd voor de wetenschappelijke inhoud, maar genieten uiteraard ook van de lokale cultuur en culinaire hoogstandjes. Ik ben blij dat jij op deze speciale dag bereid bent om naast mij te staan.

Dr. T.C.T. van Riet, beste Tom, wij verschillen als dag en nacht van mekaar. Voor velen is het een raadsel hoe wij desondanks zo goed met elkaar kunnen samenwerken. Persoonlijk denk ik dat het succes ligt in het feit dat wij vanaf het begin van de opleiding elkaar respecteren, waarderen, maar wellicht meer nog elkaar blindelings vertrouwen. Samen hebben wij de afgelopen jaren de kneepjes van het vak, het doen van organisatie en de wetenschap ons eigen gemaakt. Jij bent de stuwende kracht achter ons gezamenlijke successen. Ik kan mij geen andere collega wensen om dit pad samen te hebben bewandeld. Het was een grote eer om jouw paranimf te mogen zijn, en ik kan alleen maar hopen dat jij dezelfde eer ervaart wanneer het jouw beurt is om mijn paranimf te zijn.

Beste (oud) AMC-staf, **prof. van den Akker, Frans, Kees, Jacco en Jerome**, ik ben vereerd de kans te hebben gekregen om met jullie samen te werken. In het bijzonder wil ik twee voormalige stafleden bedanken:
Prof. dr. H.P. van den Akker, beste Hans, ik ben dankbaar voor het vertrouwen dat u in mij had, zeker het moment waarop u mij een opleidingsplaats aanbood.
Dr. J.A.H. Lindeboom, beste Jerome, oorspronkelijk wilde ik mijn eindscriptie schrijven in Australië. Gelukkig werd ik daarvoor niet geselecteerd, want als alternatief bood de ACTA mij de mogelijkheid om mijn scriptie bij jou in het AMC te schrijven. Nu ben ik zelf staflid in het AMC. Het is ongelofelijk hoe het leven soms loopt, nietwaar? Mijn eerste wetenschappelijke publicatie heb ik aan jou te danken, en lange tijd dacht ik dat het mijn enige publicatie zou blijven. Ik ben jou erg dankbaar voor de kansen die je mij hebt geboden. Gran tangi mi mati en tang boeng.

Beste (oud) Amsterdam UMC-stafleden, **Tim, Ronald, Jan (dV), Jan (dL), Ludi, Fred, Eddy, Bert, Jacco, Leander, Hakki, Brigitte, Erik, Jeroen, Jistke, Pim, Tom, Renée, Peter, Judith en Willem**. Wij vormen een gevarieerde groep, maar delen wel een gemeenschappelijk doel: het opbouwen van de meest toonaangevende afdeling MKA-chirurgie in Nederland en mogelijk daarbuiten. Eenieder van jullie heeft unieke kwaliteiten en expertise en dat geeft mij het volste vertrouwen dat wij dit kunnen bereiken. Laten wij dit bereiken met wederzijds respect en waardering voor elkaar, maar vooral ook met veel humor en plezier.

Mijn mede-AIOS-groep, **Vollie, Robbie, Bram, Maurits, Antoinette, Tom, Renée, MC en Judith**, ik heb enorm genoten van de tijd die wij samen met elkaar hebben doorgebracht. Er waren zowel hoogte- als dieptepunten. Maar bovenal hebben wij samen ontzettend veel plezier gehad. Ik wens alle AIOS een even mooie opleidingstijd toe. Jullie hebben allemaal bijgedragen aan de zorg voor de patiënten die betrokken

zijn bij de verschillende onderzoeken van deze promotie. Daarvoor wil ik jullie extra bedanken. By the way, kamertje A1-116 for life (ondanks dat de gynaecologie er nu in zit 😉).

De A(N)IOS waarmee ik heb samengewerkt, **Judith, Simone, Sophie, Joni, Johan, Willem, Kitty, Jesper, Guus, Karel, Jorrit, Stan, Brandaan, Thijs, Pamela, Robin, Rebecca, Ilkay, Boudewijn, Birgit, Serge, Maaike, Wouter, Roos, Sam, Lauren**. Het is fijn om te zien hoe jullie je dag na dag ontwikkelen. Veel dank voor de uitstekende zorg die jullie hebben verleend aan alle patiënten uit deze promotie.

Het 3D lab, **Ruud, Niels en Juliana**. Jullie inzet, expertise en hulp zijn bij iedere casus van onschatbare waarde. Veel patiënten die deelnamen aan de verschillende onderzoeken hebben jullie virtueel geopereerd en gepland. Dankzij jullie geweldige inzet is iedere operatie keer op keer een succes. Dank voor de fijne samenwerking.

Alle medische professionals en ondersteunend personeel betrokken bij het Amsterdam UMC, waaronder specialisten, polikliniek assistenten, röntgenlaboranten, administratieve assistenten, secretaresses, mondhygiënisten, verpleegkundigen, tandtechnici en operatieassistenten. Hoewel ik niet iedereen bij naam kan noemen, wil ik jullie allemaal van harte bedanken voor jullie bijdragen, variërend van afspraken, röntgenfoto's, machtigingsaanvragen, correspondentie, bestellingen van verschillende producten tot de zorg voor en de operatieve ondersteuning van de patiënten die deelnemen aan het onderzoek. Ik wil echter twee mensen in het bijzonder noemen, namelijk **Drikje en Simone**. Jullie hebben mij 17 jaar geleden zo hartelijk verwelkomd in het AMC, en tot op de dag van vandaag staan jullie voor mij klaar. Ik zeg vaak aan jullie: “als jullie besluiten te stoppen, dan overweeg ik hetzelfde te doen”.

Alle promovendi waarmee ik het voorrecht heb om samen te werken, ik hoop dat dit proefschrift een bron van motivatie voor jullie zal zijn. Eén tip: doe er niet zo lang over als ik heb gedaan.

Alle collega’s en deelnemers aan het MDO van het slaapcentrum OLVG, ook aan jullie allen spreek ik mijn oprechte waardering uit voor de fijne samenwerking. Velen van de patiënten die deelnamen aan de diverse onderzoeken in dit proefschrift zijn trouwens patiënten van jullie (geweest).

Aan de orthodontisten die de onderzoekspatiënten hebben voorbehandeld. Ik wil jullie danken voor de samenwerking. Telkens wanneer een patiënt met succes is behandeld

is dat een overwinning voor ons als team. In het bijzonder wil ik Elsje Huntjens en Petra Zuurbier bedanken, jullie hebben samen meer dan de helft van alle patiënten in deze promotie behandeld.

Ik wil mijn waardering uitspreken aan de MKA-chirurgen, polikliniek-assistenten en OK-assistenten van de Isala Klinieken voor de geweldige tijd in Zwolle. Ik ben dankbaar voor de kennis en ervaring die ik bij jullie heb opgedaan.

To all my colleagues and friends in Newcastle, dear **prof. Greenwood, James, Ann, Simon, Andy, Stuart, and last but certainly not least Matt**. I want to express my gratitude for the warmth and openness you all showed me in 2017. The knowledge and experience I gained during my time in Newcastle have provided me with the tools I continue to use daily. Some of these tools have been instrumental in the care of numerous patients involved in the various research projects of my PhD thesis. Please know that you are always welcome in Amsterdam.

Beste **Otto**, mijn fundament als tandarts en MKA-chirurg is gelegd in jouw praktijk. Ik denk vaak met veel genoegen terug aan die periode. Dank je wel voor het vertrouwen dat je in mij hebt gesteld.

Beste dames van de polikliniek MKA-chirurgie, verpleegafdeling en op de OK in NWZ, Dijklander, Marina Clinic, Mediaan Clinic en Missiehuis Kliniek, dank voor de geweldige inzet iedere dag weer. Jullie leveren ontzettend hard werk en vinden toch altijd tijd om mijn verzoeken, taken en klusjes af te handelen, of ik nu in Alkmaar, Den Helder, Hoorn of Amsterdam ben. In het bijzonder wil ik **Mo en Ellen** bedanken. Jullie maken het mogelijk dat ik zowel in de maatschap als in Amsterdam kan werken.

Beste (oud) maten, **Hans, Rolf, Andreas, Ignaz, Roeland, Manon, Roel, Dorien, Martine, Renée en Christopher**, dankzij jullie steun en flexibiliteit is dit proefschrift tot stand gekomen. Ik voel me vereerd om deel uit te maken van onze maatschap. Wij als groep leveren hoogwaardige zorg over het gehele spectrum van ons vakgebied. Ik hoop dat ik daaraan een steentje bijdraag. Het feit dat de maatschap ook ruimte biedt voor individuele ontplooiing, persoonlijke ontwikkeling en groei, is iets om trots op te zijn.

Mijn waardering gaat ook uit naar de patiënten die een waardevolle bijdrage hebben geleverd aan dit proefschrift.

Aan mijn vrienden en familie, ik wil jullie allen danken voor alle gezellige momenten en welkome afleiding wanneer ik het nodig had. Velen begrepen wellicht niet waarom ik zo vaak in het weekend moest werken. Immers, hoe kan je bijna ieder weekend dienst hebben? Dit proefschrift zal waarschijnlijk veel verklaren waarom ik er niet altijd bij kon zijn.

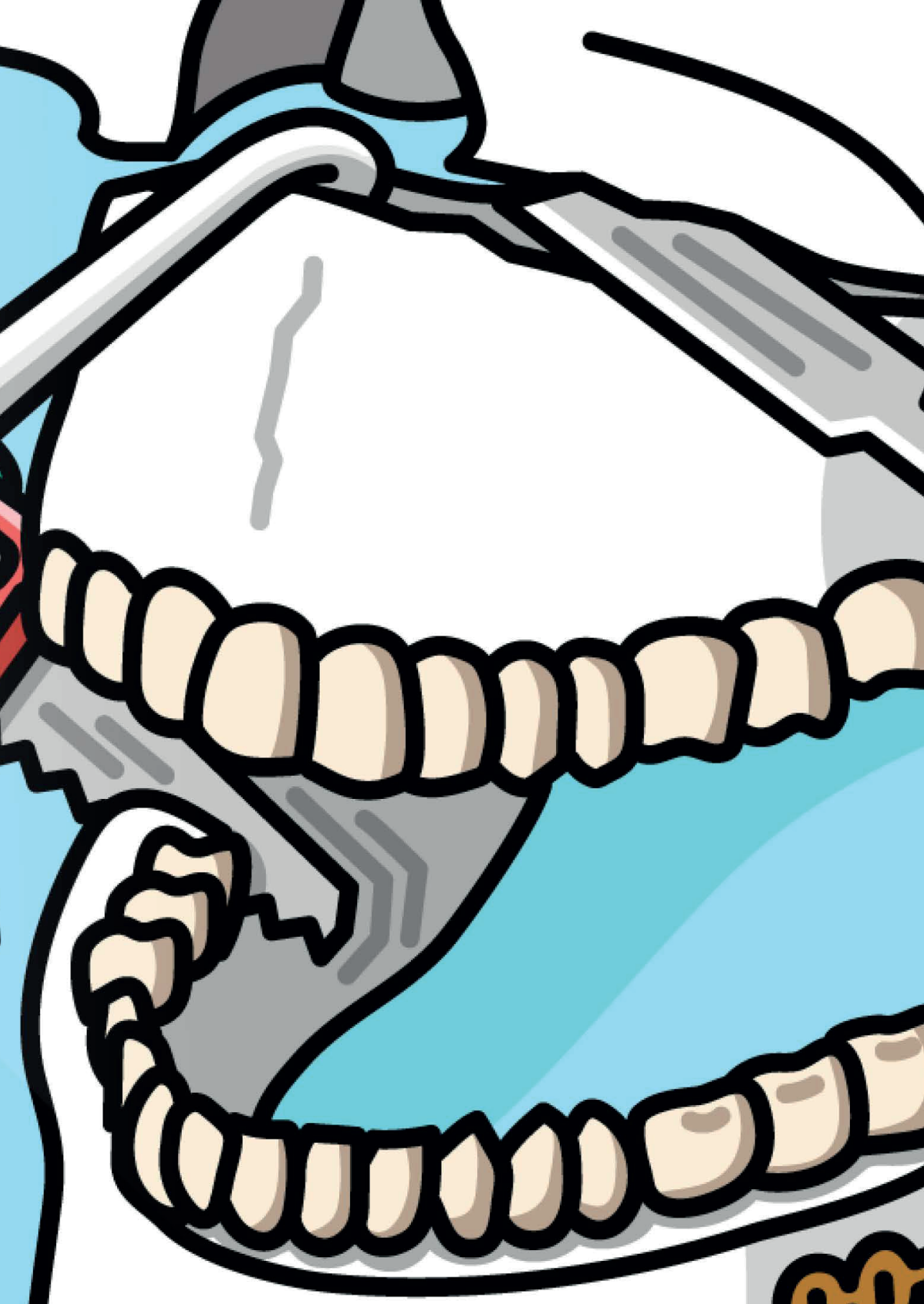
Chantal, mijn grote zus. De afgelopen jaren hebben wij elkaar veel te weinig gezien en gesproken. Ik hoop dat bij het lezen van dit proefschrift het begrip is ontstaan dat mijn afwezigheid geen onwil was, maar eerder het resultaat van de vele uren die hierin zijn geïnvesteerd. Mijn lieve nichtjes **Chiara en Faye**. Ik hoop dat ik voor jullie een inspiratie kan zijn om hard te werken en jullie dromen na te streven. En dat ik niet alleen maar die “gekke” oom ben die graag met jullie knuffelt.

Dave, mijn broertje. Voor mij zal je altijd "die kleine" blijven. Ik ben blij dat doordat jij MDL-arts wordt er ten minste één van ons twee, volgens pa, een echte dokter is geworden. Maar je weet de mond staat vooraan in de in de tractus digestivus. Dus respect, hè! Het is niet in de makkelijke momenten dat we echt laten zien wie we zijn. Echte karakter en kracht worden pas onthuld wanneer we rechtop kunnen staan en sterk blijven, zelfs wanneer het leven niet gaat zoals gepland. En dat heb je gedaan! Daarom ben ik zo ontzettend trots op je. Het is jammer dat je over anderhalf jaar terugkeert naar Suriname, maar ik bewonder je vastberadenheid om iets voor de samenleving en het land te betekenen. Meer artsen zouden zo altruïstisch mogen zijn als jij. Ondertussen heb je een prachtig gezin met **Enzo en Karolaine**. Geniet iedere dag van elkaar.

Pa en ma, uit de grond van mijn hart dank ik jullie voor de onvoorwaardelijke liefde, steun en aanmoediging die jullie me hebben gegeven gedurende mijn hele opleiding en promotie. Ik kan alleen maar hopen dat Sam ooit zal terugkijken en kan zeggen dat hij een net zo mooie jeugd heeft gehad als ik. En dat hij net zo trots is op mij als ik op jullie beiden. Dit proefschrift draag ik op aan jullie twee.

Samuel, mijn vriendje. Pappie houdt zo ontzettend veel van jou. Jij bent mijn trots. Ik hoop dat ik je in de loop der jaren de volgende waarden kan meegeven, namelijk: braaf zijn, moedig zijn, groot dromen, jezelf zijn, lief zijn, vrolijk zijn, vriendelijk zijn, gezond zijn, gehoorzaam zijn en liefdevol zijn. Je hebt de eerste twee jaar als baby zo vaak op mijn schoot gezeten terwijl ik diverse artikelen schreef, dat ik je bijna als coauteur had kunnen vermelden. Pappie hoopt zo voor je dat jij later ook je passie zult vinden.

Lieve **Kris**, ik weet echt niet waar ik moet beginnen. Als het kon, dan had ik jouw naam naast die van mij op de kaft willen plaatsen. En zelfs dat zou nog geen recht doen aan alles wat je de afgelopen jaren voor mij hebt betekend en gedaan. Jij bent de stille kracht achter mij. Ik kan elke dag meer dan 100% geven op en aan mijn werk, omdat ik weet dat ik altijd thuis kan komen naar jou. Je hebt altijd in mij geloofd en me gemotiveerd om door te zetten, zelfs op de momenten dat ik zelf twijfelde. Dank je wel dat je er altijd voor mij was met een luisterend oor, aanmoedigende woorden, begrip voor mijn hectische schema en vooral jouw onvermoeibare steun. Dit heeft me geholpen om elke hindernis te overwinnen. Ik kijk ernaar uit om samen met jou te genieten van hoe Sammy de komende jaren groot wordt. Ik houd van jullie.



About the author & curriculum vitae

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Jean-Pierre Ho was born on July 5th, 1983, in Willemstad on the island of Curaçao. He grew up in Paramaribo, Suriname, with his sister Chantal and brother Dave. He attended the Catholic primary school St. Stephanus school and the Richenel Sloote School. After graduating from A.A. Hoogendoorn Atheneum, Jean-Pierre emigrated to Amsterdam, The Netherlands. There he studied dentistry at the Vrije Universiteit (VU) Amsterdam in 2001, nurturing his aspiration to become an Oral & Maxillofacial Surgeon.

After graduating from dental school, Jean-Pierre immediately started medical school at the VU Amsterdam. During this time, he worked part-time as a physician not trained as a specialist – arts niet in opleiding tot specialist (ANIOS) – at the department of Oral & Maxillofacial Surgery in the Academic Medical Centre (AMC) under Prof. Dr. H.P. van den Akker. Additionally, he also worked part-time as a dentist in a general dental clinic. In his spare time, he assisted Dr. J.A.H. Lindeboom as a research assistant, gathering research data, which led to Jean-Pierre's first scientific publication in 2012.

After graduating from medical school, Jean-Pierre started his residency at the department of Oral & Maxillofacial Surgery at the AMC (under the program director Prof. Dr. J. de Lange), the department of Head & Neck Oncology at the Netherlands Cancer Institute (NKI) Antoni van Leeuwenhoek (under the program director Prof. Dr. L.E. Smeele), and the department of Oral & Maxillofacial Surgery at the Isala Clinics in Zwolle (under the program director Dr. E.M. Baas). During his residency training, Jean-Pierre started his PhD in maxillofacial traumatology, investigating zygomaticomaxillary complex fractures.

At the end of his residency training, Jean-Pierre visited the department of Oral & Maxillofacial surgery of the Royal Victoria Infirmary and the Freeman Hospital – The Newcastle Upon Tyne Hospitals NHS Foundation Trust – for a clinical fellowship. In the summer of 2017, Jean-Pierre was board-certified as an Oral & Maxillofacial surgeon and immediately started working as a consultant in the AMC. In 2020, in addition to working at the AMC, Jean-Pierre joined the department of Oral & Maxillofacial surgery of the Northwest Clinics and Dijklander Hospital as a consultant.

In 2020, he made the decision to switch his PhD project from maxillofacial traumatology to sleep-related breathing disorders, specifically obstructive sleep apnea.

Jean-Pierre lives in Uithoorn with his loving partner Krista and son Samuel.